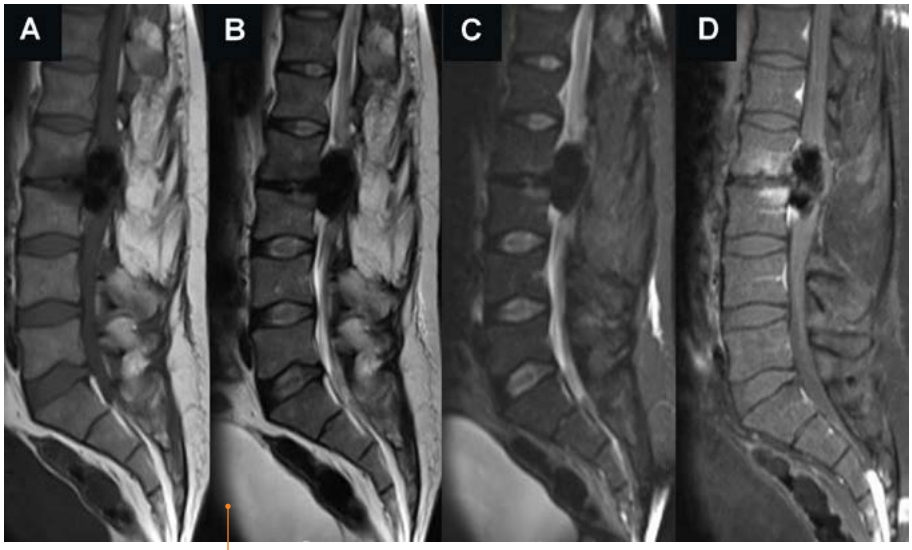
RAMB

JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

Volume **64** Number **8** **August 2018**
ISSN **0104-4230**
ISSN **1806-9282** (On-line)



SECTIONS

ARTICLES

RAMB REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

RAMB - REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA (JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION)

EDITORS-IN-CHIEF: *Carlos V. Serrano Jr. and José Maria Soares Jr.*
CO-EDITOR: *Wanderley M. Bernardo*
MANAGING EDITOR: *César Teixeira*
E-MAIL: *ramb@amb.org.br*
WEBSITE: www.ramb.org.br

Address: Rua São Carlos do Pinhal, 324
Bela Vista – São Paulo
Postal Code: 01333-903
Phone no.: (+55 11) 3178-6800 Ext. 177

The RAMB, Journal of The Brazilian Medical Association, *is an official publication of the Associação Médica Brasileira (AMB – Brazilian Medical Association), indexed in Medline, Science Citation Index Expanded, Journal Citation Reports, Index Copernicus, Lilacs, and Qualis B2 Capes databases, and licensed by Creative Commons®. Registered in the 1st Office of Registration of Deeds and Documents of São Paulo under n. 1.083, Book B, n. 2.*

Publication norms are available on the website www.ramb.org.br

THE RAMB IS INDEXED IN SCIELO - SCIENTIFIC ELECTRONIC LIBRARY ONLINE.

TIMBRO EDITORA

PUBLISHER: *Rodrigo Aguiar*
AUTHORIZING EDITOR: *Luciano Bauer Grohs*
EDITOR: *Celina Maria Morosino Lopes*
PRODUCER: *Maria Fortes*
EDITORIAL PRODUCER: *Helvânia Ferreira*
ENGLISH TRANSLATION OF ARTICLES: *Alpha & Omega*
REFERENCE REVIEWER: *Rosângela Monteiro*
PROOFREADING: *Hebe Ester Lucas e Alpha & Omega*
GRAPHIC DESIGN: *Angela Mendes*

SUMMARY

SECTIONS

EDITORIAL

GUIDELINES IN FOCUS

IMAGING IN MEDICINE

RAPID COMMUNICATIONS

ARTICLES

ORIGINAL ARTICLES

CardioER® - Using smartphone medical applications as an aid to clinical decision-making – are we ready for this?

Alexandre de Matos Soeiro[1], *MD*
Tatiana de Carvalho Andreucci Torres Leal[1], *MD*
Aline Siqueira Bossa[1]
Maria Carolina Feres de Almeida Soeiro[1], *MD*
Carlos Vicente Serrano Jr.[1], *MD PhD*
Múcio Tavares Oliveira Jr.[1], *MD PhD*

1. Clinical Emergency Unit – InCor – HCFMUSP – São Paulo - SP, Brasil

http://dx.doi.org/10.1590/1806-9282.64.08.658

INTRODUCTION

The development of medical applications for tablets or smartphones has been worldwide spread. The technology has been applied in several areas, with uses ranging from control of medicine administration, detection and control of diseases, alerting skilled people to handle emergency situations in neighboring areas, assessment of skin lesions, contraception, medical training etc.[1-9] It is not clear whether the applications have been submitted to scientific evaluation[5].

In Brazil, experience with national applications is still early and few data are known. Thus, we have developed a descriptive study with the objective of evaluating the functionality and rate of approval of a national medical application for the Brazilian population.

METHODOLOGY

We used the CardioER® application, marketed by Editora Manole Ltda. since September 2015, which is considered the first national medical application with conduct flowcharts and content related to cardiac emergencies. Between August and December 2016, an optional questionnaire with 11 multiple-choice questions on the use, degree of importance, academic/professional training of the user and role in emergencies was introduced with the latest update of the application. Of approximately 40,000 downloads via App Store and Google Play, 791 (1.9%) answered the questionnaire. The responses were evaluated, and the results are described below.

The questions made were:

1) What is your level of training?
a) Medical scholar
b) Cardiologist
c) Doctor, but not a cardiologist
d) Health professional, but not a doctor
e) Not a health professional

2) Does your work involve emergency situations?
a) Yes *b) No*

3) In your opinion, is the content of the application appropriate to its objective?
a) Yes *b) No*

ARTICLE RECEIVED: 02-Feb-2018
ACCEPTED FOR PUBLICATION: 16-Feb-2018
MAILING ADDRESS: Alexandre de Matos Soeiro
E-mail: alexandre.soeiro@bol.com.br

4) In your opinion, which feature in the application is more important to your clinical practice?

a) Guidelines
b) Flowcharts
c) Tables
d) Images
e) Calculators
f) Videos
g) Blog

5) Have you ever consulted the application for help in correcting the dosage of a medication/choice of a particular therapy?

a) Yes *b) No*

6) Has the application influenced any medical decisions?

a) Yes *b) No*

7) Do you consider the use of the application in a given situation/medical decision:

a) Was helpful
b) Got in the way
c) Made no difference
d) I did not use it in these situations

8) Do you think the use of medical applications like this is valid?

a) Yes *b) No*

9) Do you feel confident in using the application in real medical situations?

a) Yes *b) No*

10) Would you recommend the application to other people?

a) Yes *b) No*

11) What is the final assessment that you make of this application?

a) Excellent
b) Great
c) Good
d) Bad
e) Terrible

STATISTICAL ANALYSIS

Presented in the form of percentages and absolute values calculated for each question analyzed.

RESULTS

Approximately 9% of those who used the application were medical scholars, 56% were not cardiologists, 32% were training cardiologists and about 93% worked in emergency sectors (Figure 1). Ninety-six percent found the application content adequate to its objective and the flowcharts were considered the most important feature by 56%, followed by the guidelines (26%) and dosage calculators (12%). According to the users, 81% felt the application assisted them in the choice of therapy, being helpful in 88% of the cases and getting in the way 0% of the times. Approximately 99% of users found the application valid and 96% feel confident making decisions based on its information. Overall, the final assessment of

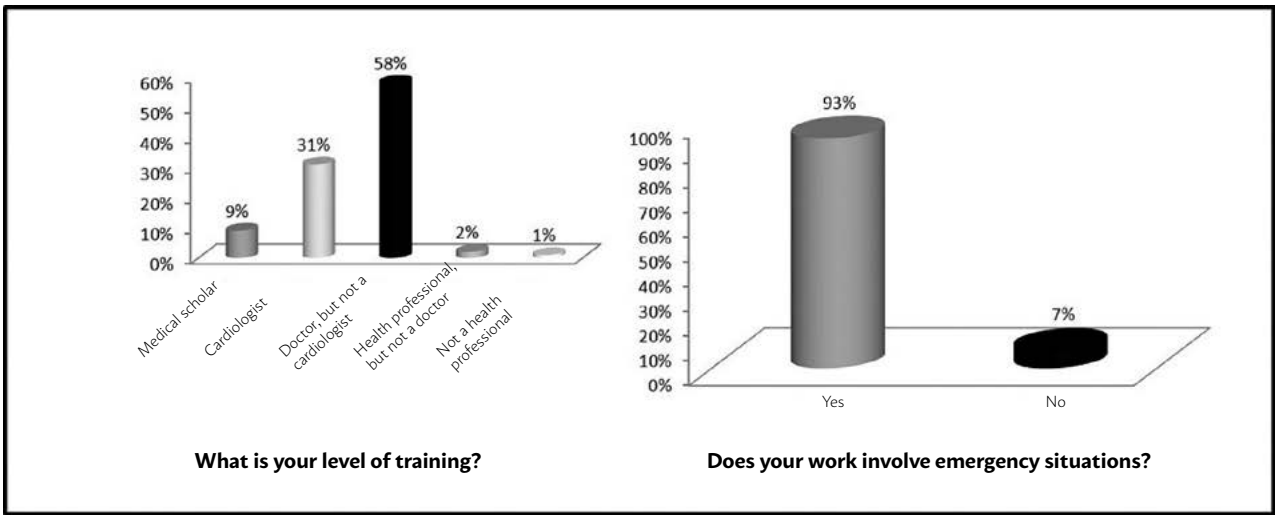


FIGURE 1. Application user profiles.

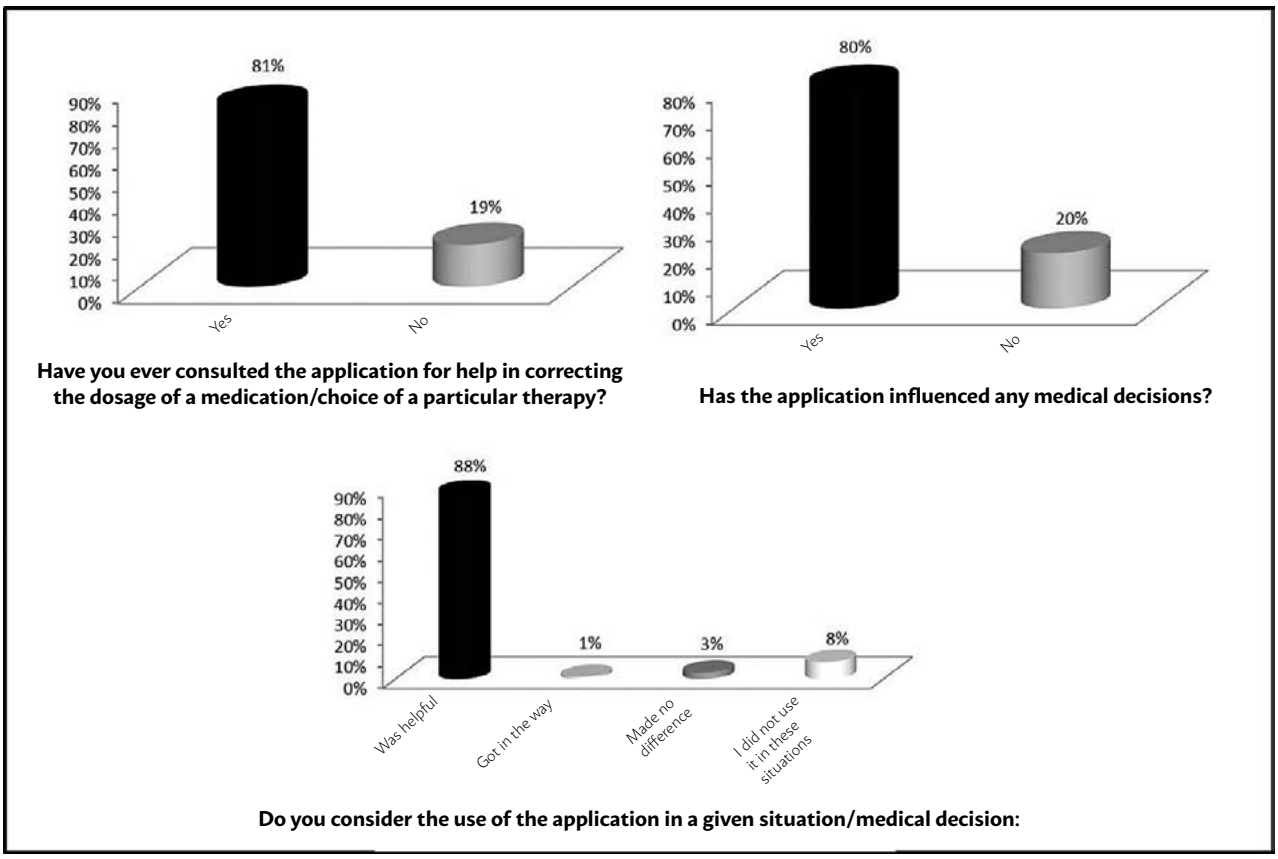


FIGURE 2. Results of the practical use of the application.

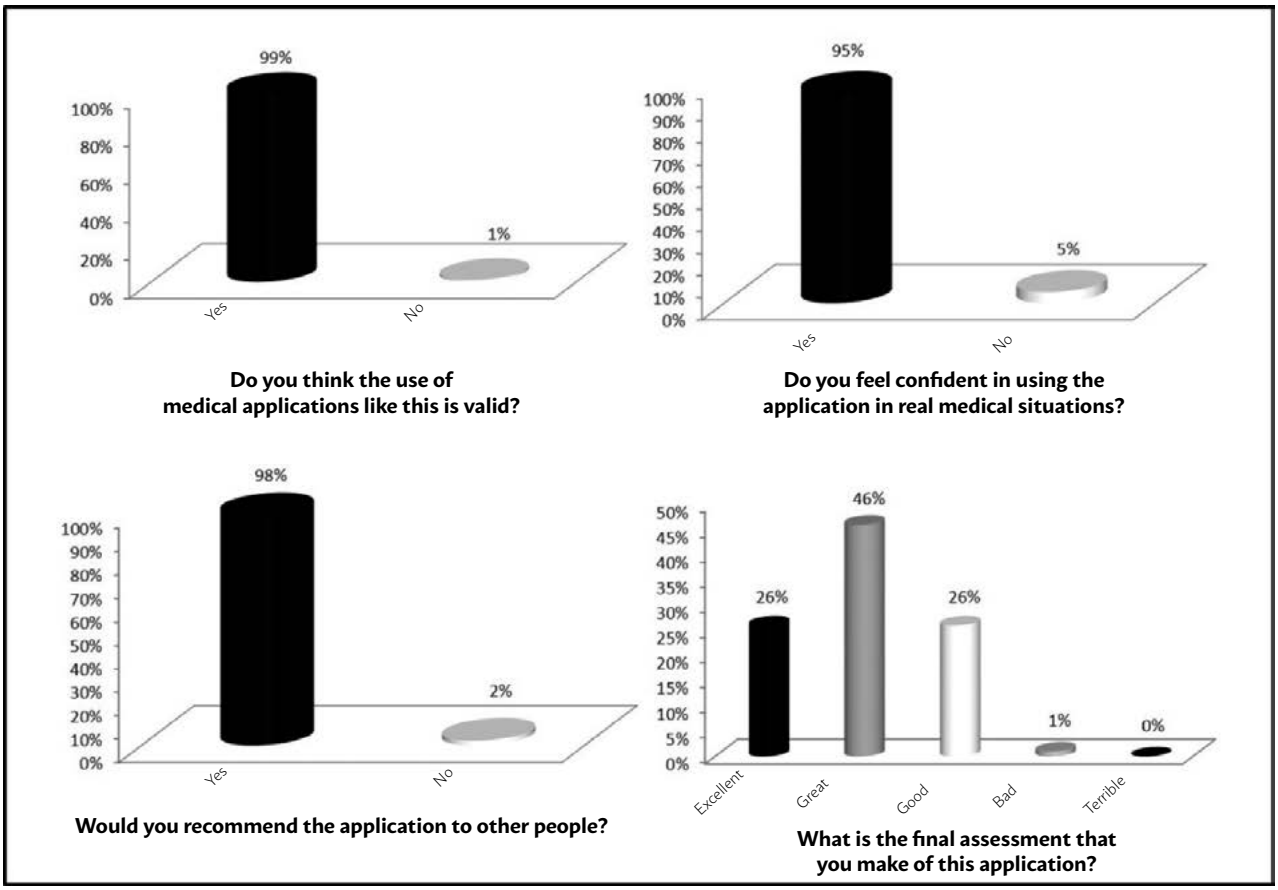


FIGURE 3. Final conclusion of the users regarding the application.

the application was excellent, great or good for 97% of users. The results of the practical use of the application and user's final opinion on it are shown in figures 2 and 3.

DISCUSSION

The study shows that the use of an application directed to the medical audience and aimed at the rapid resolution of an emergency problem can bring benefits. At least in respect of the acceptance and usefulness of the device, the evaluations were, in their majority, great or excellent, partly due to its wide range of data with quick access. Or perhaps due to the availability of the flowcharts, following a line of reasoning and being the best-rated content on the platform.

Within cardiology, some smartphone applications have become popular in recent years and allowed the publication of data related to their use and viability[6,10-19].

As an example, a study published in 2017 evaluated the AliveCor application (AliveCor Inc, California, USA), developed as a cardiac event recorder. The objective of this study was to investigate whether the smartphone-based event logger could be effectively used to obtain a correlation between the rhythm of symptoms in unselected patients with palpitations. A total of 20 patients were included for 12 weeks. A correlation with the rhythm of symptoms was obtained in 85% of the patients, with an arrhythmia detected in 45%. Of a total of 966 electrocardiograms available for review, 96% were interpretable[10,15].

On the same line, another study is evaluating a technology that provides access to a reliable means of obtaining an electrocardiogram reading through a smartphone application that works with an attachment providing all 12 leads of a standard electrocardiogram system. The *ST Leuis* study was designed to validate the smartphone application and its ability to accurately assess the presence or absence of acute myocardial infarction with ST elevation in patients with chest pain in comparison with the gold standard. Approximately 60 patients will be included per institution for a total recruitment of 300 patients. Soon we will have the result of this correlation[6].

Recently, with the collaboration of the European Society of Cardiology (ESC), applications were created on atrial fibrillation for use on smartphones and tablets. They seek to improve patient education, improving communication between patients and health professionals and encouraging the active involvement of the patient in the management of their condition. It also aims to promote best practice approaches to the care of patients with atrial fibrillation and demonstrate the value of integrating new digital technology into clinical practice, with the potential for patient involvement, optimization of pharmacological and interventional therapy, and, lastly, to improve patient outcomes. There are still no published data on the effectiveness of its use[13].

Still in the area of cardiology, at the end of 2017 another randomized trial was initiated with three months follow-up to evaluate the feasibility and effectiveness of medication-reminder applications on adherence to therapy compared to usual care. A total of 156 patients with chronic coronary disease have been randomized to one of three groups (usual care group, basic medication reminders group and advanced medication reminder group). The usual care group will receive standard care without access to a medication reminder. The basic medication reminder group will have access to a medication-reminder application with a basic feature that provides simple daily reminders without interactivity. The advanced medication reminder group will have access to a medication-reminder application with additional interactive and customizable features. The primary outcome is adherence to medication. Secondary outcomes include clinical measurements of blood pressure and cholesterol levels and knowledge of medication. An assessment of the process will also be performed to verify the feasibility of the intervention, estimating the acceptability and usefulness to the user[14].

Other applications are working on the possibility of reducing door-to-balloon time and detect arrhythmias in patients with hypertrophic cardiomyopathy or who suffered an idiopathic stroke[11,16,17].

As noted, most studies are still under evaluation. Prospects have been assessed both on the feasibility and validation of applications. In Brazil, the data presented in this study show the first evaluation of a medical application aimed at emergency situations. There are limitations for not having effective data on mortality or outcomes for the patients involved. In addition, only a small portion of users responded to the poll. However, the data presented complement and follow a trend of global publications seeking the improvement of technology in the healthcare area.

CONCLUSION

The availability of medical applications may be able to assist health professionals in their day-to-day practice. The initial experience in Brazil shows that the rate of acceptance and use was excellent, and the development of new applications should be encouraged by health professionals.

REFERENCES

1. McCarthy OL, Osorio Calderon V, Makleff S, Huaynoca S, Leurent B, Edwards P, et al. An intervention delivered by app instant messaging to increase acceptability and use of effective contraception among young women in Bolivia: protocol of a randomized controlled trial. JMIR Res Protoc. 2017;6(12):e252.
2. Robbins R, Krebs P, Jagannathan R, Jean-Louis G, Duncan DT. Health app use among US mobile phone users: analysis of trends by chronic disease status. JMIR Mhealth Uhealth. 2017;5(12):e197.
3. Feuerstein-Simon C, Bzdick S, Padmanabhuni A, Bains P, Roe C, Weinstock RS. Use of a smartphone application to reduce hypoglycemia in type 1 diabetes: a pilot study. J Diabetes Sci Technol. 2017 Dec 1:1932296817749859.
4. Beukenhorst AL, Schultz DM, McBeth J, Lakshminarayana R, Sergeant JC, Dixon WG. Using smartphones for research outside clinical settings: how operating systems, app developers, and users determine geolocation data quality in mHealth studies. Stud Health Technol Inform. 2017;245:10-4.
5. Buechi R, Faes L, Bachmann LM, Thiel MA, Bodmer NS, Schmid MK, et al. Evidence assessing the diagnostic performance of medical smartphone apps: a systematic review and exploratory meta-analysis. BMJ Open. 2017;7(12):e018280.
6. Barbagelata A, Bethea CF, Severance HW, Mentz RJ, Albert D, Barsness GW, et al. Smartphone ECG for evaluation of ST-segment elevation myocardial infarction (STEMI): design of the ST LEUIS International Multicenter Study. J Electrocardiol. 2018;51(2):260-4.
7. Poulton A, Pan J, Bruns LR Jr, Sinnott RO, Hester R. Assessment of alcohol intake: retrospective measures versus a smartphone application. Addict Behav. 2018;83:35-41.
8. Nørgaard SK, Nichum VL, Barfred C, Juul HM, Secher AL, Ringholm L, et al. Use of the smartphone application "pregnant with diabetes". Dan Med J. 2017;64(11). pii: A5417.
9. Machado GC, Pinheiro MB, Lee H, Ahmed OH, Hendrick P, Williams C, et al. Smartphone apps for the self-management of low back pain: a systematic review. Best Pract Res Clin Rheumatol. 2016;30(6):1098-109.
10. Newham WG, Tayebjee MH. Excellent symptom rhythm correlation in patients with palpitations using a novel Smartphone based event recorder. J Atr Fibrillation. 2017;10(1):1514.
11. Magnusson P, Mörner S. EvaLuation Using Cardiac Insertable Devices And TelephonE in Hypertrophic Cardiomyopathy (ELUCIDATE HCM)-rationale and design: a prospective observational study on incidence of arrhythmias in Sweden. BMJ Open. 2017;7(12):e019541.
12. Mandoli GE, D'Ascenzi F, Cameli M, Mondillo S. Cardiology: is the smartphone era? G Ital Cardiol (Rome). 2017;18(12):832-6.
13. Kotecha D, Chua WWL, Fabritz L, Hendriks J, Casadei B, Schotten U, et al. European Society of Cardiology smartphone and tablet applications for patients with atrial fibrillation and their health care providers. Europace. 2018;20(2):225-33.
14. Santo K, Chow CK, Thiagalingam A, Rogers K, Chalmers J, Redfern J. MEDication reminder APPs to improve medication adherence in Coronary Heart Disease (MedApp-CHD) Study: a randomised controlled trial protocol. BMJ Open. 2017;7(10):e017540.
15. Tabing A, Harrell TE, Romero S, Francisco G. Supraventricular tachycardia diagnosed by smartphone ECG. BMJ Case Rep. 2017 Sep 11;2017. pii: bcr-2016-217197.
16. Tu HT, Chen Z, Swift C, Churilov L, Guo R, Liu X, et al. Smartphone electrographic monitoring for atrial fibrillation in acute ischemic stroke and transient ischemic attack. Int J Stroke. 2017;12(7):786-9.
17. Chauhan V, Negi PC, Raina S, Raina S, Bhatnagar M, Guleri R, et al. Smartphone-based tele-electrocardiography support for primary care physicians reduces the pain-to-treatment time in acute coronary syndrome. J Telemed Telecare. 2017 Jan 1:1357633X17719395.
18. Scali MC, Azevedo Bellagamba CC, Ciampi Q, Simova I, Castro e Silva Pretto JL, et al. Stress echocardiography with smartphone: real-time remote reading for regional wall motion. Int J Cardiovasc Imaging. 2017;33(11):1731-6.
19. Mamorita N, Arisaka N, Isonaka R, Kawakami T, Takeuchi A. Development of a smartphone app for visualizing heart sounds and murmurs. Cardiology. 2017;137(3):193-200.

Spine surgery - the use of vancomycin powder in surgical site for postoperative infection prevention

Author: Brazilian Society of Neurosurgery - Spine Department
Participants: *Andrei Fernandes Joaquim, Jerônimo Buzetti Milano, Jefferson Walter Daniel, Fernando Luiz Rolemberg Dantas, Franz Jooji Onishi, Eduardo de Freitas Bertolini, Marcelo Luiz Mudo, Ricardo Vieira Botelho*
Final version: *August 17, 2017*

http://dx.doi.org/10.1590/1806-9282.64.08.663

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

METHODOLOGY FOR EVIDENCE COLLECTION

This guideline followed the pattern of a systematic review with evidence collection based on the movement of Evidence-Based Medicine, in which clinical experience is integrated with the ability of critical analysis, rationally applying scientific information, thus improving the quality of medical assistance.

We used the structured version of the PICO question, in which **P** refers to **patients who underwent spine surgery**; **I** stands for intervention, in this case the use of topical **vancomycin power during surgery (intraoperative)**; **C** stands for control formed by **patients who underwent spine surgery and did not use this antibiotic**; and **O** meaning outcome, in this case the **infection rates and postoperative complications**.

Through the elaboration of relevant clinical questions related to the proposed theme, based on the structured question, we identified the keywords that served as the basis for searching the databases: Medline - PubMed; Embase - Elsevier; Lilacs - Bireme. A total of 27 studies were selected to answer the clinical questions **(Annex I)**.

CLINICAL QUESTIONS:

What is the effect of the vancomycin powder applied directly on the surgical site on postoperative infection rates for patients who undergo spine surgery?

Are there any complications or adverse effects to patients when the vancomycin powder is used?

What is the recommended dose of vancomycin powder to be inserted in the surgical site to prevent infections in dorsal surgical approaches in the spinal column?

GRADES FOR RECOMMENDATION AND LEVELS OF EVIDENCE:

A: Experimental or observational studies of higher consistency

B: Experimental or observational studies of lower consistency

C: Case reports (uncontrolled studies)

D: Opinion deprived of critical evaluation, based on consensus, physiological studies or animal models

OBJECTIVE

The objective of this review is to use primary studies to assess the effect of the use of intraoperative vancomycin power as a prevention for postoperative infections in the spinal column, its adverse reactions or complications, and the recommended dose.

CONFLICT OF INTEREST

There are no conflicts of interest to be declared by any of the participants regarding this review.

INTRODUCTION

Postoperative infections after spine surgeries are relatively frequent complications with great morbidity, such as increased length of hospital stay, need for reapproaches, worse functional prognoses, loss of instrumentation, amongst others[1,2].

The incidence of infections at the surgical site in spine surgeries depends of many factors, varying from 0.5% to 15% with higher rates for instrumented surgeries and deformities[3]. Staphylococcal infections (S. Aureus and S. epidermidis) are the most common agents, with increased incidence of methicillin-resistant S. aureus (MRSA)[4,5].

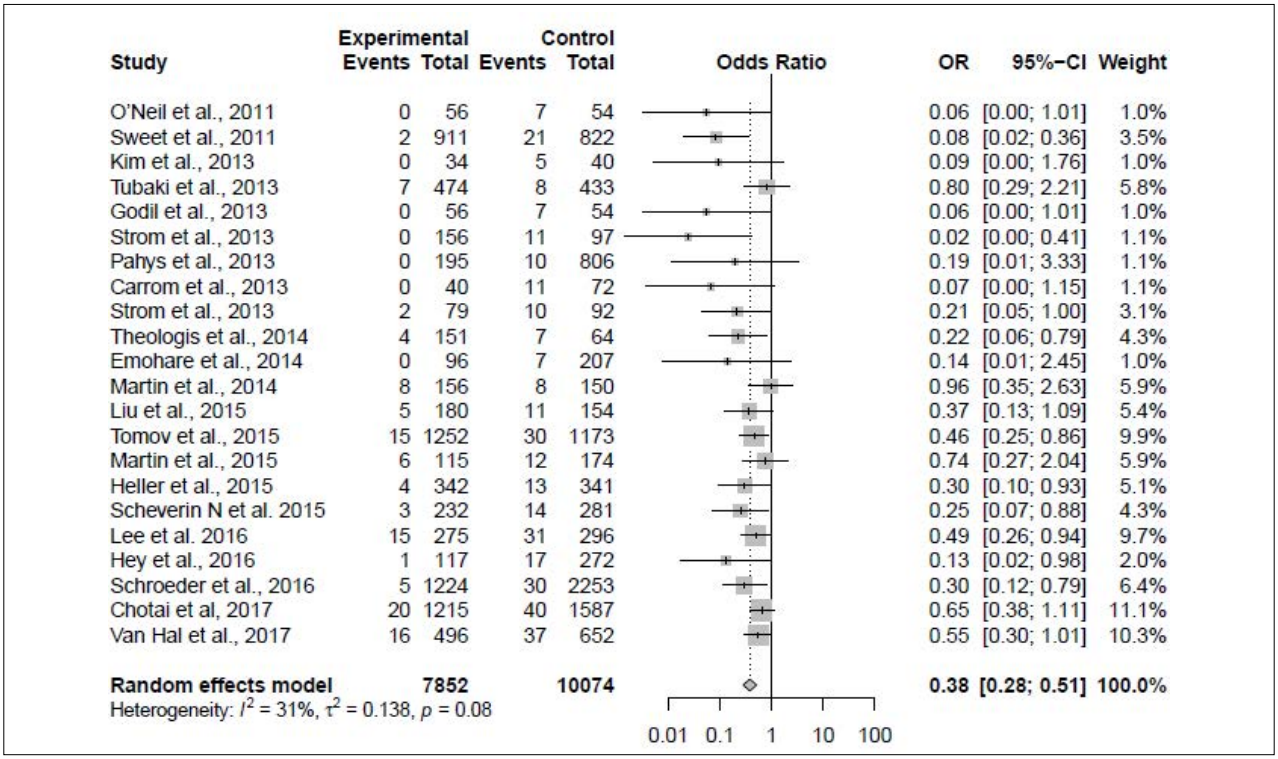
Amongst measures to reduce infection rates, is intravenous antibiotic therapy, with proven but limited effectiveness. Recently, some studies suggested the use of vancomycin powder applied directly to the surgical site can reduce the incidence of infection in spine surgery without relevant additional risks[6]. In this context, it is of the utmost importance to assess the effectiveness of the use of vancomycin powder at the surgical site to prevent infections, as well as the safety of its use.

PRESENTATION OF RESULTS

1. What is the effect of the vancomycin powder applied directly on the surgical site on postoperative infection rates for patients who undergo spine surgery?

The number of combined studies was 22[5-26](B) The only randomized study had an infection rate too low to show the effect. Using the same infection rate of the study and considering a test power of 80%, an estimated error of 5%, and type B error of 5% of 20%, the sample size necessary to reveal the effects would be over double the one used. Thus, the study was demoted regarding methodological quality and evaluated as part of a group along with the other

TABLE 1 - META-ANALYSIS OF THE GROUPED RESULTS



Number of combined studies: k = 22. Odds Ratio: 0.380395%-CI [0.2810 0.5146;] z=-6.26 p-value<0.0001. Random effects model. Quantification of heterogeneity: tau^2 = 0.1380; H = 1.21 [1.00, 1.57]; I^2 = 31.5% [0.0%; 59.2%]. Test for heterogeneity: Q=30.64 d.f.= 21 p= 0.0798

studies. The odds ratio of infection with the use of vancomycin compared to that of surgery without it was of 0.38 (Random effects model), 0.3803 [0.2810; 0.5146], p=0.0001.

2. Which are the risks when the vancomycin powder is used?

The authors suggested that the use of vancomycin powder can increase the incidence of infection by gram-negative bacteria and seromas (since they reported collections with negative culture results in their series)[27] **(B)**.

Another study reported the use of the vancomycin to be safe regarding nephrotoxicity, ototoxicity, and rashes. However, it highlights there are studies that have shown lower fusion rates for cases of vancomycin associated with bone grafting, for high concentrations of vancomycin cause cytotoxicity over in vitro osteoblasts[13] **(B)**. In 911 cases studied, when a dose of 2 g (highest dose found in the studies – range from 500 mg to 2 g) was used, there were no reported adverse effects that could be attributed to the vancomycin powder in any of the cases. It was concluded that the vancomycin powder does not reach toxic levels, nor does it alter kidney function in patients. Therefore, it is safe to use it. The clear majority of the studies did not report any side effect to the use of intraoperative vancomycin powder at the surgical site[8] **(B)**.

TABLE 2 - DOSE OF TOPICAL VANCOMYCIN USED BY EACH STUDY

Study	Dose
O'Neil et al., 2011	1 g
Sweet et al., 2011	2 g
Pahys et al., 2013	0,5 g
Strom et al., 2013	1 g
Strom et al., 2013	1 g
Caroom et al., 2013	1 g
Kim et al., 2013	1 g
Godil et al., 2013	1 g
Tubaki et al., 2013	1 g
Martin et al., 2015	2 g
Emohare et al., 2014	1 g
Theologis et al., 2014	2 g
Martin et al., 2014	2 g
Scheverin et al. 2015	1 g every three levels
Tomov et al., 2015	1 g
Liu et al., 2015	0.5 g - 2 g
Heller et al., 2015	0.5 g - 2 g
Schroeder et al., 2016	1 g
Lee et al. 2016	1 g
Hey et al., 2016	1 g
Van Hal et al, 2017	1 g
Chotai et al, 2017	1 g

3. What is the recommended dose of vancomycin powder to be inserted in the surgical site to prevent infections in dorsal surgical approaches in the spinal column?

Out of the 22 studies, 15 used a 1 g dose of vancomycin powder, four used 2 g, and three adjusted the dose according to the extent of the surgery, ranging from 500 mg to 2 g, and only one[11] **(B)** used 500 mg as the standard dose of vancomycin powder, studying only patients who underwent posterior cervical surgery. **(Table 2)**

The dose most frequently used was 1 g. One author[21] **(B)** used 1 g of vancomycin powder for every three segments addressed.

The studies by Martin[16,19] **(B)** using a 2 g dose at the surgical site did not show any benefits regarding protection from infections.

RECOMMENDATIONS

The intraoperative use of the vancomycin power reduced the number of postoperative infections in the spinal column **(B)**.

There were no serious or unwanted side effects in the studies assessed **(B)**.

The recommended dosage is of 1 g of vancomycin power at the surgical site **(B)**.

This recommendation is mostly based on case-control studies with no evidence of significant adverse effects (Moderate quality). Future studies may influence or change the estimate of the observed effect.

APPENDIX I
Structured question

The clinical questions were structured according to the search strategy based on PICO structured questions (meaning "Patient", "Intervention", "Control", and "Outcome").

P - Patients of all ages who underwent spine surgery in any segment (cervical, thoracic, and lumbar).
I - The use of topical vancomycin power during surgery (intraoperative).
C - Patients who underwent spine surgery and did not use this antibiotic.
O - Postoperative infection rates for spine surgeries and complications with the use of vancomycin.

Methodology for evidence search

We reviewed articles from the Medline (PubMed), Embase, and Lilacs databases, with no time limit.

PubMed-Medline (07/07/2017)

"vancomycin" [MeSH Terms] OR "vancomycin" [All Fields]) AND ("powders"[MeSH Terms] OR "powders"[All Fields] OR "powder"[All Fields]) AND ("spine"[MeSH Terms] OR "spine"[All Fields]) AND ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields]

Selection of papers

The evidence used was retrieved by the following steps elaboration of clinical question, structuring of the question, search for evidence, critical evaluation, and selection of evidence.

The studies were initially selected by title, then by summary and, lastly, by their complete text, being the last one subject to critical evaluation and the extraction of all results relating to outcomes.

Language

Only studies available in Portuguese, English, or Spanish were included.

According to publication

Only studies with texts available in its entirety were considered for critical evaluation.

The primary studies to be assessed were random studies; when these were not available, then comparative studies.

The articles returned from the search were initially assessed by their titles. The titles identified were reassessed by their abstracts, and those selected were fully evaluated. Two authors were responsible for the independent evaluation of the results and all disagreements were resolved through discussions between them. Controlled observational studies and randomized studies, both prospective and retrospective, were included. Studies with less than 20 patients were excluded.

Critical evaluation and level of evidence

With the aim of reducing biased data from systematic reviews, some instruments were used to help assess the methodological quality of each of the articles included.

Randomized clinical trials were assessed using the Cochrane tool for quality of clinical trials.

Studies such as cases and controls, and cohort studies can have their quality assessed using the New Castle-Ottawa Scale (NOS)[29]. This instrument uses an evaluation system called star system, which considers three different aspects: study selection, group comparability, and desired outcome assessment[29].

Data Analysis

The statistical analysis used the meta-analysis software "R package".

For continuous variables: mean difference and confidence interval (CI) of 95%.

Dichotomous variables: relative risk of 95% CI.

The statistical heterogeneity was assessed using the chi-squared test and I2. The fixed effects of the model were used in cases with no calculated heterogeneity.

The inconsistencies of the studies were interpreted with I2:

0% to 40% - may not be relevant,

30% to 60% - may represent heterogeneity,

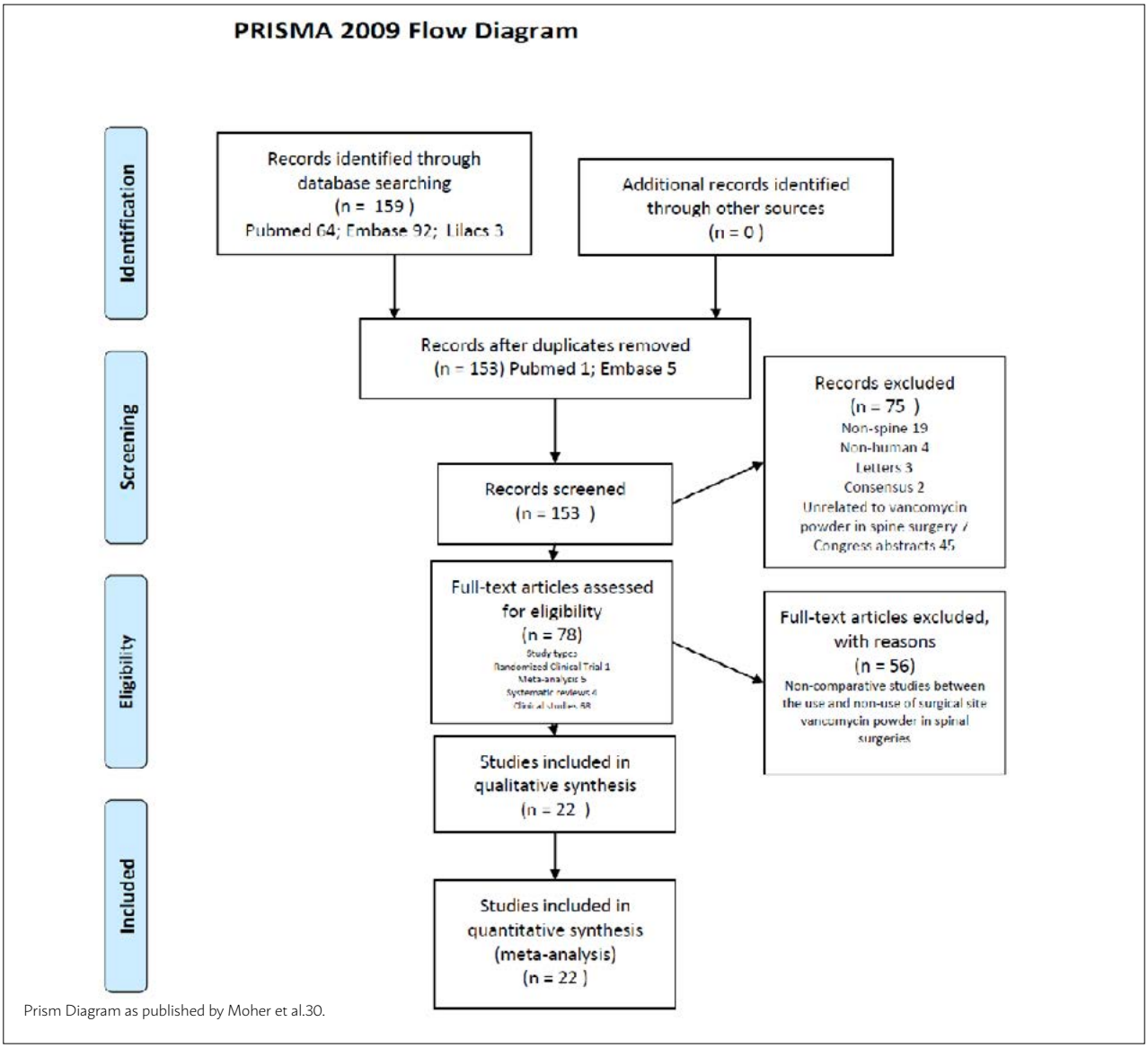
50% to 90% - may represent substantial heterogeneity, and

75% to 100% - has considerable heterogeneity.

Fixed and randomized effects were used according to the quality of inconsistencies found. Moderate and high inconsistencies were analyzed according to the random effects model.

Presentation of results

A total of 78 papers were retrieved, out of which 22 were fully assessed after our inclusion and exclusion criteria were applied. Amongst the 22 studies, we found 21 of the case-control type and one randomized clinical trial.



Prism Diagram as published by Moher et al.30.

METHODOLOGICAL QUALITY ASSESSMENT

Randomized clinical trial

Tubaki et al. published, in 2013, the only randomized clinical trial identified in this review[9].

Selection bias: The randomization was computer generated. Both groups, of use and non-use of vancomycin, did not present differences in baseline characteristics. These groups were comparable.

Performance bias: There was no attempt at a blinded grouping for treatment. Neither patients nor result evaluators were blinded. All patients had a 12-week follow up after the surgery.

Attrition bias: There were no described losses in the segment. There was no differentiation between loss of results and abandonment from the study. Patients had a follow-up long enough to assess the outcome (18 months). In the group treated with vancomycin, the infection rate was of 1.61%, and in the control group of 1.68%. These extremely low infection rates might have contributed to demonstrate the lack of effectiveness of vancomycin in these studies.

Based on the infection rates described for both samples and estimating a confidence interval of 95% and a statistical test with 80% of power, the estimated sample size necessary to reveal statistical differences would be much greater than the one studied.

NON-RANDOMIZED STUDIES (OBSERVATIONAL)

Twenty-one studies were of the case-control type, comparing infection rates in surgeries using and not using the intraoperative vancomycin power. The selection of cases and controls was considered adequate in all of them, for every patient was operated and used or did not use the antibiotic. In the comparability for infection odds (primary outcome), even though some studies used a logistic regression isolating possible confounding risk factors for the outcome, (such us age and diabetes mellitus), none of them performed an adjusted risk assessment for confounders. Regarding the exposure to the causal factor criteria, almost all studies used retrospective cohorts as comparators, with different times and samples, impairing the homogeneity of exposure to the risk of infection.

Case-control studies – New Castle-Ottawa Scale (NOS) (Table 3)

Publication bias of the studies evaluated (funnel plot):

The funnel plot reveals study asymmetry with a prevalence of studies with lower standard error (bigger sample size).

TABLE 3 – TWENTY-ONE STUDIES WITH QUALITY ASSESSMENT ACCORDING TO THE NOS CLASSIFICATION

Study	Selection	Comparability	Exposure	Details of the study
O'Neil et al., 2011	****	*	**	Patients with trauma. Posterior spinal fusions. The treatment and control groups were statically similar.
Sweet et al., 2011	****	*	**	Non-concurrent case-controls. Thoracolumbar fusions.
Caroom et al., 2013	****	*	**	Non-concurrent case-controls. The intervention group tended a bit to more complex procedures.
Godil et al., 2013	****	*	**	Not controlled for confounding factors but with no differences between samples.
Kim et al., 2013	****	*	**	Current vs. Previous. Instrumented spinal column in every level.
Pahys et al., 2013	****	*	**	Data collected and analyzed by three independent reviewers. Significant differences between the samples.
Strom et al., 2013	****	*	**	Current vs. Previous. Cases with instrumentation and cases without it. Balanced for instrumentation.
Strom et al., 2013	****	*	**	Current vs. Previous. Cases with instrumentation and cases without it.
Emohare et al., 2014	****	*	**	Grouping of patients according to surgeon recommendation or admission call. Significant differences between the samples.
Martin et al., 2014	****	*	**	Current vs. Previous. Association between infection and the vancomycin powder with and without risk adjustment.
Theologis et al., 2014	****	*	**	Current vs. Previous. Significant differences between samples
Heller et al., 2015	****	*	**	Current vs. Previous. Posterior instrumented surgeries. 8% of segment loss. Samples not balanced for age.
Liu et al., 2015	****	*	**	Current vs. Previous. Significant differences between the samples.
Martin et al., 2015	****	*	**	Current vs. Previous. Significant differences between samples.
Tomov et al., 2015	****	*	**	Current vs. Previous. Current terminology codes. Data from the US Center for Infection Prevention and Control.
Scheverin N et al. 2015	****	*	**	Vancomycin prescribed according to the preference of the surgeon. Significant differences between samples.
Hey et al., 2016	****	*	**	Significant differences between samples.
Lee et al. 2016	****	*	**	Current vs. Previous. Uni and Multivariate analysis for covariables.
Schroeder et al., 2016	****	*	**	Current vs. Previous. Significant differences between samples.
Chotai et al., 2017	****	*	**	Not controlled for confounding factors but with no differences between the samples.
Van Hal et al., 2017	****	*	**	Current vs. Previous

RECOMMENDATION

The articles were selected after a critical assessment of the level of evidence by specialists of the participant societies with the recommendation for publication of those with greater level of evidence.

The recommendations of outcomes were based on the GRADE guidelines[31].

REFERENCES

1. Savage JW, Anderson PA. An update on modifiable factors to reduce the risk of surgical site infections. Spine J. 2013 Sep;13(9):1017-29
2. Epstein NE. Preoperative, intraoperative, and postoperative measures to further reduce spinal infections. Surg Neurol Int. 2011 Feb 21;2:17
3. Massie JB, Heller JG, Abitbol JJ, McPherson D, Garfin SR. Postoperative posterior spinal wound infections. Clin Orthop Relat Res 1992; 284:99–108
4. Morange-Saussier V, Giraudeau B, van der Mee N, Lermusiaux P, Quentin R. Nasal car- riage of methicillin-resistant Staphylococcus aureus in vascular surgery. Ann Vasc Surg. 2006; 20(6):767-772.
5. Kim HS, Lee SG, Kim WK, Park CW, Son S. Prophylactic intrawound application of vancomycin powder in instrumented spinal fusion surgery. Korean J Spine. 2013 Sep;10(3):121-5. doi: 10.14245/kjs.2013.10.3.121. Epub 2013 Sep 30.
6. Godil SS, Parker SL, O'Neill KR, et al. Comparative effectiveness and cost-benefit analysis of local application of vancomycin powder in posterior spinal fusion for spine trauma . J Neurosurg Spine 2013 ; 19 : 331 – 5 .
7. O'Neill KR , Smith JG , Abtahi AM , et al. Reduced surgical site infections in patients undergoing posterior spinal stabilization of traumatic injuries using vancomycin powder . Spine J 2011; 11 :641 – 6
8. Sweet FA, Roh M, Sliva C. Intrawound application of vancomycin for prophylaxis in instrumented thoracolumbar fusions: efficacy, drug levels, and patient outcomes. Spine (Phila Pa 1976) 2011; 36:2084–8
9. Tubaki VR, Rajasekaran S, Shetty AP, et al. Effects of using intravenous antibiotic only versus local intrawound vancomycin antibiotic powder application in addition to intravenous antibiotics on postoperative infection in spine surgery in 907 patients . Spine (Phila Pa1976) 2013; 38:2149–55.
10. Strom RG, Pacione D, Kalhorn SP, Frempong-Boadu AK. Decreased risk of wound infection after posterior cervical fusion with routine local application of vancomycin powder. Spine (Phila PA 1976). 2013,http://dx.doi.org/10.1097/BRS.0b013e318285b219 [Epub ahead of print].
11. Pahys JM, Pahys JR, Cho SK, Kang MM, Zebala LP, Hawasli AH, Sweet FA, Lee DH, Riew KD. Methods to decrease postoperative infections following posterior cervical spine surgery. J Bone Joint Surg Am. 2013 Mar 20;95(6):549-54.
12. Caroom C, Tullar JM, Benton EG Jr, Jones JR, Chaput CD. Intrawound vancomycin powder reduces surgical site infections in posterior cervicalfusion. Spine (Phila Pa 1976). 2013 Jun 15;38(14):1183-7. doi: 10.1097/BRS.0b013e31828fcfb5.
13. Strom RG, Pacione D , Kalhorn SP , et al. Lumbar laminectomy and fusion with routine local application of vancomycin powder:decreased infection rate in instrumented and noninstrumented cases . Clin Neurol Neurosurg 2013 ; 115 : 1766 – 9
14. Theologis AA, Demirkiran G, Callahan M, Pekmezci M, Ames C, Deviren V. Local intrawound vancomycin powder decreases the risk of surgical site infections in complex adult deformity reconstruction: a cost analysis. Spine (Phila Pa 1976). 2014 Oct 15;39(22):1875-80. doi: 10.1097/BRS.0000000000000533.
15. Emohare O, Ledonio CG, Hill BW, Davis RA, Polly DW Jr, Kang MM. Cost savings analysis of intrawound vancomycin powder in posterior spinal surgery. Spine J. 2014 Nov 1;14(11):2710-5. doi: 10.1016/j.spinee.2014.03.011. Epub 2014 Mar 17.
16. Martin JR, Adogwa O, Brown CR, et al. Experience with intrawound vancomycin powder for spinal deformity surgery. Spine (Phila Pa 1976) 2014; 39: 177–84 .
17. Liu N, Wood KB, Schwab JH, Cha TD, Puhkan RD, Osler PM, Grottkau BE. Comparison of Intrawound Vancomycin Utility in Posterior Instrumented Spine Surgeries between Patients with Tumor and Nontumor Patients. Spine (Phila Pa 1976). 2015 Oct 15;40(20):1586-92. doi: 10.1097/BRS.0000000000001133.
18. Tomov M, Mitsunaga L, Durbin-Johnson B, Nallur D, Roberto R. Reducing surgical site infection in spinal surgery with betadine irrigation and intrawound vancomycin powder. Spine (Phila Pa 1976). 2015 Apr 1;40(7):491-9. doi: 10.1097/BRS.0000000000000789.
19. Martin JR, Adogwa O, Brown CR, Kuchibhatla M, Bagley CA, Lad SP, Gottfried ON. Experience with intra wound vancomycin powder for posterior cervical fusion surgery. J Neurosurg Spine 22:26–33, 2015
20. Heller A, McIff TE, Lai SM, Burton DC. Intrawound Vancomycin Powder Decreases Staphylococcal Surgical Site Infections After Posterior Instrumented Spinal Arthrodesis. J Spinal Disord Tech. 2015 Dec;28(10):E584-9. doi: 10.1097/BSD.0000000000000045.
21. Scheverin N, Steverlynck A, Castelli R, Sobrero D Kopp NV, Dinelli D, Sarotto A, Falavigna. Prophylaxis of surgical site infection with vancomycin in 513 patients that underwent to lumbar fusion. Coluna/Columna [online]. 2015, vol.14, n.3, pp.177-180. http://dx.doi.org/10.1590/S1808-185120151403149776.
22. Lee GI, Bak KH, Chun HJ, Choi KS. Effect of Using Local Intrawound Vancomycin Powder in Addition to Intravenous Antibiotics in Posterior Lumbar Surgery: Midterm Result in a Single-Center Study. Korean J Spine. 2016 Jun;13(2):47-52. doi: 10.14245/kjs.2016.13.2.47. Epub 2016 Jun 30.
23. Hey HWD, Wei DT, Darren KZ, Shantakumar JT, Kumar N, Lau LL, Po GL, Wong HK. Is Intraoperative Local Vancomycin Powder the Answer to Surgical Site Infections in Spine Surgery? Spine (Phila Pa 1976). 2016 May 23.
24. Schroeder JE, Girardi FP, Sandhu H, Weinstein J, Cammisa FP, Sama A. The use of local vancomycin powder in degenerative spine surgery. Eur Spine J. 2016 Apr;25(4):1029-33. doi: 10.1007/s00586-015-4119-3. Epub 2015 Aug 7.
25. Chotai S, Wright PW, Hale AT, Jones WA, McGirt MJ, Patt JC, Devin CJ. Does Intrawound Vancomycin Application During Spine Surgery Create Vancomycin-Resistant Organism? Neurosurgery. 2017 May 1;80(5):746-753. doi: 10.1093/neuros/nyw097.
26. Van Hal M, Lee J, Laudermilch D, Nwasike C, Kang J. Vancomycin Powder Regimen for Prevention of Surgical Site Infection in Complex Spine Surgeries. Clin Spine Surg. 2017 Mar 6. doi: 10.1097/BSD.0000000000000516.
27. Ghobrial GM, Cadotte DW, Williams K Jr, Fehlings MG, Harrop JS. Complications from the use of intrawound vancomycin in lumbar spinal surgery: a systematic review. Neurosurg Focus. 2015 Oct;39(4):E11.
28. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343:d5928.
29. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. http:// www.ohri.ca/programs/clinical_epidemiology/oxford.asp (2017).
30. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
31. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. Chest 2006; 129: 174-81. PMID: 16424429

A rare cause of acute abdomen in an elderly patient

Rafael Sampaio[1]
Andreia Martin[2]
Rodolfo Queiroz[3]
Fred Bernardes Filho[4]

1. São Francisco Hospital - Department of Surgery, Ribeirão Preto/SP, Brasil
2. University of Ribeirao Preto - Medical School, Ribeirão Preto/SP, Brasil
3. Department of Radiology and Imaging Diagnosis, DOCUMENTA, Hospital São Francisco, Ribeirão Preto/SP, Brasil
4. Department of Internal Medicine, São Francisco Hospital, Ribeirão Preto, São Paulo, Brasil

http://dx.doi.org/10.1590/1806-9282.64.08.670

KEYWORDS: *Diverticulum. Abdomen, acute. Abdominal pain. Intestinal perforation.*

An 83-year-old previously healthy woman arrived at the emergency department with a one-day history of intense abdominal pain in the epigastrium after eating. Generalized peritonitis was observed on physical examination; the patient had a pulse rate of 135/min, blood pressure of 86/40 mmHg and respiratory rate of 23/min. Computed tomography of the abdomen showed small bowel loop densification, pneumoperitoneum, jejunal diverticulum without inflammation signs, and a foreign body (Figures A-C). A small piece of chicken bone was found within the jejunal diverticulum (Figure D).

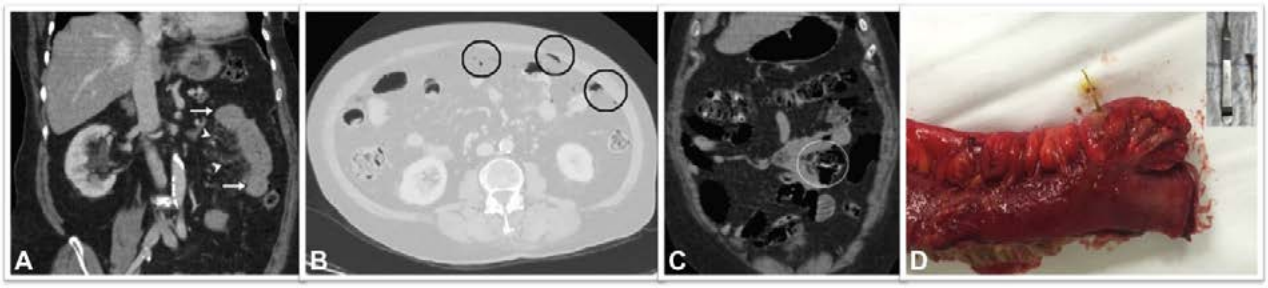


FIGURE (A) CT of the abdomen (coronal view), portal phase after intravenous administration of contrast showing regular parietal thickening in the jejunum segment (arrows) locoregionally associated with densification of its respective mesentery (arrowheads); (B) CT of the abdomen (axial view, lung window) showing intraperitoneal free focuses in an accentuated hypoattenuation representing pneumoperitoneum; (C) CT of the abdomen (coronal view) showing high-density linear image within the jejunum segment, seemingly extending along its wall in the mesenteric side (foreign body); (D) Resected intraoperative specimen showing a jejunal diverticulum perforation by a chicken bone. In the upper right corner, note the chicken bone size in relation to the size of the scalpel handle.

DATE OF SUBMISSION: 29-Oct-2017
DATE OF ACCEPTANCE: 07-Jan-2018
CORRESPONDING AUTHOR: Fred Bernardes Filho
Av. Bandeirantes, 3900, Monte Alegre, Ribeirao Preto/SP, Brasil 14040-900
Tel:+ 55 16 982065490
E-mail: f9filho@gmail.com

cruzrios@hotmail.com
deialmartin@hotmail.com
rod_queiroz@hotmail.com

Segmental bowel resection with entero-enteroanastomosis was performed.

Accidental and unnoticed ingestion of foreign bodies is not very uncommon.[1] A very small percentage of ingested foreign bodies can cause perforation of the bowel, leading to acute abdomen that requires surgical intervention. Foreign bodies such as dentures, fish bones, chicken bones, toothpicks, and cocktail sticks have been known to cause bowel perforation. Most of such foreign bodies pass through the gastrointestinal tract uneventfully and only on rare instances cause obstruction or perforation.[1,2]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

PALAVRAS-CHAVE: *Divertículo. Abdome agudo. Dor abdominal. Perfuração intestinal.*

REFERENCES

1. Aydin I, Pergel A, Yucel AF, Sahin DA. A rare cause of acute abdomen: jejunal diverticulosis with perforation. J Clin Imaging Sci. 2013;3:31.
2. Staszewicz W, Christodoulou M, Proietti S, Demartines N. Acute ulcerative jejunal diverticulitis: case report of an uncommon entity. World J Gastroenterol. 2008;14(40):6265-7.

Pediatric Multiple Sclerosis: The role of magnetic resonance imaging and chemokine profile in the diagnosis and follow-up

Alessandra Penna e Costa[1]
Tania Saad[1]
Lúcio Santa Ignez[1]
Gabriel Gamarano[1]
Ana Paula Lazzari[1]
Zilton Vasconcelos[1]

1. Fernandes Figueira Institute, Fiocruz, Rio de Janeiro/RJ, Brasil.

http://dx.doi.org/10.1590/1806-9282.64.08.672

KEYWORDS: *Multiple sclerosis. Child. Magnetic resonance imaging. Cytokines.*

INTRODUCTION

The early diagnosis for pediatric multiple sclerosis (PMS) is a major challenge for neurology specialists, either by lack of knowledge or difficulty in the differential diagnosis in this specific population. Recent studies estimated that only 5% of adult patients report neurological symptoms before the second decade of life[1]. PMS patients tend to reach an irreversible neurological sequel stage later in time but at an earlier age when compared to adult MS patients. Early and precise diagnosis is key for specific treatment initiation and improvement of pediatric patients' prognosis, since earlier neurological symptoms onset in PMS correlates positively with permanent sequelae risk. Guidelines for PMS diagnosis were recently reviewed and follow definitions published by the International Pediatric MS Study Group. Neurological examination, Kurtzke Expanded Disability Status Scale (EDSS), specific laboratory tests and radiological imaging were considered. CNS lesions dissemination both in time and space observed by Mag-

DATE OF SUBMISSION: 01-Dec-2017
DATE OF ACCEPTANCE: 07-Jan-2018
CORRESPONDING AUTHOR: Zilton Vasconcelos
Oswaldo Cruz Foundation - FIOCRUZ
Fernandes Figueira Institute - IFF – Department of Clinical Research
Av. Rui Barbosa, 716 – Flamengo – Cep: 22250-020 - Rio de Janeiro/RJ – Brasil
E-mail: zvasconcelos@iff.fiocruz.br

aapennaecosta@gmail.com
tsaadmd@gmail.com
lucio.santaignez@gmail.com
gabrielgamarano@gmail.com
anapaularla@hotmail.com
zvasconcelos@gmail.com

netic Resonance Imaging (MRI) is pathognomonic for MS and critical for its evolutionary follow-up[2]. Clinically useful tools to anticipate the PMS diagnosis, predict disease evolution and treatment response are urgently needed. Potential inflammatory-related biomarkers are under extensive investigation, but only oligoclonal band (OCB) in cerebrospinal fluid (CsF), serum and CsF anti-aquaporin-4 (Aqp4) and anti-myelin oligodendrocyte glycoprotein (MOG) are clinically useful. So far, there is no consensus on serum or CsF inflammatory cytokine as biomarkers.

CASE REPORT

ALAPL, 9-years-old, female, black, natural of Rio de Janeiro, good neuropsychomotor development, in May 2014, showed acute left hemiparesis. ALAPL denied visual changes, headache, vomiting, recent vaccination or fever. Brain MRI was performed showing hypointense oval images in T1 and T2 with fluid-attenuated inversion recovery (FLAIR), restricted diffusion signal with varied sizes in white matter at frontal lobes and periventricular pons, right thalamus, cerebellar peduncles, and right cerebral peduncle. In addition, the thalamus showed tenuous contrast impregnation compatible with demyelination. Subsequent spontaneous improvement with overall neurological regression was observed without drug therapy. Rheumatic and hematologic function tests were normal, IgM and IgG serology positive for Epstein Barr virus, CsF OCB positive and serum Aqp4 negative. Control MRI in September 2014 revealed no disease evolution without new contrast-enhancing CNS lesions and reduction of major lesions (Figure 1A). In November 2014, neurological examination detected only discrete dysmetria (EDSS=1), normal fundoscopy, normal spinal chord MRI, classified as a clinically isolated syndrome (CIS). A regular follow up was started with a quarterly neurological examination and cytokine profile measurement with biannual MRI. ALAPL's neurological examination remained unchanged, EDSS and brain MRI (Figure 1B) with no image evolution. Nevertheless, serum cytokine evaluation performed in a period between those images (Figure 1F), detected the highest inflammatory relative index in interleukin-8 (IL8), Macrophage inflammatory protein-1β (MIP-1b), Platelet-derived growth factor-BB (PDGF-BB), Eotaxin and Monocyte chemoattractant protein-1 (MCP-1). Subsequent cytokine dosage showed still higher index (Figure 1G and H) in comparison with initial dosage (Figure 1E). On May 2016, brain MRI detected hyperintense areas that did not exhibit contrast enhancement, confirming CNS lesions disseminated in time and space, despite normal neurological examination and unchanged EDSS (Figure 1C). One month later, the cytokine pro-

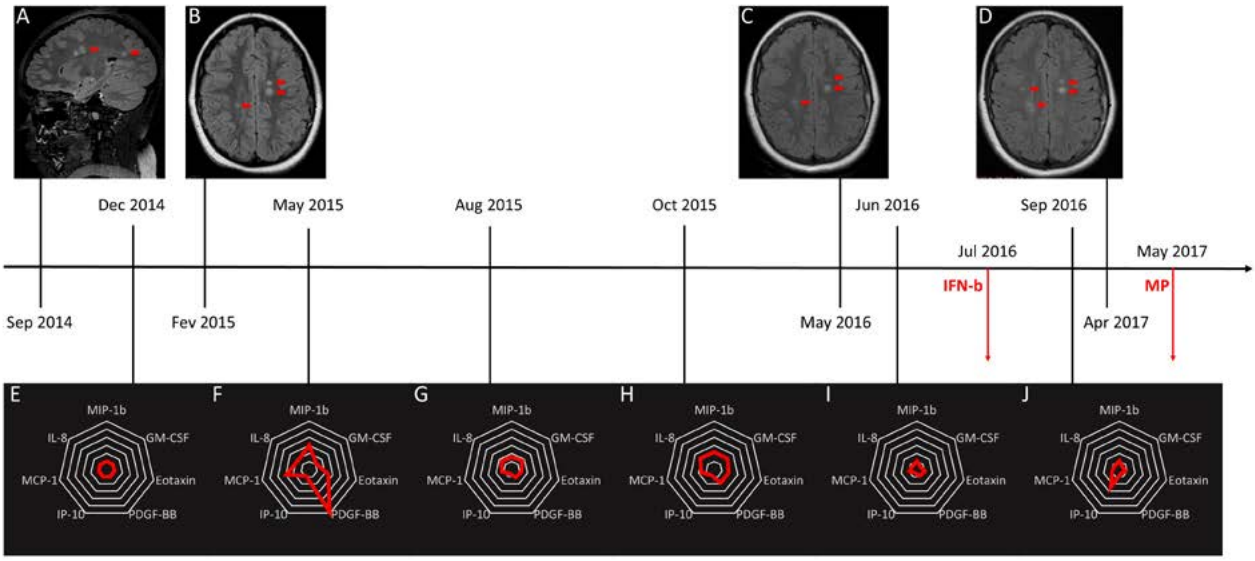


FIGURE 1. Timeline of follow-up with MRI and cytokine inflammatory profile: Whole-brain sagittal (A) and axial (B-D) sections showing CNS FLAIR lesions (red arrows); Cytokine profile (red line) in heptamerised spider charts with 6 concentric axis, index normalized to first serum dosage (E) compared with subsequent measurements (F-J). Therapeutic interventions are shown in the timeline as transversal red arrows. EDSS (score=1) and clinical neurological assessment were performed in the same cytokine profile moments and did not change during this timeline evaluation.

file showed the lowest index for all cytokines. The initial diagnosis was modified to PMS, and subcutaneous interferon beta 1a (IFN-1a) therapy was initiated in July 2016. Just after IFN-1a therapy, the cytokine profile showed a specific IP-10 index peak. On March 2017, clinical evaluation showed unchanged neurological and EDSS results, good school performance, and recent menarche report. However, MRI at April 2017 showed novel CNS lesions with contrast enhancement in the right semi-oval center, characterizing subsequent demyelination event (Figure 1D). On May 2017, ALAPL was hospitalized, and methylprednisolone treatment indicated.

DISCUSSION

We report a patient initially diagnosed with CIS with no subsequent neurological symptoms, who progressively presented changes in inflammatory cytokines preceding brain MRI compatible with PMS. Those findings demonstrate no temporal coincidence between the clinical, imaging, and inflammatory evaluations. Out of a total of 27 cytokines evaluated, only IL8, MIP-1b, PDGF-BB, Eotaxin, MCP-1, and IP-10 showed significant variation during our analysis. The highest inflammatory peak was observed one year before radiological correlation, with a second smaller peak halfway before the MRI conclusive for PMS. The most prominent cytokine, PDGF-BB, is described as a potential proinflammatory biomarker because it induces oligodendroglial progenitor cell growth and contributes to angiogenesis. However, Su et al.[3] were not able to correlate its increased levels and CNS lesions in adults with MS. MIP-1b is associated with a possible immune response to interferon beta[4]; our result showed an increase during the first cytokine storm prior to immunomodulatory treatment. Only diminished levels of Eotaxin were previously reported by Tejera-Alhambra et al.[5], a study in which an association was found with recurrent remitting MS in adults. Moreover, IP-10, a proinflammatory cytokine, was found to have a substantial increase after the onset of interferon beta therapy, as previously reported by Buttman et al.[6], in 2004.

According to Banwell et al.[2], one-third of children with acquired demyelinating syndrome will be diagnosed with PMS within two to four years after the first cortical demyelination. MS increased risk factors are first demyelination in adolescence, female individual, and polyfocal deficits; smaller children with ADEM have a lower risk. ALAPL presented her first demyelination manifestation before adolescence, with focal clinical manifestations and spontaneous regression. However, due to the regular radiological follow-up, it was possible to follow subsequent lesions and establish an early immunomodulatory treatment. A close MRI follow-up for outpatients should be implemented to anticipate PMS diagnosis and adopt early targeted therapies. Further studies are needed to establish new biomarkers with a better temporal association between PMS and cytokine levels, MRI, or neurological examination.

ACKNOWLEDGMENTS

The authors acknowledge the support of the FIOCRUZ Technological Platform Network for Luminex dosages. This work was supported by the IFF Research Grant Program – 2015.

AUTHOR CONTRIBUTIONS

A.P.C. performed the patient's follow up, analyzed the results and wrote the paper; T.S. designed the research, supervised patient follow up and medical records; L.S.I. revised patient's radiologic images and medical records; G.G. performed the Luminex experiments, analyzed the results, and wrote the paper; A.P.L revised the patient's radiologic images and medical records; Z.V. designed the research, supervised the experiments and their analysis, and wrote the paper.

DECLARATION OF CONFLICT OF INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

PALAVRAS-CHAVE: *Esclerose múltipla. Criança. Imagem por ressonância magnética. Citocinas.*

REFERENCES

1. Fragoso YD, Ferreira ML, Morales NM, Arruda WO, Brooks JB, Carneiro DS, et al. Multiple sclerosis starting before the age of 18 years: the Brazilian experience. Arq Neuropsiquiatr. 2013;71(10):783-7.
2. Banwell B, Arnold DL, Tillema JM, Rocca MA, Filippi M, Weinstock-Guttman B. MRI in the evaluation of pediatric multiple sclerosis. Neurology. 2016;87(9 Suppl 2):S88-96.
3. Su JJ, Osoegawa M, Matsuoka T, Minohara M, Tanaka M, Ishizu T, et al. Upregulation of vascular growth factors in multiple sclerosis: correlation with MRI findings. J Neurol Sci. 2006;243(1-2):21-30.
4. Hegen H, Adrianto I, Lessard CJ, Millonig A, Bertolotto A, Comabella M, et al. Cytokine profiles show heterogeneity of interferon-β response in multiple sclerosis patients. Neurol Neuroimmunol Neuroinflamm. 2016;3(2):e202.
5. Tejera-Alhambra M, Casrouge A, Andrés C, Seyfferth A, Ramos-Medina R, Alonso B, et al. Plasma biomarkers discriminate clinical forms of multiple sclerosis. PLoS One. 2015;10(6):e0128952.
6. Buttmann M, Merzyn C, Rieckmann P. Interferon-beta induces transient systemic IP-10/CXCL10 chemokine release in patients with multiple sclerosis. J Neuroimmunol. 2004;156(1-2):195-203.

Spinal metallosis as a complication of a lodged bullet from a firearm wound: an image-centered case

Isabela Machado [1]
Daniel de Paula Garcia [1]
Carolina Souza Tannus [1]
Koji Tanaka [2]
Fred Bernardes Filho [3]
Mauro Jose Brandao da Costa [1,4]
Rodolfo Mendes Queiroz [1,4]

1. Department of Radiology and Imaging, DOCUMENTA, São Francisco Hospital, Ribeirão Preto, SP, Brasil
2. Division of Neurosurgery of the Department of Surgery and Anatomy, Hospital das Clínicas of the Faculty of Medicine of Ribeirão Preto of the University of São Paulo, Ribeirão Preto, SP, Brasil
3. Division of Dermatology of the Department of Clinical Medicine, Hospital das Clínicas of the Faculty of Medicine of Ribeirão Preto of the University of São Paulo, Ribeirão Preto, SP, Brasil
4. Department of Radiology and Imaging, SER IMAGEM, Santa Casa de Misericórdia de Sertãozinho Hospital, Sertãozinho, SP, Brasil

http://dx.doi.org/10.1590/1806-9282.64.08.676

KEYWORDS: *Wounds, gunshot. Spine. Spinal injuries. Stainless steel/adverse effects.*

INTRODUCTION

A male patient, 43 years old, with strong lumbar pain, paresthesia of the lower limbs and progressive ambulation difficulty for four years, with complete disability in the last month. History of firearm wound in the lumbar spine 21 years ago. At the time, surgery was conducted to decompress the spinal canal in a distinct hospital unit at another location, without the use of cement or grafting, or the removal of the projectile. Normal general laboratory results.

In a computed tomography (CT) of the lumbar spine, it was found L2 and L3 laminectomy with a voluminous material with metallic density occupying part of the internal space of the spinal canal and intervertebral foramen (figures 1A, 1B, 1C, and 1D) In the magnetic resonance imaging (MRI), the same material was characterized with hypointense signal on all sequences, including T1-weighted (Figure 2A), T2-weighted (Figure 2B), and Stir (Figure 2C), with a slight highlight of surrounding tissues in T1 after the administration of intravenous contrast medium (Figure 2D), in addition to strong compression effect on the conus medullaris.

The exams performed for determining the levels of serum and urinary lead presented normal values.

Surgery was performed to remove the material (Figure 3A). Which showed not only the fragmented projectile but also a great amount of locoregional tissue impregnated by metal residue.

The patient showed improvement of signs and symptoms after surgery. The fact that symptoms were compatible with spinal cord compression that progressively evolved over the years, with no associ-

DATE OF SUBMISSION: 24-Dec-2017
DATE OF ACCEPTANCE: 06- Jan -2018

CORRESPONDING AUTHOR: Rodolfo Queiroz
Rua Bernardino de Campos, 980, Bairro: Centro, Ribeirão Preto/SP, Brasil 14015-130
Phone:(16) 3977 3007
E-mail: rod_queiroz@hotmail.com

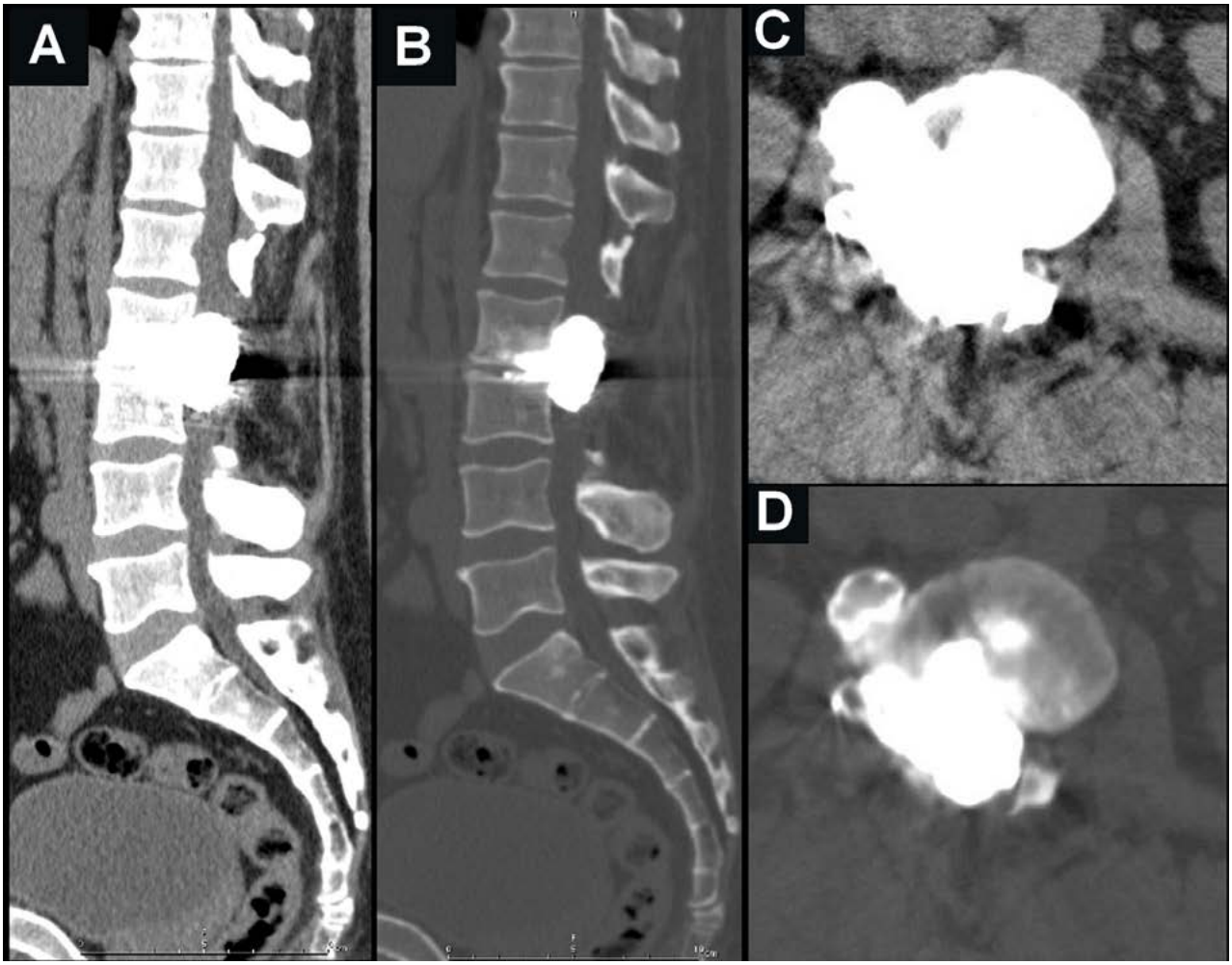


FIGURE 1. CT of the lumbar spine (A,B,C,D) characterizing a large irregular material with metal density occupying most of the spinal canal and disc space at L2-L3.

ated central neurological or systemic symptoms, in addition to the metal impregnated tissued removed being bigger than the projectile, explains the gradually increasing effect and the findings as a whole suggest a metallosis diagnosis.

DISCUSSION

With the increase in crime rates, the number of patients with firearm wounds in the spinal column has also increased. It is estimated that this is responsible for 17% of spine trauma cases, surpassed only by car accidents, which are still the main cause of such lesions.

Lead poisoning due to firearm wounds is unusual and can occur in individuals with bullets lodged for a short period of time, but there are also reported cases of trauma that happened over 50 years. The location of the projectile is the main risk factor. When the bullet is located inside of the joints, a fibrous barrier is formed, but the constant contact with fluids may release lead particles that are absorbed by the bloodstream[2].

The nervous system is the most sensitive to high levels of lead. The patient presents peripheral neuropathy associated with paresthesias, parkinsonism, and ataxia. Furthermore, extraneurologic symptoms can be found, such as weakness, abdominal pain, arthralgia, and anorexia[3]. Blood levels are considered elevated when above 25 ug/dL in children and 40 ug/dL in adults[3].

Metallosis is another complication that can occur in cases of chronic exposure to lead and other metals. It is mostly reported is cases of metallic implants or internal fixation of fractures, rarely in the spinal cord, with less than 50 cases reported[4,5]. It is a disease caused by microparticles resulting from an inflammatory process which form a metalloma. It begins with the building up of interstitial fluid around the projectile and micromovements that wear the metal. Then

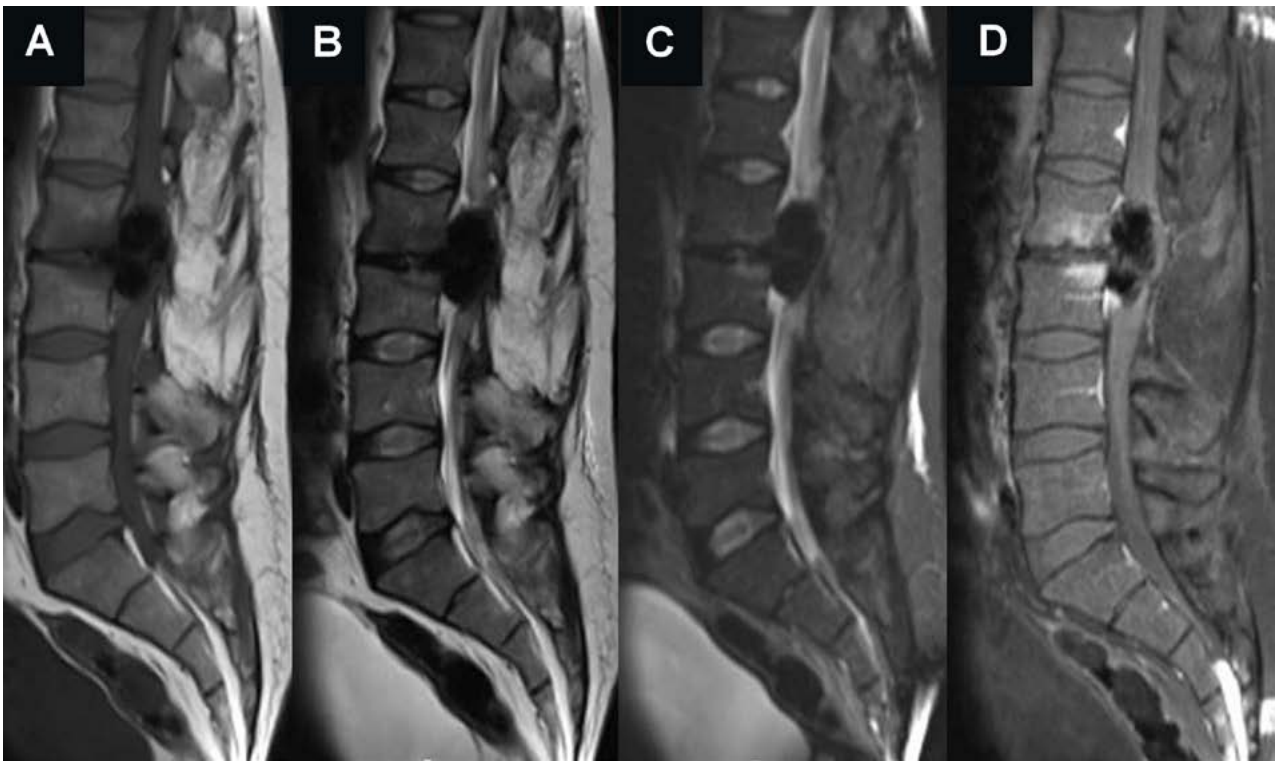
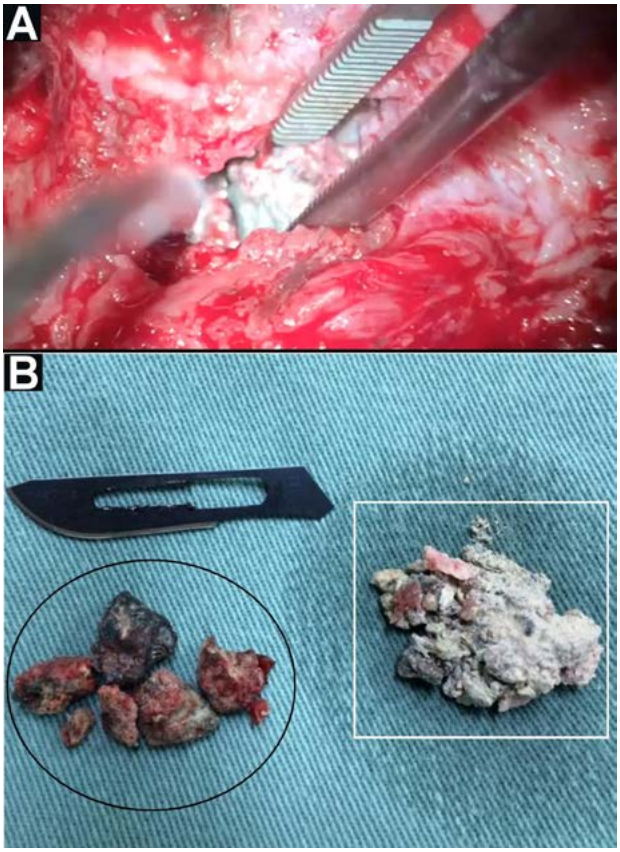


FIGURE 2. MRI of the lumbar spine showing a material characterized with a hypointense signal on all weighted sequences at T1 (A), T2 (B), and STIR (C), with a slight highlight of surrounding tissues in T1 after the administration of intravenous contrast medium, in addition to a strong compression effect on the conus medullaris.



an inflammatory reaction occurs, with the migration of macrophages. The phagocytosis accentuates the inflammatory process with bone resorption and granuloma formation. If that process is not interrupted, the granuloma results in a metalloma[5].

The imaging exam of choice is the CT myelogram. Artifacts may occur in CT scans and MRIs due to the presence of metallic material, which makes the assessment more difficult[5,6]. The CT highlights bone erosion, spinal instability, and spinal canal impairment. MRIs can be contraindicated depending on the composition and location of the bullet, and it is not recommended in acute cases or in cases of incomplete spinal cord injuries[5,7].

There is no consensus regarding the surgical approach, especially when there is no clear evidence of corrosion, and it is mostly used in critical situations[1-5,8]. According to data analyzed by Azevedo-Filho, in some patients that underwent decompressive laminectomy, a higher mortality rate was found, and some specific complications were more frequent, such as spinal cord injuries, fistulas, meningitis, and locoregional post-surgery infections.

FIGURE 3. Exeresis of the material described in the lumbar spine (A), evidencing, in a macroscopic visual analysis, (B) the fragmented projectile (black circle) and an accentuated amount of tissue impregnated with metal residues (white rectangle), which characterizes a metalloma.

PALAVRAS-CHAVE: *Ferimentos por arma de fogo. Coluna vertebral. Traumatismos da coluna vertebral. Aço inoxidável/efeitos adversos.*

REFERENCES

1. Pimentel MG, Gomes EGF, Gusmão MS, Amorim Junior DC, Simões MTV, Gomes JF, et al. Epidemiological study of trauma of spinal cord trauma by a projectile of firearm in the hospital geral do Estado da Bahia. Coluna/Columna. 2012;11(4):298-301.
2. Cristante AF, Souza FI, Barros Filho TE, Oliveira RP, Marcon RM. Lead poisoning by intradiscal firearm bullet: a case report. Spine (Phila Pa 1976). 2010;35(4):E140-3.
3. Bustamante ND, Macias-Konstantopoulos WL. Retained lumbar bullet: a case report of chronic lead toxicity and review of the literature. J Emerg Med. 2016;51(1):45-9.
4. Oliveira CA, Candelária IS, Oliveira PB, Figueiredo A, Caseiro-Alves F. Metallosis: a diagnosis not only in patients with metal-on-metal prostheses. Eur J Radiol Open. 2014;2:3-6.
5. Goldenberg Y, Tee JW, Salinas-La Rosa CM, Murphy M. Spinal metallosis: a systematic review. Eur Spine J. 2016;25(5):1467-73.
6. Marconato JA, Aesse FF, Ferreira JHP, Pinheiro CP, Mazzola AA. Lumbar spine computed tomography after arthrodesis with metal implant: a qualitative evaluation of images reconstructed with different mathematical algorithms. Radiol Bras. 2007;40(1):17-22.
7. Rentfrow B, Vaidya R, Elia C, Sethi A. Lead toxicity and management of gunshot wounds in the lumbar spine. Eur Spine J. 2013;22(11):2353-7.
8. Barros Filho TE, Cristante AF, Marcon RM, Ono A, Bilhar R. Gunshot injuries in the spine. Spinal Cord. 2014;52(7):504-10.
9. Azevedo-Filho HRC. Gunshot wounds to the spine: study of 246 patients. Arq Neuro-Psiquiatr. 2001;59(3A):645-6.

Rectal ulcer due to Kayexalate deposition – an unusual case

Ana Alves Oliveira[1]
Filipa Pedro[1]
Nuno Craveiro[1]
Ana Vera Cruz[1]
Raquel Sousa Almeida
Pedro Pereira Luís[2]
Cristina Santos[1]

1. Internal Medicine Department, Medicine Service III – Santarém Hospital – Santarém, Santarém, Portugal.
2. Pathological Anatomy Service – Santarém Hospital – Santarém, Santarém, Portugal.

http://dx.doi.org/10.1590/1806-9282.64.08.680

SUMMARY

Sodium polystyrene sulfonate (PSP) or Kayexalate is a cation-exchange resin, widely used in the management of hyperkalaemia due to renal disease. A rare, yet potentially dangerous, adverse event related to sodium polystyrene sulfonate use is intestinal mucosal injury, especially in the colon. The injury to the gastrointestinal mucosa can range from mild and superficial to wall necrosis and bowel perforation. The mechanism that leads to mucosal damage remains unclear. However, it is believed that sorbitol, commonly given to counteract PSP's tendency to cause constipation, may play an important role in the development of gastrointestinal injury. Other potential risk factors are uraemia or end-stage renal disease, hemodynamic instability, solid organ transplantation, postoperative status and concomitant opioid administration. The authors present a case of diarrhoea and haematochezia after the administration of PSP without sorbitol, in a patient with hyperkalaemia due to acute kidney injury, in the absence of other risk factors. A colonoscopy was performed and revealed a rectal ulcer which histological findings were suggestive of mucosal injury due to Kayexalate deposition. This case supports the concept that this widely used drug can itself, without sorbitol, cause injury to the gastrointestinal wall. Even though this is a rare adverse effect, the widespread use of this medication may put a large population at risk.

KEYWORDS: *Ion exchange resins. Intestinal mucosa/pathology. Cathartics/adverse effects. Colitis, ulcerative. Polystyrenes/adverse effects.*

INTRODUCTION

Sodium polystyrene sulfonate (PSP) or kayexalate is an ion exchange resin, composed of an insoluble structure that acts by binding to potassium ions along the digestive tract, by exchange with sodium ions, promoting its elimination. The first studies on the use of these drugs in the treatment of hyperkalaemia date back to the 1950s and are currently widely used in the treatment of hyperkalaemia secondary to renal failure[1-4]. The oral route is the preferred form of administration, and rectal administration is still possible when oral administration is not available. Although it is primarily used in the treatment of hyperkalaemia secondary to chronic renal disease, its relatively fast onset (2-12 hours) allows its use in acute situations, in association with other hypocalcaemia drugs[5]. Gastrointestinal side effects, such as nausea and constipation, are relatively frequent, and colic ulceration and/or colic necrosis is a rare but well documented complication of this therapy[5-7]. Concomitant administration of PSP and sor-

DATE OF SUBMISSION: 16-Dec-2017
DATE OF ACCEPTANCE: 24-Dec-2017
CORRESPONDING AUTHOR: Ana Alves Oliveira
Avenida Bernardo Santareno, 2005-177 – Santarém, Portugal
Tel.: +351917441847 +351917447847
E-mail: ana.sra.oliveira@gmail.com

filipa_sofia25@hotmail.com
nuno_craveiro@hotmail.com
anaveracruz.mail@gmail.com
almeida.raquelsousa@gmail.com
pedro.luis@hds.min-saude.pt
cristina.rodsantos@gmail.com

bitol to counterbalance the obstipation effect of PSP is a common practice, with the majority of reported cases of kayexalate crystal colitis occurring after the administration of this treatment combination. The mechanism by which PSP damages the intestinal mucosa is not fully understood and until recently it was thought that sorbitol was responsible for the lesion, possibly through hemodynamic phenomena of vasospasm and stimulation of prostaglandin production[9-11]. Lillemeo et al.[9] reported for the first time in 1987 five cases of colic necrosis following the administration of PSP and sorbitol, as an enema, in uremic patients. In the same work, the authors compared the effects of PSP alone, PSP and sorbitol, and sorbitol alone in rats, verifying that only rats exposed to sorbitol (with or without PSP) developed pathological gastrointestinal histological alterations with an impact on morbidity[9]. For this reason, the use of PSP with sorbitol has been discouraged[12].

However, a recent systematic review of a total of 58 published cases has identified 17 cases of PSP gastrointestinal injury without sorbitol, demonstrating that intestinal necrosis may also occur when the resin is not associated with sorbitol[6]. Previously, Haupt and Hutchins[13] had already demonstrated how inoculation of PSP into the airway of rats led to the development of inflammation after only 24 hours[12]. Thus, it is currently accepted that PSP itself causes tissue damage.

CLINICAL CASE

We present the case of an 83-year-old female patient with a personal history of major depressive disorder and hypertension. The patient went to the emergency department for a clinical diagnosis, with about two weeks of evolution, of asthenia, anorexia and weight loss. According to the patient's family, she also had bizarre behaviour, urging her children to feed her, refusing to eat alone, emotional lability and isolation. She also mentioned that the onset of this condition coincided with the diagnosis of neoplasia in her husband. The objective examination performed at the emergency department revealed only signs of dehydration, without hypotension or signs of peripheral hypoperfusion. From the analytical evaluation, a new alteration of renal function was observed, with creatinine of 2.2 mg/dL and urea of 177 mg/dL (Acute Kidney Injury Network stage 2 rating) and severe hyperkalaemia (9 mEq/dL). Renal ultrasound did not show any changes. In view of the two-week dietary refusal, acute renal injury was considered secondary to hypovolemia due to dehydration. Serum therapy and ion-exchange resin (PSP without sorbitol) were prescribed for the treatment of severe hyperkalaemia, and the patient was admitted to the medical ward. Observation was requested by psychiatry, who considered that the patient presented a probable Histrionic Personality Disorder, proceeding to the adjustment of the psychiatric therapy. On the second day of hospitalization, there was noticeable improvement in renal function and normalization of the calemia, and resin therapy was suspended. The next day, about 48 hours after the first PSP, the patient started complaints of colicky abdominal pain and liquid diarrhoea without blood, mucus, or pus. Simultaneously, an increase in inflammatory parameters was observed, and microbiological examinations were carried out, such as uroculture, coproculture, parasitological examination, and C. difficile toxin investigation in faeces. Once the diagnosis of infectious diarrhoea was excluded, the elevation of inflammatory parameters was attributed to a urinary tract infection after isolation of Proteus mirabilis in uroculture. It was prescribed targeted antibiotic therapy and optimization of therapy and diet was performed. Due to the maintenance of diarrhoea, abdominal pain and the appearance of haematocrits, colonoscopy and abdominal and pelvic tomography (CT) were proposed, which the patient refused. Only after three weeks of hospitalization, with maintenance of the symptoms, the patient agree to these tests. A colonoscopy was performed and, despite poor intestinal preparation, which allowed only the visualization of the rectum, a depressed area in the lower rectum, partially ulcerated, without apparent necrosis was found and biopsied (Figure 1). Abdominal and pelvic CT revealed a diffuse parietal thickening of the sigmoid loops and rectal ampulla, more evident in the right anterior slope of the rectosigmoid transition, which may correspond to the inflammatory process. Finally, rectal ulcer biopsy revealed the presence of basophilic structures with mosaic pattern, similar to fish scales, surrounded by an intense active chronic inflammatory infiltrate, aspects compatible with lesion caused by ion exchange resin deposition (kayexalate crystals) (Figure 2). There was a slow and gradual symptomatic improvement, and no endoscopic or CT reassessment was performed at the option of the patient.

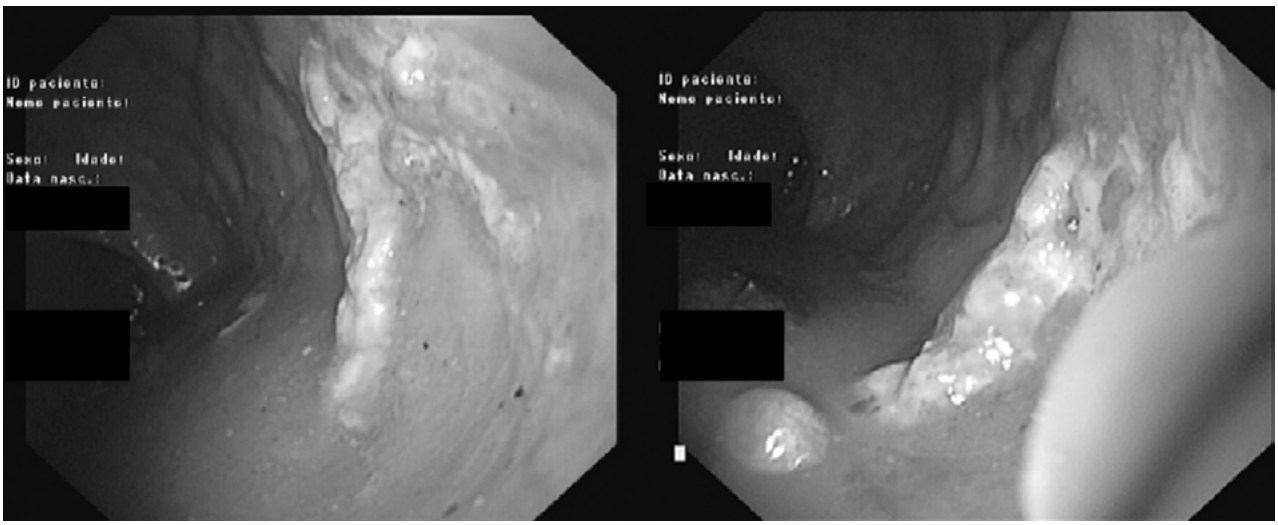


FIGURE 1

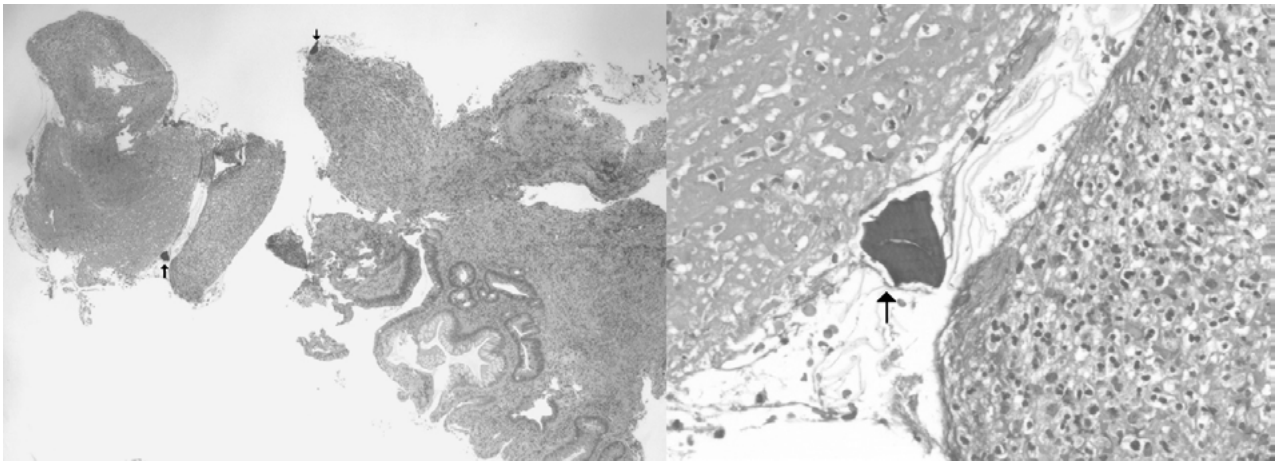


FIGURE 2

DISCUSSION

PSP crystals deposition colitis appears to occur in about 1% of patients receiving PSP and sorbitol treatment[14,15]. The lower number of reported cases suggests that the incidence in patients exposed to PSP alone is lower, which makes this case even more uncommon[6]. Several risk factors for colic injury by kayexalate crystals have been identified in the literature. In most reports, at least one of the following conditions would be present: uraemia or end-stage renal disease, hemodynamic instability, postoperative, post-renal transplantation, and concomitant administration of opioids[6,9,14,16-18]. Furthermore, as already mentioned, the administration of sorbitol seems to increase the risk of development of this entity. As in the case presented, a retrospective American study identified some cases of intestinal involvement in stable patients and without chronic kidney disease, however, all had been submitted to combined sorbitol and PSP therapy[8].

It can be argued that the presence of hypovolemia due to dehydration may have contributed to the development of colic injury, despite the absence of hemodynamic instability. Nonetheless, this case demonstrates that even in the absence of many known risk factors, short-term exposure (about 24 hours) to PSP without sorbitol may cause gastrointestinal damage.

Regarding the clinical presentation, the case is in agreement with the described one, since the most common symptoms are abdominal pain, low digestive haemorrhage and diarrhea[5,6,8]. As observed in this case, on average the symptoms appear two days after the beginning of exposure to the resin[6].

It was impossible to assess the extent of the disease since the patient refused to undergo a new colonoscopy. However, although only ulcerated rectal lesion without necrosis has been documented, the presence of more extensive and severe disease is suggested by

the results of the CT scan and the clinical presentation, which has not been proven by colonoscopy. PSP colitis presents a broad spectrum of severity ranging from superficial mucosal lesion to transmural necrosis with colic perforation[6,8,16]. Many less serious cases are likely to go undetected and underdiagnosed. The impossibility of performing further tests also limited the differential diagnosis to other causes of colitis. However, the temporal relationship between the onset of symptoms and exposure to PSP, clinical characteristics, biopsy result and resolution of symptoms without specific therapy allows us to affirm this diagnosis.

CONCLUSION

In this unusual case, it has been found that even a short exposure to PSP without sorbitol can cause lesion with ulceration of the intestinal mucosa. Although this type of report has proved that PSP is not an innocuous drug, presenting potentially serious adverse effects, its use is still frequent in current clinical practice. Although this is a rare adverse effect, the widespread use of PSP puts a large population at risk, so its prescription should always be weighed, especially in the presence of other therapeutic options.

RESUMO

O polistireno sulfonato de sódio (PSP) ou kayexalato é uma resina de troca iônica, amplamente usada no tratamento da hipercalemia associada à doença renal. Um efeito adverso raro, mas potencialmente grave, dessa terapêutica é a agressão à parede do trato gastrointestinal, principalmente ao nível do cólon, que pode ser ligeira e superficial ou culminar em necrose e perfuração intestinal. O mecanismo pelo qual o PSP lesa a mucosa intestinal não é totalmente conhecido. Contudo, pensa-se que o sorbitol, frequentemente administrado em simultâneo para contrabalançar o efeito obstipante do PSP, possa ter um papel preponderante no desenvolvimento de lesão gastrointestinal. Outros potenciais fatores de risco são a presença de uremia ou doença renal em estágio terminal, instabilidade hemodinâmica, pós-operatório, pós-transplante renal e a administração concomitante de opioides. Os autores descrevem um caso de diarreia e hematoquesias após a administração de PSP sem sorbitol, numa paciente com hipercalemia secundária a lesão renal aguda, sem outros fatores de risco para o desenvolvimento desse efeito adverso. A investigação etiológica com colonoscopia revelou a presença de uma úlcera retal, cujo estudo histológico foi compatível com lesão por deposição de cristais de kayexalato. Este relato incomum reforça o conceito de que este fármaco de uso frequente, mesmo na ausência de sorbitol, pode ser lesivo para a mucosa intestinal. Assim, e apesar de este ser um efeito adverso raro, a utilização difundida do PSP coloca uma vasta população em risco.

PALAVRAS-CHAVE: *Resinas de troca iônica. Mucosa intestinal/patologia. Catárticos/efeitos adversos. Colite ulcerativa. Poliestirenos/efeitos adversos.*

REFERENCES

1. Irwin L, Berger EY, Rosenberg B, Jackenthal R. The effect of a cation exchange resin on electrolyte balance and its use in edematous states. J Clin Invest. 1949;28(6 Pt 2):1403-11.
2. Elkinton JR, Clark JK, Squires RD, Bluemle LW Jr, Crosley AP Jr. Treatment of potassium retention in anuria with cation exchange resin; a preliminary report. Am J Med Sci. 1950;220(5):547-52.
3. Evans BM, Jones NC, Milne MD, Yellowlees H. Ion-exchange resins in the treatment of anuria. Lancet. 1953;265(6790):791-5.
4. Palmer RA, Price JD, Eden J. The treatment of hyperkalaemia by carboxylic acid resins in the upper and lower gastrointestinal tract. Can Med Assoc J. 1959;80(6):432-5.
5. Pachaly MA. Resinas trocadoras de cátions na hipercalemia aguda grave. Rev Med UFPR. 2014;1(3):103-8.
6. Harel Z, Harel S, Shah PS, Wald R, Perl J, Bell CM. Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review. Am J Med. 2013;126(3):264.e9-24.
7. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? J Am Soc Nephrol. 2010;21(5):733-5.
8. McGowan CE, Saha S, Chu G, Resnick MB, Moss SF. Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol. South Med J. 2009;102(5):493-7.
9. Lillemoe KD, Romolo JL, Hamilton SR, Pennington LR, Burdick JF, Williams GM. Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. Surgery. 1987;101(3):267-72.
10. Kelsey PB, Chen S, Lauwers GY. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 37-2003. A 79-year-old man with coronary artery disease, peripheral vascular disease, end-stage renal disease, and abdominal pain and distention. N Engl J Med. 2003;349(22):2147-55.
11. Zijlstra FJ. Sorbitol, prostaglandins, and ulcerative colitis enemas. Lancet. 1981;2(8250):815-6.
12. Abuelo JG. Moving away from Kayexalate, sodium polystyrene sulfate. Am J Emerg Med. 2016;34(8):1716.
13. Haupt HM, Hutchins GM. Sodium polystyrene sulfonate pneumonitis. Arch Intern Med. 1982;142(2):379-81.
14. Gerstman BB, Kirkman R, Platt R. Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. Am J Kidney Dis. 1992;20(2):159-61.
15. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (Kayexalate) in sorbitol: an underrecognized condition. Am J Surg Pathol. 1997;21(1):60-9.
16. Joo M, Bae WK, Kim NH, Han SR. Colonic mucosal necrosis following administration of calcium polystryrene sulfonate (Kalimate) in a uremic patient. J Korean Med Sci. 2009;24(6):1207-11.
17. Albeldawi M, Gaur V, Weber L. Kayexalate-induced colonic ulcer. Gastroenterol Rep (Oxf). 2014;2(3):235-6.
18. Scott TR, Graham SM, Schweitzer EJ, Bartlett ST. Colonic necrosis following sodium polystyrene sulfonate (Kayexalate)-sorbitol enema in a renal transplant patient. Report of a case and review of the literature. Dis Colon Rectum. 1993;36(6):607-9.

ORIGINAL ARTICLE

Width of sulcus and thickness of gyrus in patients with cerebral atherosclerosis: a new tool for the prevention of vascular cognitive impairment

Luciana Santos Ramalho[1]
Luciano Alves Matias da Silveira[2]
Bárbara Cecílio Fonseca[3]
José Eduardo Reis Félix[4]
Lourimar José Morais[5]
Maria Helena Soares[6]
Mara Lúcia Fonseca Ferraz[7]
Vicente de Paula Antunes Teixeira[8]
Sanívia Aparecida Lima Pereira[9]

1. PhD in Pathology, Student of Postgraduate Course Health Sciences, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brasil.
2. MS in Pathology, Anesthesiologist, Professor of Anesthesiology, Department of Surgery, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brasil.
3. Medical Student at UFTM, Scientific Initiation Grant from UFTM (BIC/Fapemig), Uberaba (MG), Brasil.
4. Department of Radiology, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brasil.
5. MS in Pathology, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brasil.
6. MS in Pathology, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brasil.
7. PhD in Pathology, Professor of Postgraduate Course Health Sciences, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brasil.
8. Pathologist, Professor of General Pathology, Institute of Biological and Natural Sciences, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brasil.
9. PhD in Pathology, Professor of Postgraduate Course Health Sciences, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba (MG), Brasil.

http://dx.doi.org/10.1590/1806-9282.64.08.684

SUMMARY

BACKGROUND AND PURPOSE: *Cerebral atherosclerosis is the main cause of lesions that contribute to vascular cognitive impairment and vascular dementia, followed by arteriosclerosis of small vessels and cerebral amyloid angiopathy. The purpose of this study was to compare the post-mortem radiological alterations of autopsied adults with the macroscopic alterations in the posterior region of these brains in order to establish a relationship between the two forms of analysis and to discuss the relevance of the prevention of vascular cognitive impairment in patients with encephalic atherosclerosis.*

MATERIALS AND METHODS: *Thirteen brains were analysed macroscopically to assess the degree of atherosclerosis of the basilar and the posterior cerebral arteries. The patients were autopsied in the Subject of General Pathology at General Hospital of Triângulo Mineiro Federal University in Uberaba, state of Minas Gerais, Brazil. The qualitative analysis of atherosclerosis was performed with classification into mild, moderate or severe. In the posterior region of the brains, width of sulcus and thickness of gyrus were measured by macroscopic analysis and by tomographic analysis.*

RESULTS AND CONCLUSIONS: *There was a decrease in calcarine sulcus width and an increase in medial temporal occipital gyrus thickness in patients with a higher degree of atherosclerosis, macroscopically and in tomography, respectively. Low oxygenation caused by atherosclerosis probably leads to an encephalic parenchyma inflammation that causes microglial cells hypertrophy provoking increase in the gyrus thickness and decrease in the sulcus width, as observed in the present study.*

KEYWORDS: *Intracranial arteriosclerosis. Cognitive dysfunction. Cerebrovascular disorders. Cognition disorders. Tomography, X-ray computed.*

DATE OF SUBMISSION: 31-Aug-2017
DATE OF ACCEPTANCE: 24-Dec-2017

CORRESPONDING AUTHOR: Luciano Alves Matias da Silveira
Discipline of General Pathology, Institute of Biological and Natural Sciences,
Universidade Federal do Triângulo Mineiro (UFTM) – Avenida Frei Paulino, nº 30
Uberaba (MG) — Brasil – CEP 38025-180 – Tel. (+55 34) 3700-6454
E-mail: drluciano@hotmail.com

lsantosramalho@yahoo.com.br
bacecilio@live.com; felix@anomati.net
lourimar_morais@yahoo.com.br
mhmais@hotmail.com
mara@patge.uftm.edu.br
vicente@patge.uftm.edu.br
sanivia.pereira@uniube.br

BACKGROUND

Cerebral atherosclerosis is the main cause of lesions that contribute to vascular cognitive impairment (VCI) and vascular dementia, followed by arteriosclerosis of small vessels and cerebral amyloid angiopathy[1]. Autopsy studies have already identified atherosclerotic plaques in the vertebrobasilar system in 50% of the cadavers examined, and most patients with atherosclerotic plaques in the basilar artery had severe plaques[2]. VCI encompasses discrete cognitive deficit, which does not necessarily lead to dementia[3]. There is suspicion of VCI when there is atherosclerosis, arteriolosclerosis, amyloid angiopathy, focal or diffuse ischemic changes, or haemorrhagic foci[4]. There are currently no tomographic diagnostic criteria for VCI and there is a need to establish evidence to base these criteria for assessing the contribution of cerebrovascular disease for VCI[5].

There are studies that emphasize the importance of in vivo imaging studies of ischemic brain lesions such as PET scan, magnetic resonance imaging (MRI), CT and computed angiotomography (CAT)[6,7] and post-mortem CT[8]. Post mortem CT was introduced about 14 years ago and several researchers have demonstrated its usefulness primarily in cases of post-traumatic bone injury[9,10], and also in cases of vascular injury with the aid of CAT[11,12].

To date, there are no studies to identify radiological changes in VCI of patients with cerebral atherosclerosis, so the present study emphasizes the importance of imaging in the identification of pathological processes, contributing to the prevention of diseases such as VCI. It is probable that patients with atherosclerosis in arteries that irrigate the posterior portion of the brain, such as the basilar and the posterior cerebral arteries, present changes

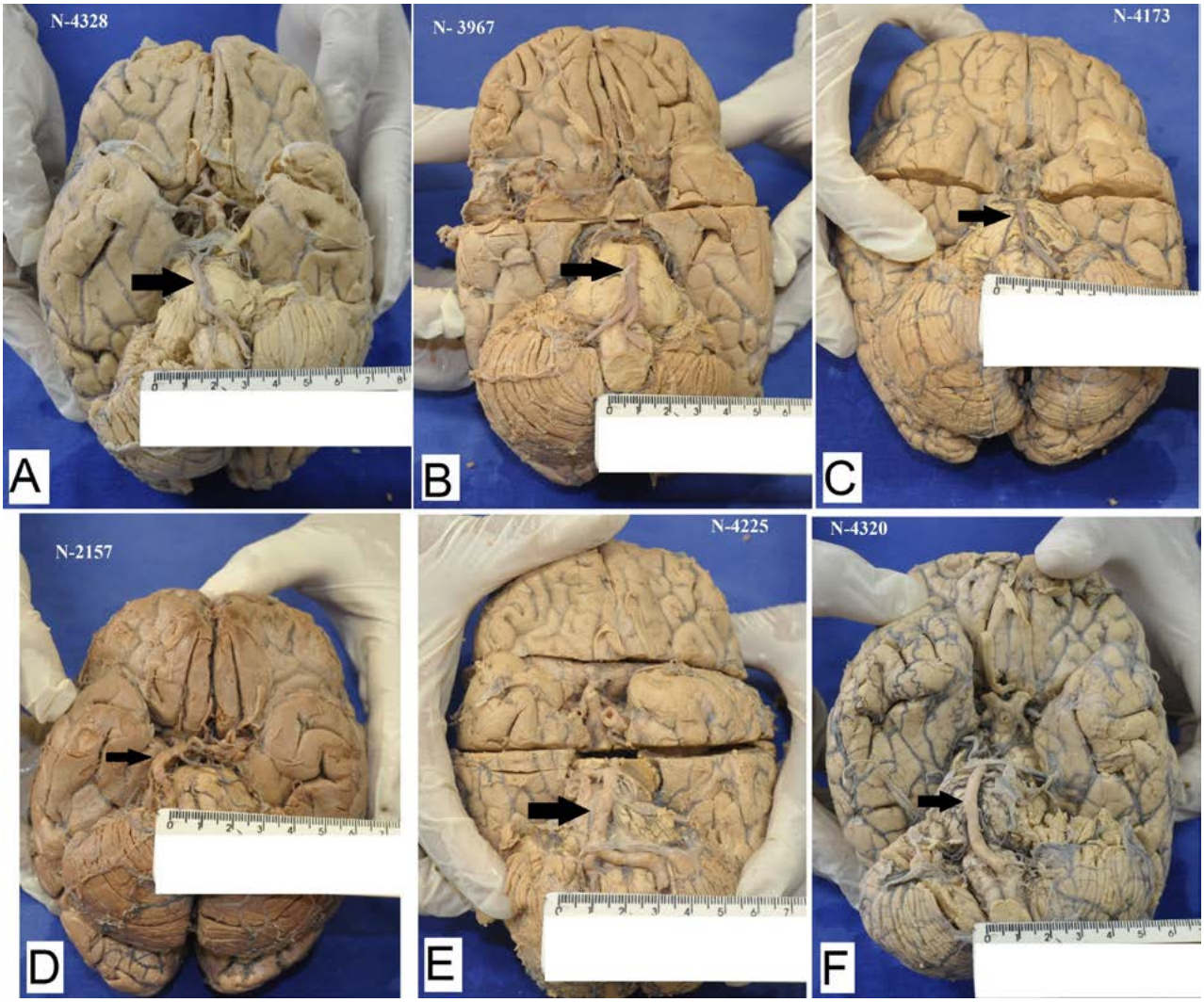


FIGURE 1. Microscopical analysis. The basilar arteries were evaluated according to the presence of atheromatous plaques and aneurysms. The black narrow point the basilar arteries. A and B: mild atherosclerosis, C: moderate atherosclerosis, D, E and F: severe atherosclerosis with a mild aneurysm.

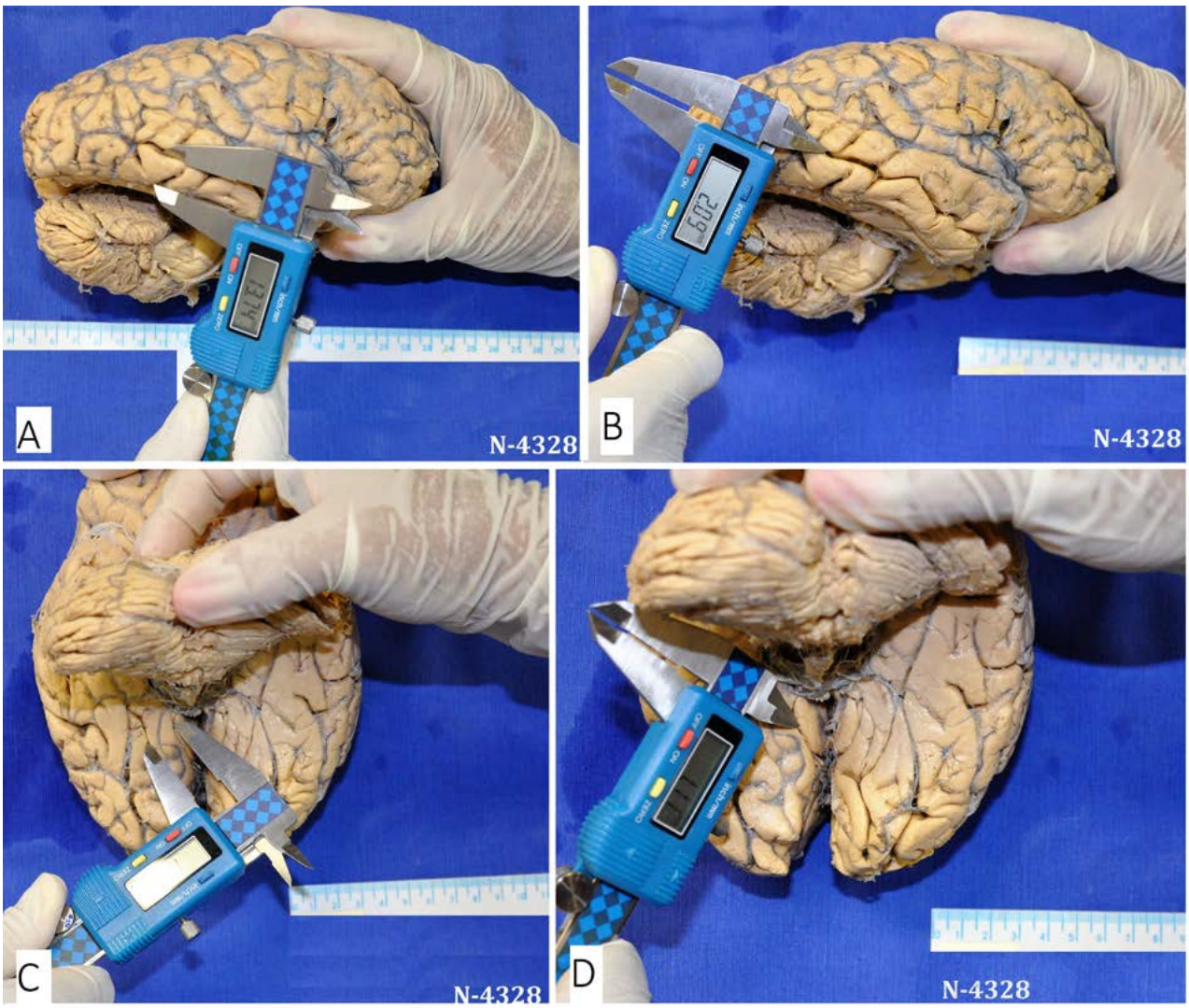


FIGURE 2. Macroscopic location of the sulcus and gyrus macroscopically measured with caliper. Measurement of the transverse thickness of the right inferior temporal gyrus in the posterior medial portion of the gyrus (A). Measurement of the width of the right inferior temporal sulcus just above the measurement site of the right inferior temporal gyrus (B). Measurement of the transverse thickness of the right medial temporal occipital gyrus in the central portion of the gyrus (C). Measurement of the width of the right calcarine sulcus laterally to the measurement site of the calcarine sulcus (D).

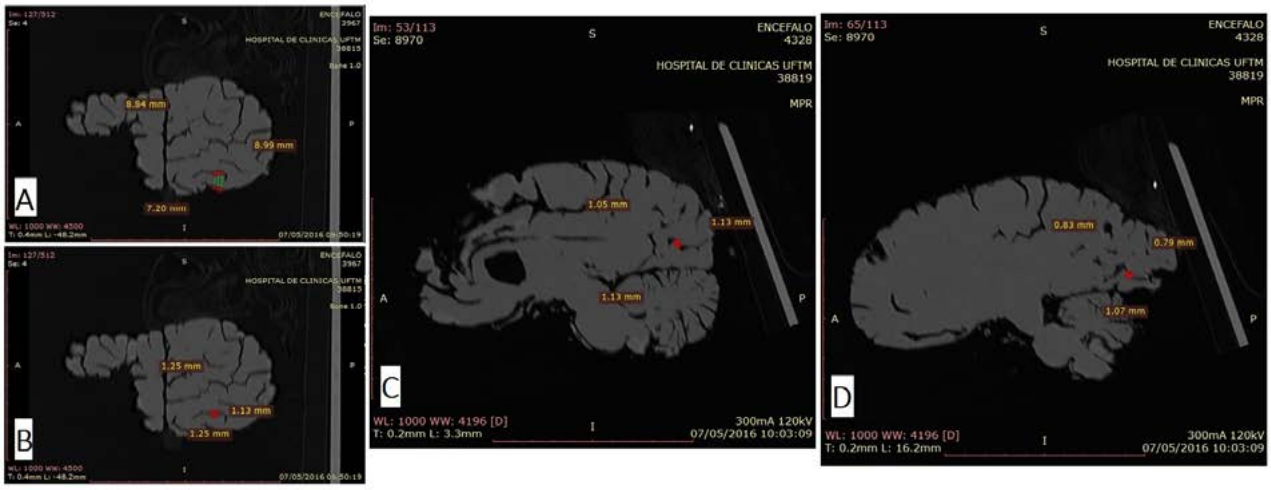


FIGURE 3. Sagittal sections of encephala. A: Right ITG measure. B: Left ITS measure. C: Right CS measure D: Left CS measure.

in the encephalic mass such as oedema or hypotrophy due to insufficient irrigation in this region.

AIMS

Thus, this study compared the post-mortem radiological alterations of autopsied adults with the macroscopic alterations in the posterior region of these brains in order to establish a relationship between the two forms of analysis and to discuss the relevance of the prevention of VCI in patients with encephalic atherosclerosis.

METHODS

Selection of patients

The study was performed with 13 patients autopsied in the Subject of General Pathology at General Hospital of Triângulo Mineiro Federal University (GH-UFTM) in Uberaba, state of Minas Gerais, Brazil. We evaluated 3000 autopsy protocols from 1963 to 2016. Patients were selected by means of autopsy reports regardless of cause of death or underlying disease. Inclusion criteria were: patients over 65 years of age. The exclusion criterion was: brains that were fragmented and therefore did not have good conditions to perform the macroscopic and imaging analysis.

Macroscopic analysis of atherosclerosis

The brains were analysed macroscopically to assess the degree of atherosclerosis of the basilar and the posterior cerebral arteries. The qualitative analysis of atherosclerosis was performed with classification into mild, moderate or severe. The arteries that presented lipid streaks or vessel wall stiffness but did not present lumen narrowing were considered mild atherosclerosis. Moderate atherosclerosis was classified as arteries that showed vessel lumen narrowing of less than 50% and visible atheroma plaques. The arteries that presented aneurysms, calcifications, or narrowing of more than 50% and visible atheroma plaques (Figure 1) were classified as severe atherosclerosis.

In the posterior region of the brains, measurements were taken for the inferior temporal gyrus (ITG), the medial temporal occipital gyrus (MTOG), the inferior temporal sulcus (ITS), and the calcarine sulcus (CS) on the left and right sides, using a digital caliper Digital 100.174B (Digimess, São Paulo, SP-Brazil). The location of the measured regions was standardized in all brains. The thickness of the right and left ITG was measured transversely, in the posterior region of the gyrus, near the occipital lobe. (Figure 2A). The width of the right and left ITS was measured transversely at a location just above the ITS measurement (Figure 2B). The left and right MTOG thickness was measured transversely in the medial portion of the gyrus (Figure 2C). The width of CS on the left and right sides was measured transversely and laterally to the MTOG measurement (Figure 2D). Three measurements of the gyrus and sulcus were made and the average of the three calculated. Measurements were recorded in millimetres.

During the macroscopic evaluation, the presence of haemorrhagic foci, infarctions, calcifications and hypotrophy or oedema were also evaluated in all brains.

Acquisition of images

Through a partnership with the GH-UFTM imaging service, the selected brains were taken for tomographic analysis in the equipment Aqulion 64 (TSX-101 A / H) (Toshiba Medical System Corporation, Otawara-Japan), which uses 1 mm thick slices, with interpolation of 0.5 mm reconstruction of the images, which increases the quality of reconstruction of the images processed in other planes and even in third dimension.

Processing and interpretation of images

With the aid of the software RadiAnt DICOM Viewer 3.4.2 (Medixant, Poznan-Poland), the images obtained were analysed and the measurements of the ITG and MTOG and the right and left ITS and CS of each patient were analysed. The ITG was measured in sagittal sections close to the macroscopic measurement (Figure 3A). The ITS was measured in a sagittal section just above the macroscopic measurement of the ITG (Figure 3B). Calcarine sulcus were measured using sagittal sections, at the mid-posterior location just above MTOG (Figure 3C and D). Medial temporal occipital gyrus was measured using axial slices close to the macroscopic measurement (Figure 4 A and B). Three measurements of the gyrus and sulcus were taken and the average of the three calculated. Measurements were recorded in millimetres.

Ethical aspects

The Human Research Ethics Committee of UFTM approved this research with the CAAE nº 59931316600005154.

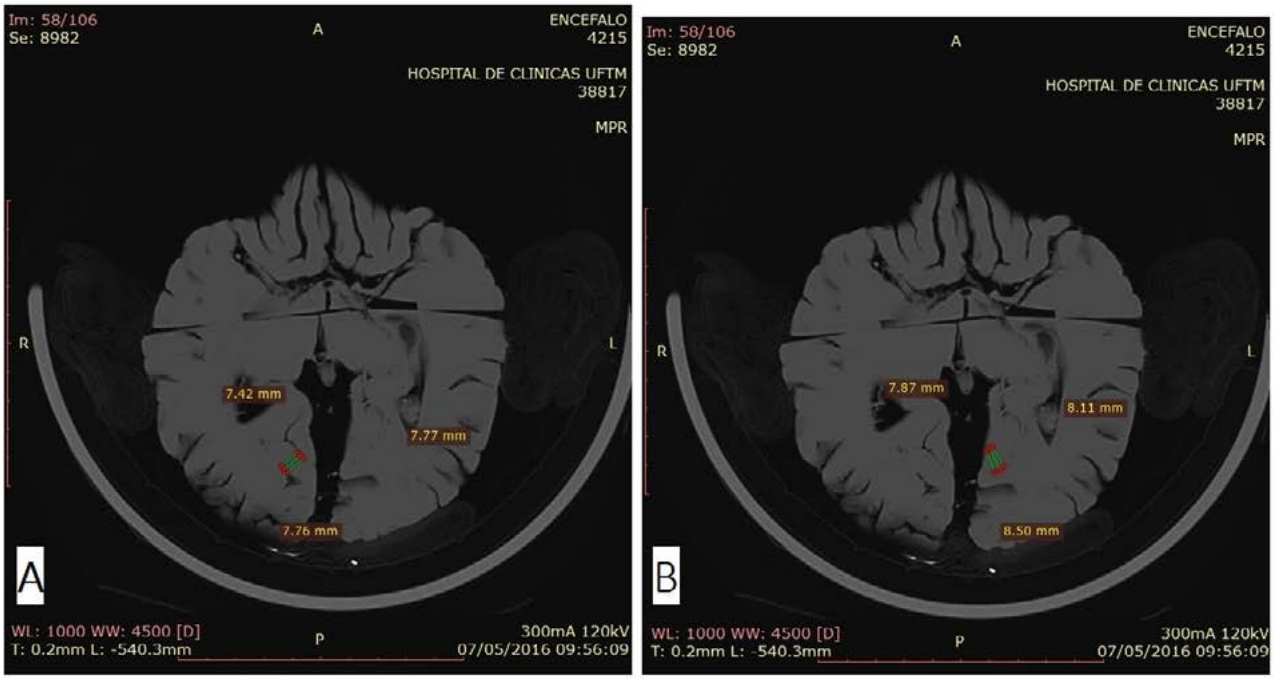


FIGURE 4. Axial sections of encephala. A: Right MTOG measure. B: Left MTOG measure

Statistical analysis

Prism® (GraphPad Software, San Diego, California-USA) software was used for data analysis. Variable distribution type was verified using the Kolmogorov-Smirnov statistical test. As the result of the distribution of the variables was non-normal, Mann-Whitney U test was used to compare 2 groups, and Kruskal-Wallis test was used to compare 3 or more groups, followed by One way ANOVA (Dunn's test) and by Tukey's test that were used to compare three or more groups. Then, a Spearman correlation coefficient was used. Differences in which the probability (p) was less than 5% ($p<0.05$) were considered statistically significant.

RESULTS

Among the 13 patients evaluated, 6 were men (46.15%). The ages ranged from 67 to 88 years old, with an average of 73 years old. The body mass index (BMI) of the patients ranged from 18.3 to 43 kg/m² with an average of 22.87 kg/m². Regarding the basilar artery, 4 patients had mild atherosclerosis (30.8%), 3 patients had moderate atherosclerosis (23.1%) and 6 patients had severe atherosclerosis (46.1%). With respect to the right posterior cerebral artery, 3 patients had mild atherosclerosis (23.1%), 7 patients had moderate atherosclerosis (53.8%) and 3 patients had severe atherosclerosis (23.1%). With respect to the left posterior cerebral artery, 5 patients had mild atherosclerosis (38.5%), 2 patients had moderate atherosclerosis (15.4%) and 6 patients had severe atherosclerosis (46.1%). Cerebral oedema was found in 2 patients and all had cerebral hypotrophy. No areas of haemorrhage or cerebral infarct were observed in the patients. Three patients had aneurysm in the basilar artery, one patient had a cysticercus, and two patients presented encephalic congestion. Thrombi were evidenced in the basilar artery of 1 patient.

There was no statistical difference between the patients with regard to gender and degree of atherosclerosis, or the colour and degree of atherosclerosis in any of the analysed arteries.

Gyrus and sulcus of the posterior brain region presented variation according to the degree of atherosclerosis of the patients. Macroscopically, only CS had a statistically significant difference between the degrees of atherosclerosis in the basilar artery ($p = 0.021$), so that patients with mild atherosclerosis (median = 1.827 mm) had sulcus wider than patients with moderate atherosclerosis did (median = 1.203 mm), $H = 7.726$ (Figure 4).

When evaluating CT images, only MTOG exhibited a significant difference between the degrees of atherosclerosis in the basilar artery ($p = 0.0156$), in which patients with mild atherosclerosis (median = 6.838 mm) had sulcus wider than patients with severe atherosclerosis did (median = 9.259 mm) (H=

5.832). Regarding the right and left posterior cerebral arteries alone, there was no significant difference between the degree of atherosclerosis and the measurements of gyrus or sulcus both macroscopically and in the CT images.

DISCUSSION

Both methods of analysis presented significant results. Nevertheless, although macroscopically all patients presented clear signs of cerebral hypotrophy, there was a decrease in CS width and an increase in MTOG thickness in patients with a higher degree of atherosclerosis, macroscopically and in tomography, respectively. Macroscopically, there were no signs of brain oedema in most cases. The narrowing of the basilar artery lumen of atherosclerotic cause, in the posterior cerebral arteries and their branches, is the main cause of posterior cerebral hypoperfusion[13]. Patients were expected to present hypotrophy in this region because of hypoxia caused by atherosclerosis. Vascular risk factors such as hypertension and hypercholesterolemia cause damage to the neurovascular unit (NVU) composed of endothelial cells, astrocytes, pericytes, microglia, neurons and circulatory inflammatory cells. The damage in the NVU leads to chronic hypoperfusion, hypoxia, inflammatory activation and oxidative stress[14].

Although there is a compensatory rearrangement of vessels in an attempt to reduce hypoxia, the blood flow of individuals with hypoperfusion is still lower when compared to individuals with normal perfusion[15]. The formation of a hypoxia environment in the NVU contributes to an inflammatory activation that induces the NVU to various adaptations and interactions presenting flow disturbances, angiogenesis, vascular remodelling, loss of junction and adhesion proteins, pericyte retraction, basal membrane disruption, neurovascular decoupling and neuronal impairment. This cascade of events associates injury in the NVU and in the cerebral microcirculation to the tissue damage, which causes neuronal degeneration and cognitive impairment[16]. There is also evidence of foci of gliosis and scars in these individuals[15].

Gliosis, also called gemioscytic gliosis, is characterized by the hypertrophy and hyperplasia of astrocytes activated by inflammatory signs following a tissue injury of any type, such as hypoxia, the presence of tumours and traumas[17]. It can be identified microscopically, but macroscopically there is no obvious sign. However, in the present study, the increase in the thickness of the gyrus, which could only be detected with the digital caliper and with the tomographic image analysis software, may be a sign of the occurrence of gliosis in these cases of more severe atherosclerosis. Changes in white brain matter are also factors that indicate risk of cerebrovascular events, stroke, cognitive impairment, or dementia, and death[18]. Meanwhile, in the present study, this factor was not evaluated because brains formalin-fixed for a long time lose the ability to demonstrate areas of hyperdensity, calcifications or haemorrhages at the CT examination (personal communication).

There is evidence in experimental models that in mice with astrocyte reduction in white brain matter and in the presence of inflammation, there is axonal degeneration, demyelination and gliosis, as well as cognitive deficit. This suggests that astrocytes are involved in the pathophysiology of VCI and that anti-inflammatory interventions can bring beneficial effect[19]. Karen Horsburgh discussed the contribution of microglial proliferation to axon-glial disruption and impairment of white matter function in an experimental model of VCI. Studies like these support that, in situations of inflammation, the NVU reacts with diverse pathological responses, including gliosis, which may temporarily increase the size of the affected tissue[20].

Our patients were expected to have a high degree of atherosclerosis because of the average age of the group, 67 years old. Thus, it is probable that most of them presented a condition of brain hypoperfusion in the posterior region of the encephalon due to the narrowing of the lumen of the posterior and the basilar cerebral arteries. VCI is not synonymous with dementia but it is used to describe an intermediate stage between normal cognition and vascular-caused dementia with the presence of mild cognitive impairment[21]. Dementia affects 7% of the population over 65 years old, and 30% of people over 80 years old[22]. In addition, it is now recognized that vascular diseases lead to dementia[23]. There is also close relationship between vascular dementia and Alzheimer's disease as common risk factors: systemic hypertension[24], diabetes, smoking[25] and hypercholesterolemia[26].

Vascular cognitive impairment encompasses individuals who have stroke-related cognitive impairment, multiple cortical or subcortical infarcts, silent infarcts, small vessel disease with white matter lesion and lacunae[3]. Criteria for identifying VCI should still be better established. Symptoms may vary depending on the

location of the infarcts, for example. Nonetheless, subcortical ischemia often leads to attention deficit and executive dysfunction, with slow motor development and slowness in processing information. Episodic memory is not as apparent as in Alzheimer's disease. Psychiatric symptoms are as common and important as in Alzheimer's disease, and mood swings such as depression, emotional instability and apathy are frequent and persistent[27]. Until this moment, this group of researchers did not conduct a survey of the diagnosis or symptom of some type of cognitive impairment in our patients, which does not allow us to establish a direct relationship between symptoms and macroscopic or imaging findings.

CONCLUSIONS

This study demonstrated that it is possible to establish a post-mortem parameter of thickness measurements of gyrus and sulcus according to the degree of atherosclerosis of patients. Thus, in vivo, monitoring the thickness of the patient's gyrus and sulcus may provide information on the increase or decrease of gyrus and sulcus, and thus prevent future complications, such as VCI.

ACKNOWLEDGMENTS

The authors are grateful to the professionals of the Laboratory of Histopathology, and Professor Silvia Azevedo Terra of the Discipline of General Pathology of the Federal University of Triângulo Mineiro, Uberaba, Minas Gerais, Brasil.

CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

RESUMO

INTRODUÇÃO E OBJETIVO: *A aterosclerose cerebral é a principal causa de lesões que contribuem para o comprometimento cognitivo vascular (CCV) e demência vascular, seguida da arteriosclerose de pequenos vasos e da angiopatia amiloide cerebral. Sendo assim, este estudo comparou as alterações radiológicas* ***post mortem*** *de adultos autopsiados com as alterações macroscópicas na região posterior desses encéfalos a fim de estabelecer uma relação entre as duas formas de análise e discutir sobre a relevância da prevenção do CCV em pacientes com aterosclerose encefálica.*

MATERIAL E MÉTODOS: *Treze encéfalos foram analisados macroscopicamente para avaliar o grau de aterosclerose das artérias basilar e cerebral posterior. Os pacientes foram autopsiados na disciplina de Patologia Geral no HC-UFTM em Uberaba, Minas Gerais, Brasil. A análise qualitativa da aterosclerose foi realizada com as classificações discreta, moderada ou acentuada. A espessura dos giros e a largura dos sulcos na região posterior dos encéfalos foram analisadas macroscopicamente e por tomografia computadorizada.*

RESULTADOS E CONCLUSÃO: *Houve diminuição na largura do sulco calcarino e aumento na espessura do giro occipital temporal medial de acordo com o aumento do grau de aterosclerose macroscopicamente e por tomografia, respectivamente. A baixa oxigenação causada pela aterosclerose provoca a inflamação do parênquima encefálico, provavelmente levando à hipertrofia das células da micróglia e ao consequente aumento dos giros e estreitamento dos sulcos, como observado no presente estudo.*

PALAVRAS-CHAVE: *Arteriosclerose intracraniana. Disfunção cognitiva. Transtornos cerebrovasculares. Transtornos cognitivos. Tomografia computadorizada por raios X.*

REFERENCES

1. Thal DR, Grinberg LT, Attems J. Vascular dementia: different forms of vessel disorders contribute to the development of dementia in the elderly brain. Exp Gerontol. 2012;47(11):816-24.
2. Ravensbergen J, Ravensbergen JW, Krijger JK, Hillen B, Hoogstraten HW. Localizing role of hemodynamics in atherosclerosis in several human vertebrobasilar junction geometries. Arterioscler Thromb Vasc Biol. 1998;18(5):708-16.
3. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, et al. Vascular cognitive impairment. Lancet Neurol. 2003;2(2):89-98.
4. Ferrer I. Cognitive impairment of vascular origin: neuropathology of cognitive impairment of vascular origin. J Neurol Sci. 2010;299(1-2):139-49.
5. Grinberg LT, Thal DR. Vascular pathology in the aged human brain. Acta Neuropathol. 2010;119(3):277-90.
6. Koc ZP, Balci TA, Akarsu S, Unal K. The role of positron emission tomography/CT in hypoxic ischaemic encephalopathy in children. BMJ Case Rep. 2013;2013. pii: bcr0320126001.
7. Wake-Buck AK, Gatenby JC, Gore JC. Hemodynamic characteristics of the vertebrobasilar system analysed using MRI-based models. PLoS One. 2012;7(12):e51346.
8. Mokrane FZ, Savall F, Rérolle C, Blanc A, Saint Martin P, Rousseau H, et al. The usefulness of post-mortem CT angiography in injuries caused by falling from considerable heights: three fatal cases. Diagn Interv Imaging. 2014;95(11):1085-90.
9. Robert IS, Benamore RE, Benbow EW, Lee SH, Harris JN, Jackson A, et al. Post-mortem imaging as an alternative to autopsy in the diagnosis of adult deaths: a validation study. Lancet. 2012;379(9811):136-42.
10. Dedouit F, Otal P, Costagliola R, Loubes Lacroix F, Telmon N, Rouge D, et al. Role of modern cross-sectional imaging thanatology: a pictorial essay. J Radiol. 2006;87(6 Pt 1):619-38.
11. Grabherr S, Doenz F, Steger B, Dirnhofer R, Dominguez A, Sollberger B, et al. Multi-phase post-mortem CT angiography: development of a standardized protocol. Int J Legal Med. 2011;125(6):791-802.

12. Palmiere C, Binaghi S, Doenz F, Bize P, Chevallier C, Mangin P, et al. Detection of haemorrhage source: the diagnostic value of post-mortem CT-angiography. Forensic Sci Int. 2012;222(1-3):33-9.

13. Voetsch B, DeWitt LD, Pessin MS, Caplan LR. Basilar artery occlusive disease in the New England Medical Center Posterior Circulation Registry. Arch Neurol. 2004;61(4):496-504.

14. Stanimirovic DB, Friedman A. Pathophysiology of the neurovascular unit: disease cause or consequence? J Cereb Blood Flow Metab. 2012;32(7):1207-21.

15. Boehm-Sturm P, Füchtemeier M, Foddis M, Mueller S, Trueman RC, Zille M, et al. Neuroimaging biomarkers predict brain structural connectivity change in a mouse model of vascular cognitive impairment. Stroke. 2017;48(2):468-75.

16. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci. 2011;12(12):723-38.

17. Latov N, Nilaver G, Zimmerman EA, Johnson WG, Silverman AJ, Defendini R, et al. Fibrillary astrocytes proliferate in response to brain injury: a study combining immunoperoxidase technique for glial fibrillary acidic protein and radioautography of tritiated thymidine. Dev Biol. 1979;72(2):381-4.

18. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2010;341:c3666.

19. Delekate A, Füchtemeier M, Schumacher T, Ulbrich C, Foddis M, Petzold GC. Metabotropic P2Y1 receptor signaling mediates astrocytic hyperactivity in vivo in an Alzheimer's disease mouse model. Nat Commun. 2014;5:5422.

20. Demuth HU, Dijkhuizen RM, Farr TD, Gelderblom M, Horsburgh K, Iadecola C, et al. Recent progress in translational research on neurovascular and neurodegenerative disorders. Restor Neurol Neurosci. 2017;35(1):87-103.

21. Consoli A, Pasi M, Pantoni L. Vascular mild cognitive impairment: concept, definition, and directions for future studies. Aging Clin Exp Res. 2012;24(2):113-6.

22. Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, et al. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54(1 Suppl 5):S4-9.

23. Ballard C, McKeith I, O'Brien J, Kalaria R, Jaros E, Ince P, et al. Neuropathological substrates of dementia and depression in vascular dementia, with a particular focus on cases with small infarct volumes. Dement Geriatr Cogn Disord. 2000;11(2):59-65.

24. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43(2):250-60.

25. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology. 1999;53(9):1937-42.

26. Rockwood K, Kirkland S, Hogan DB, MacKnight C, Merry H, Verreault R, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch Neurol. 2002;59(2):223-7.

27. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfield S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet. 2002;359(9314):1283-90.

ORIGINAL ARTICLE

Is doctor-patient relationship influenced by health online information?

Luciana Rodrigues Alves da Mota[1]
Carolina Cavalcanti Gonçalves Ferreira[1]
Henrique Augusto Alves da Costa Neto[1]
Ana Rodrigues Falbo[1]
Suélem de Barros Lorena[1]

1. Health College of Pernambuco

http://dx.doi.org/10.1590/1806-9282.64.08.692

SUMMARY

OBJECTIVES: *To analyse the opinions and attitudes reported by medical specialists regarding online health information and their interference in the doctor-patient relationship. Methods: A cross-sectional study developed between 2016 and 2017 in Recife-Pernambuco-Brazil, which used a questionnaire in person in a population of 183 specialists from the Instituto de Medicina Integral Prof. Fernando Figueira. The results were analysed through the Statistical Package for the Social Sciences. Obtained approval of the Ethics Committee under the voucher number 121004/2016. Results: In the opinion of 85.2% of physicians, online health information has both positive and negative impacts on the physician-patient relationship. Faced with a questioning patient who claims to have researched information on the internet, 98.9% of the physicians said they would try to explain the reasons for their diagnosis and treatment. 59% already had a patient who modified the treatment recommended after seeing health information on the Internet. 73.8% agreed that online health information has positive effects for the general public, but 89.1% feel that most patients do not know which online health information is reliable.*

CONCLUSION: *The physicians surveyed view online health information in a positive way, but realize that it is necessary to be cautious as to their repercussions on the treatment of patients. There is concern about the accuracy of online health information, and it is incumbent upon the physician and health institutions to instruct patients about the sources of quality and that they are able to understand, as its known the patients have an active voice through the guarantee of the ethical principle of autonomy.*

KEYWORDS: *Internet. Physician-patient relations. Physician's role. Patient participation.*

INTRODUCTION

The massive use of the internet and other media as sources of research to obtain information about health-disease processes has been causing impacts on the doctor-patient relationship. The Priestly Model of the doctor-patient relationship, as defined by Robert Veatch in 1972, which proposes complete submission of the patient to the physician, has been replaced by the Collegial Model, in which decision-making power is shared equally and there is no relation of superiority or inferiority.[1]

Some foreign studies have shown that over 40% of patients seek information online before undergoing a procedure or before consulting a physician.[2,3] After consultation, many base their health decisions

DATE OF SUBMISSION: 11-Jan-2018
DATE OF ACCEPTANCE: 13-Jan-2018
CORRESPONDING AUTHOR: Luciana Mota
Avenida Mal. Mascarenhas de Morais, 4861, Imbiribeira, Recife/PE, Brasil – 51150-004
E-mail: luucianarodrigues@hotmail.com

carolina.cavalcantigf@gmail.com
costa_henrique94@hotmail.com
anarfalbo@gmail.com
suelem.barros@fps.edu.br

on information found online without discussing about this information with the healthcare professional.[4,5] In this sense, the doctor is often not aware of the whirlwind of doubts and expectations that the patient presents. This mismatch of information may omit important details in the anamnesis, which has repercussions on the treatment and prognosis of the patient, generating mistrust between the two subjects in communication.

Often online health research among patients reflects the dissatisfaction and discontent that some patients have when they formally consult a medical professional.[2] It is possible that this dislike expressed by many patients stems from the current fragmentation of medicine in specialized areas, so that today the doctor tends not to look at the patient as a subject that expresses desires, wants and expectations, but as a part of the whole. In this way, the biopsychosocial aspect of the disease is forgotten.[6]

Although online health and disease information is often enlightening, the patient may have multiple and different answers to his/her questions, since many of the sources present wrong information. In addition, the intellectual level of the patient is a factor that has an impact on the interpretation of the information collected, which makes the patient vulnerable to emotional expressions of anxiety about this information.[2]

Given the broad access to health information, what should be the physician's attitude in face of this new reality of numerable technological subsidies? The Code of Medical Ethics of the Brazilian Federal Council of Medicine, in its Chapter XIII, "Medical Advertising", in Article 144, says that the physician should not prescribe, consult or diagnose through mass communication.[7] Thus, the doctor-patient relationship in the online scope imposes responsibilities and new challenges to these professionals.

Physicians' opinions about the impact of health information that is available online and in the mass media need to be better known in Brazil. In addition, it is recognized the real need to discuss the topic of the doctor-patient relationship in the information age, in order to improve communication between the medical professional and their client. In this perspective, the present study aims to analyse opinions and attitudes reported by medical specialists regarding online health information and their interference in the doctor-patient relationship.

METHODS

It refers to a cross-sectional analytical study developed between April 2016 and July 2017 in Recife, Pernambuco, Brazil. In this study, 183 specialist physicians who provide care at the outpatient clinics of Gynaecology and Obstetrics, Medical Clinic and subspecialties, Dermatology, General Surgery, Clinical Oncology, Oncology Surgery and Plastic Surgery at the Instituto de Medicina Integral Professor Fernando Figueira (IMIP) have received, personally, during intervals of their professional activities, a questionnaire prepared by the researchers based on the literature.

The sample of participating professionals was obtained from the consultation in the National Registry of Health Institutions (CNES). The respondents were selected at the time of collection, upon their availability, to respond to the questionnaire, since they were approached by the researchers at their workplace. Physicians who did not make themselves available to answer the questionnaire and to participate in the survey and those who were dismissed from their professional activities during the period of data collection were excluded.

Data collection was performed in two phases: the first corresponded to the semantic validation of the structured questionnaire with ten professionals who did not participate in the study, in order to assess the clarity and relevance of the questions and the adequacy of the response scale for possible corrections, prior to its application in the study. After semantic validation of the questionnaire, the second phase of the collection was performed, in which the volunteers answered the final questionnaire.

The questionnaire contained, in addition to information on the sociodemographic profile of the respondents, questions about the attitudes and opinions of physicians regarding health information on the Internet and other media. The last part of the questionnaire was a Likert-type scale with five options for answering the sentences (totally disagree, disagree, no opinion, agree and totally agree), on the same theme: the impact of online information on the doctor- patient relationship.

The questionnaire data were analysed descriptively by obtaining absolute and percentage frequencies for the categorical variables. For the age variables and variables of the part of the questionnaire with the Likert-type scale, there was the inferential analysis through the average Ranking statistics and

standard deviation. In the calculation of the average Ranking, points 1 to 5 were considered for the answer options, with the number 1 corresponding to the "totally disagree" answer and number 5 corresponding to "totally agree". Also referring to the part of the questionnaire with the Likert scale, to compare the answers according to the medical specialties, the Kruskal-Wallis test was used. In the case of a significant difference with the Kruskal-Wallis test, the multiple comparisons tests (among specialty peers) of the test were used. For the calculation of statistically significant relationships in relation to the categorical variables, Pearson's Chi-square test or Fisher's Exact test was used when the condition for using the Chi-square test was not verified. The margin of error used in the statistical test decision was 5%.

The data was entered in the Microsoft Office Excel spreadsheet and the program used to make the statistical calculations was the Statistical Package for the Social Sciences (SPSS) version 23.

The research project was analysed and approved by the Ethics Committee for Research with Human Beings of the *Faculdade Pernambucana de Saúde*, under number CAAE 56167516.6.0000.5569 and voucher number 044236/2016. All participants were informed about the research objectives and guided towards the confidentiality of the questionnaire responses. Participants were also informed that they could withdraw their participation in the survey at any time. After agreement with the Informed Consent Form (TCLE), the participants who declared that they were willing to answer the self-administered questionnaire did so. There are no conflicts of interest.

RESULTS

The total number of physicians participating in the survey was 183 and the socio-demographic profile of the respondents is detailed in Table 1. The age of the professionals surveyed ranged from 24 to 73 years, with an average of 38.29 and a standard deviation of 9.88 years old.

Regarding the opinions and attitudes reported by the respondents about the interference of online health information in the doctor-patient relationship, the data obtained are shown in Table 2. It was verified that, for the fixed margin of error (5%), no significant associations between the specialties were registered, with none of the variables described in Table 2 ($p > 0.05$).

Figure 1 shows the average Ranking and standard deviation of the answers of the sentences of the portion of the questionnaire with the Likert-type scale. When analysing physicians' responses to this part of the questionnaire by percentage calculations, it was found that 73.8% of respondents agree that online health information has positive effects for the general public. Among them, 91.2% agreed that participation of patients in online forums made up of people with the same condition/disease can improve the patient's self-esteem and improve the doctor-patient relationship. For the sentence "Online health information can encourage patients to follow recommended treatments and seek medical professionals' instructions", a very significant percentage (91.2%) agreed. About whether online information encourages patients who neglect their disease to take better care of themselves,

FIGURE 1 – Mean ranking of Likert scale sentences, presented in ascending order, of the physicians' answers in outpatient clinics of Gynaecology and Obstetrics, Medical Clinic and subspecialties, Dermatology, General Surgery, Clinical Oncology, Oncology Surgery and Plastic Surgery. Data collected at the Instituto de Medicina Integral Professor Fernando Figueira (IMIP) in Recife, Pernambuco, Brazil, between December 2016 and April 2017.

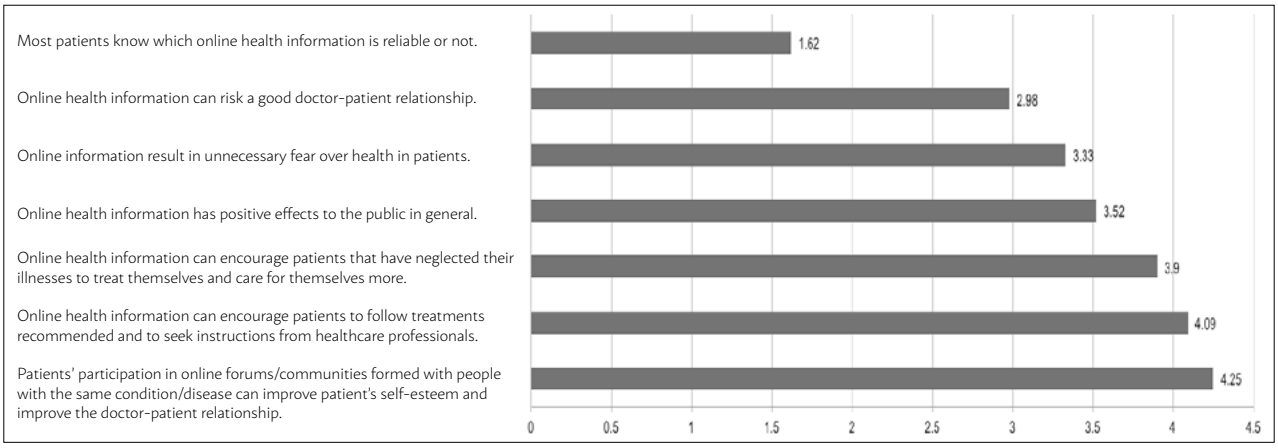


TABLE 1 – Sociodemographic profile of physicians from outpatient clinics of Gynaecology and Obstetrics, Medical Clinic and subspecialties, Dermatology, General Surgery, Clinical Oncology, Oncology Surgery and Plastic Surgery – Data collected at the Instituto de Medicina Integral Professor Fernando Figueira (IMIP) in Recife, Pernambuco, Brazil, between December 2016 and April 2017.

Variable	n	%
TOTAL	183	100.0
Gender		
Male	77	42.1
Female	106	57.9
Age group (years)		
24 to 39	120	65.6
40 to 59	54	29.5
60 to 73	9	4.9
Year of graduation in Medicine		
1968 to 1999	55	30.1
2000 to 2010	79	43.2
2011 to 2016	49	26.8
Graduation institution		
Public	159	86.9
Private	24	13.1
Place of graduation		
Recife	139	76.0
Outside Recife	44	24.0
Specialty		
Gynaecology and Obstetrics	51	27.9
Medical clinic	70	38.3
Dermatology	4	2.2
General surgery	30	16.4
Clinical oncology	18	9.8
Oncology surgery	3	1.6
Plastic surgery	7	3.8
Employment relationship		
Public outpatient clinic	18	9.8
Private/public outpatient clinic	40	21.9
Hospital sector	1	0.5
Public outpatient clinic and hospital sector	60	32.8
Private/public outpatient clinic and hospital sector	64	35.0

83.1% agreed. Although most agree on the above sentences, 59.6% of physicians believe that this information results in unnecessary fears about the patients' health. In addition, 50.3% agreed that this information online could "jeopardize the good doctor-patient relationship" and 89.1% of the respondents disagree with the sentence: "most patients know what health information online are reliable or not".

Comparing the average Ranking of the answers of the physicians from different specialties, a statistically significant difference ($p = 0.032$) was observed in relation to the sentence "Online health information results in unnecessary health fears on the part of the patients", so that for Gynaecology and Obstetrics physicians the value obtained was 3.57; for those of Clinical Oncology, 2.72; for those of Surgery

TABLE 2 – Answers of physicians from outpatient clinics of Gynaecology and Obstetrics, Medical Clinic and subspecialties, Dermatology, General Surgery, Clinical Oncology, Oncology Surgery and Plastic Surgery about opinions about the impact of online health information on doctor-patient relationship – Data collected at the Instituto de Medicina Integral Professor Fernando Figueira (IMIP) in Recife, Pernambuco, Brazil, between December 2016 and April 2017.

Variable	n	%
TOTAL	183	100.0
*Q1 – Before a patient who claims to have researched information about a particular disease on the internet and comments on this information with you, questioning your behaviour or diagnostic hypotheses, you:		
- Feel that your authority has been questioned.	1	0.5
- Try to explain to the patient the reasons for your hypotheses or conduct.	181	98.9
- Indicate your diagnosis/conduct for considering it the best, but without explaining why.	-	-
- That never happened to you, and you'd be in doubt about how to react.	1	0.5
*Q2 – Do you indicate or have indicated websites or other media sources for better instruction of patients or when requested by them?		
– Yes.	96	52.5
– No.	87	47.5
*Q2A – If so, how often do you indicate to your patients websites or other reliable sources to instruct them about their illness?(1)		
- Rarely.	23	12.6
- Eventually.	61	33.3
- Frequently.	12	6.6
*Q2B – If not, why have you never indicated to your patients websites or other reliable sources to instruct them about their illnesses (it is possible to choose more than one alternative)?(2)		
- Patient's low instruction level	26	29.9
- No patient I've cared for has presented such demand.	35	40.2
- Most websites are not reliable.	21	24.1
- I need to research websites and other sources for patient information, as I do not know much about these sources.	17	19.5
- Other.	11	12.6
*Q3- Do you have a webpage on any social media, a website or blog (other than personal profile) on which you share health information relating to your specialty or general health directed to patient clarification?		
- Yes.	24	13.1
- No and I'm not interested in having it.	112	61.2
- No, but I intend to have it.	47	25.7
*Q4 – In a hypothetical situation, if a patient is interested in knowing more about their illness/health issue and asks you about which source(s) on the internet is (are) reliable and which is (are) in a language accessible to them, you:		
- Say that you will provide the sources in the next appointment, because you need to research good sources.	45	24.6
- Already have sources in mind that meet the patient's needs.	49	26.8
- Know some sources for patient education, but say you can research more and provide others in the next appointment.	75	41.0
- Do not present research sources for not considering the Internet as a safe way of providing information.	10	5.5
- None of the above.	4	2.2
*Q5 – In your opinion, the information accessed online and in social media can change patients' attitudes towards the treatment?		
- No.	1	0.5
- Yes. It can positively change patients' attitudes.	12	6.6
- Yes. It can negatively change patients' attitudes.	8	4.4
- Yes. It can change both positively and negatively patients' attitudes.	162	88.5

Variable	n	%
*Q6 – Have you had any experience in which the patient reported that they changed aspects of the recommended treatment after having seen information about the disease on the internet or other media?		
- Yes.	108	59.0
- No.	27	14.8
- No, but there was questioning about the recommended treatment.	36	19.7
- This never happened to me but I've heart accounts from colleagues who had a similar experience.	12	6.6
*Q7 – How do you assess the impact of online and media health information on the doctor-patient relationship?		
- Positive impact.	12	6.6
- Negative impact.	10	5.5
- Both positive and negative impact.	156	85.2
- I need to research more about the impact of this information, as I do not have any opinion about this.	5	2.7

(General, Oncology and Plastic), was 3.15, and for the Medical Clinic and Dermatology group it was 3.42.

DISCUSSION

The physicians' profile of the studied sample understands that before a questioning patient, the physician should make them understand the diagnosis and treatment, making the patient an active agent. In the study by Murray et al.[8], a national study in the United States found that a minority of physicians feel challenged by patients who bring health information to the appointment, a finding similar to this study. In the city of Santos, São Paulo, Brazil, Coelho et al.[9] found that the minority of physicians (4.76%) surveyed reported extreme discomfort when confronted with data that the patient researched before or after the appointment. Stevenson et al.[10] concluded that increasing patient activism in the search for information does not interrupt the existing balance of power and does not change roles (physician and patient) in the appointment; the online health information is complementary to the patient's care and, therefore, would support the therapeutic relationship.[10]

This research found that more than half of physicians indicate websites or sources of other media besides the internet for patient enlightenment. Similar results were found in a cross-sectional study conducted by Schwartz et al.[11], which evaluated 92 physicians in the United States, noting that 63% of them reported having already suggested a specific website to their patients. Thus, a study in seven European countries solidifies the importance of online access to information, demonstrating a beneficial effect in investigating citizens' health-related internet use patterns and finding that it was twice as common to feel reassured after online use than experiencing feelings of anxiety.[12] However, the practitioner should be familiar with the internet to better guide his/her patients about medical knowledge, since most are composed of lay people, and should be engaged more in the improvement of websites with health content available.

It is observed that a favourable assessment of online health information predominates among those surveyed as to its possible positive effects on the patients' condition in general. However, one can note medical uncertainty regarding patients' judgment about the information accessed as to its truthfulness, since about 89% of physicians agreed that most lay people do not know what online health information is reliable or not. Murray et al.[8], still in the 2003 publication of the national study with US physicians, concluded that quality information accessed by patients has a beneficial effect, but misinformation has a detrimental effect. This effect could generate deleterious consequences to the patient insofar as they changes aspects related to their treatment.

Knowing the risks of misuse of online content, most health websites are an important market source in today's culture, as it is kept apart from any regulation or validation of the information it disseminates, thus allowing publication of scientific data with subjective impressions, possibly marked by resentment, exhibitionism or ideology propagation.[13] Moretti et al.[14], in an interview with physicians from São Paulo, Brazil, observed that the interviewees gave great emphasis to the importance of public sector initiatives

in the sense of qualifying health information that is made available on the Internet, and the Ministry of Health was the most mentioned agency among the entities that could be responsible for the certification of websites. This could minimize the damaging effect of misinformation about health on the internet.

Corroborating the importance of indicating appropriate websites, a survey, conducted in Australia based on patient perception, concluded that healthcare professionals were referred to as the most commonly selected option to help patients find reliable information on the internet.[15, 16] The Code of Medical Ethics, in its Chapter XIII, states that physicians may be allowed to participate in any mass media exclusively for the purpose of enlightening and educating society.[5] In this way, the physician could be a reliable source of information for patients, which is positive for enhancing the patient's ability to appropriately decide on diagnostic and treatment processes, making the doctor-patient relationship more reliable and safe. Percentage of 13% of those surveyed in this study reported having an online webpage to publish health information intended for patients.

In this study, most of the respondents have had some experience in which the patient reported that changed aspects of the recommended treatment. In this regard, a study carried out in Canada noted that although health information on the internet has some effect on the process of agreement between patients and physicians, it is up to the practitioner to develop communication skills to convince the patient of his/her convictions through empathy.15 Thus, the physician should not fear this new and established tool, nor regard it as his competitor, and he/she must consider the patient's effort to find the information and discuss it with him/her. Certifying this idea, in a Spanish survey, 80.8% of patients believe that their physician would be willing to talk to them about the information found in the web.17

That said, this survey conducted in the city of Madrid, Spain found that the majority of Internet users commented on changes in health behaviour with their physician and among those who changed their way of thinking about health after searching online information, the majority also feel more interested in such issues.[17] Thus, we can observe patients more committed to their health and therefore more participative in the decisions to be made, proving the finding in this study in which dominance is observed (91.2 %) of physicians agreeing that online health information can encourage patients to follow recommended treatments and seek the advice of medical professionals.

It was observed in this research that, among medical specialties, oncologists tend to disagree with the sentence "Online health information results in unnecessary patient fears about health", while other specialties tend to show "no opinion". In parallel with this result, a greater number of oncology patient surveys were found gaining support in forums/communities for patient assistance.[18-21] Thus, oncologists may have a more positive opinion regarding the search for online websites due to existing evidence. But further research needs to be carried out to explain this phenomenon.

It is also worth noting that the following assertions of the Likert scale – "Online health information has positive effects on the general public", "Online information results in unnecessary health fears for the patients" and "Online health information may jeopardize good doctor-patient relationship" – bring results that reveal a discrepancy in responses among respondents due to the numerical value observed when applying the standard deviation. The variation of responses between total agreement and total disagreement of reported opinions suggests a lack of consensus in the medical class consulted and/or little personal involvement with online publications in the healthcare area.

Among the limitations of the study, the difficulty of reaching the correct population and sample size among the medical specialties stands out, since the data obtained through the National Registry of Health Institutions did not match the reality present in the outpatient clinics of the collection place. It is important to emphasize that the research carried out was based on calculations made by the personal impression of the physicians, and does not necessarily reflect what happens in practice in relation to the attitude adopted by patients.

CONCLUSION

It is understood that access to health information on the internet is not without risk, such as insecurity and fears, both for patients and physicians. On the other hand, the promotion of benefits through the internet, such as the creation of instruments to cope with life situations and emotional relief, is already

recognized as a positive effect for certain patients. It should be understood the cognitive aspect of the patient as determinant for interpretations of the online health information and the medical ability of critical assessment for the discernment of the impact on the patient of the information found by them, in order to determine if it is relevant to the condition of the patient and whether it is based on the best evidence available, since patients started to have an active voice in the definition and choice of treatments through the principle of autonomy, a right guaranteed by the Code of Medical Ethics. Thus, recognizing the information age as a social advance is necessary, weighing positive and negative aspects, to continue the endless process of improving communication and the doctor-patient relationship.

RESUMO

OBJETIVOS: *Analisar opiniões e atitudes relatadas por médicos especialistas diante das informações de saúde on-line e suas interferências na relação médico-paciente. Métodos: Estudo transversal desenvolvido entre 2016 e 2017 em Recife, Pernambuco, Brasil, que utilizou um questionário presencialmente em uma população de 183 médicos especialistas do Instituto de Medicina Integral Prof. Fernando Figueira. Os resultados foram analisados por meio do* Statistical Package for the Social Sciences. *Obtida aprovação do Comitê de Ética sob o número de comprovante 121004/2016. Resultados: Na opinião de 85,2% dos médicos, as informações on-line sobre saúde têm tanto impacto positivo quanto negativo na relação médico-paciente. Diante de um paciente questionador, que diz ter pesquisado informações na rede, 98,9% dos médicos fazem com que o usuário entenda as razões sobre seu diagnóstico e tratamento; 59% já tiveram paciente que modificou o tratamento recomendado por ter visto informações na internet; 73,8% concordam que as informações on-line sobre saúde têm efeitos positivos para o público em geral, mas 89,1% opinam que a maioria dos pacientes não sabe quais informações sobre saúde on-line são confiáveis.*

CONCLUSÃO: *Os médicos pesquisados veem as informações on-line sobre saúde de forma positiva, mas percebem que é necessário ter cautela quanto às repercussões destas sobre o tratamento dos pacientes. Há preocupação quanto à acurácia dessas informações, cabendo ao médico e às instituições de saúde instruir os pacientes quanto às fontes de qualidade e que estejam acessíveis ao entendimento de leigos, visto que os pacientes passaram a ter voz ativa por meio da garantia do princípio ético da autonomia.*

PALAVRAS-CHAVE: *Internet. Relações médico-paciente. Papel do médico. Participação do paciente.*

REFERENCES

1. Goldin JR, Franciscone CF. Modelos de relação médico-paciente. [Citado 16 maio 2017]. Disponível em: http://www.ufrgs.br/bioetica/relacao.htm.
2. Briet JP, Hageman MG, Blok R, Ring D. When do patients with hand illness seek online health consultations and what do they ask? Clin Orthop Relat Res. 2014;472(4):1246-50.
3. Kurup V, Considine A, Hersey D, Dai F, Senior A, Silverman DG, et al. Role of the Internet as an information resource for surgical patients: a survey of 877 patients. Br J Anaesth. 2013;110(1):54-8.
4. Liszka HA, Steyer TE, Hueston WJ. Virtual medical care: how are our patients using online health information? J Community Health. 2006;31(5):368-78.
5. Rose S, Bruce J, Maffulli N. Accessing the Internet for patient information about orthopedics. JAMA. 1998;280(15):1309.
6. Rocha BV, Gazim CC, Pasetto CV, Simões JC. Relação médico-paciente. Rev Med Res. 2011;13(2):114-8.
7. Conselho Federal de Medicina – CFM. Código de ética médica: Resolução CFM nº 1931, de 17 de setembro de 2009 (versão de bolso). 2010. [Citado 16 maio 2017]. Disponível em: http://www.cremers.org.br/pdf/codigodeetica/codigo_etica.pdf.
8. Murray E, Lo B, Pollack L, Donelan K, Catania J, Lee K, et al. The impact of health information on the Internet on health care and the physician-patient relationship: national U.S. survey among 1.050 U.S. physicians. J Med Internet Res. 2003;5(3):e17.
9. Coelho EQ, Coelho AQ, Cardoso JED. Informações médicas na internet afetam a relação médico-paciente? Rev Bioét. 2013; 21(1):142-9.
10. Stevenson FA, Kerr C, Murray E, Nazareth I. Information from the Internet and the doctor-patient relationship: the patient perspective: a qualitative study. BMC Fam Pract. 2007;8:47.
11. Schwartz KL, Roe T, Northrup J, Meza J, Seifeldin R, Neale A. Family medicine patients' use of the Internet for health information: a MetroNet study. J Am Board Fam. 2006;19(1):39-45.
12. Andreassen HK, Bujnowska-Fedak MM, Chronaki CE, Dumitru RC, Pudule I, Santana S, et al. European citizens' use of E-health services: a study of seven countries. *BMC Public Health. 2007;*7:53.
13. Schmidt E, Viana SMSA, Andrade EBM, Fernandes MD, Rezende SPI, Reis PVS, et al. A inclusão da internet na relação médico-paciente: apenas prós? Rev Bras Clin Med. 2013;11(4).
14. Moretti FA, Oliveira VE, Silva EMK. Acesso a informações de saúde na internet: uma questão de saúde pública? Rev Assoc Med Bras. 2012;58(6):650-8.
15. Laugesen J, Hassanein K, Yuan Y. The impact of Internet health information on patient compliance: a research model and an empirical study. J Med Internet Res. 2015;17(6):e143.
16. Lee K, Hoti K, Hughes J, Emmerton L. Dr Google is here to stay but health care professionals are still valued: an analysis of health care consumers' Internet navigation support preferences. J Med Internet Res. 2017;19(6):e210.
17. Marin-Torres V, Valverde Aliaga J, Sánchez Miró I, Sáenz Del Castillo Vicente MI, Polentinos-Castro E, Garrido Barral A. Internet as an information source for health in primary care patients and its influence on the physician-patient relationship. Aten Primaria. 2013;45(1):46-53.
18. Chiu YC. Probing, impelling, but not offending doctors: the role of the internet as an information source for patients' interactions with doctors. Qual Health Res. 2011;21(12):1658-66.
19. Broom A, Tovey P. The role of the Internet in cancer patients' engagement with complementary and alternative treatments. Health (London). 2008;12(2):139-55.
20. Bylund CL, Gueguen JA, D'Agostino TA, Imes RS, Sonet E. Cancer patients' decisions about discussing Internet information with their doctors. Psychooncology. 2009;18(11):1139-46.
21. Chen X, Siu LL. Impact of the media and the Internet on oncology: survey of cancer patients and oncologists in Canada. J Clin Oncol. 2001;19(23):4291-7.

ORIGINAL ARTICLE

Clinical features of patients with chronic non-specific neck pain per disability level: A novel observational study

Hector Beltran-Alacreu, PT, PhD[1,2,3]
Ibai López-de-Uralde-Villanueva, PT, PhD[1,2,3,4]
César Calvo-Lobo PT, PhD[5]
Josué Fernández-Carnero, PT, PhD [2,3,4,6]
Roy La Touche , PT, PhD[1,2,3,4]

1. Department of Physical Therapy, Superior Center for University Studies La Salle, Autonomous University, Autónoma University of Madrid, Spain.
2. Motion in Brains Research Group, Institute of Neuroscience and Movement Sciences (INCIMOV), Superior Center for University Studies La Salle, Autonomous University, Autónoma University of Madrid, Spain.
3. Institute of Neuroscience and Craniofacial Pain (INDCRAN), Madrid, Spain
4. Hospital La Paz Institute for Health Research, IdiPAZ, Madrid, Spain.
5. Nursing and Physical Therapy Department, Faculty of Health Sciences, Universidad de León, Ponferrada, León, Spain.
6. Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain.

http://dx.doi.org/10.1590/1806-9282.64.08.700

BACKGROUND: *To date, there are no cross-sectional studies considering the influence of disability level in patients with non-specific chronic neck pain. Therefore, the main aim of this study was to determine kinesiophobia, active cervical range of movement (CROM), and pressure pain threshold (PPT) differences between different disability levels (mild, moderate, and severe) in subjects with non-specific chronic neck pain and asymptomatic subjects.*

METHODS: *A descriptive cross-sectional study. Subjects were recruited from a primary health care center and an outpatient department hospital. A total sample of 128 subjects, 96 of them with nonspecific chronic neck pain and 32 asymptomatic, were recruited. The NDI was used to divide the subjects with chronic neck pain into 3 groups (mild, moderate, and severe disability). The main outcome measurement was the Tampa Scale of kinesiophobia (TSK-11). The secondary outcome measurements were the Visual Analogue Scale (VAS), PPT (trapezius and tibialis anterior), CROM (flexion, extension, rotation, and lateral inclination) and pain duration.*

RESULTS: *The ANOVA results revealed, in the comparisons between groups, statistically significant differences for the VAS between the mild-severe ($P < 0.01$) and moderate-severe groups ($P < 0.01$), but not between the mild-moderate groups ($P > 0.05$); for the TSK, differences were not statistically significant ($P > 0.05$).*

CONCLUSION: *Kinesiophobia may not be influenced by disability level in patients with chronic non-specific neck pain. Nevertheless, pain intensity and chronicity of patients with severe neck disability are increased with respect to mild and moderate disability index.*

KEYWORDS: *Neck pain. Chronic pain. Disability evaluation.*

ABBREVIATIONS: *Cervical range of movement (CROM); Neck disability index (NDI); Pressure pain threshold (PPT); Tampa Scale of Kinesiophobia (TSK-11); Visual Analogue Scale (VAS).*

DATE OF SUBMISSION: 15-Dec-2017
DATE OF ACCEPTANCE: 24-Dec-2017
CORRESPONDING AUTHOR: César Calvo Lobo
Av. Astorga, s/n – Ponferrada – León – Spain – 24401 – Tel: 605811782
E-mail: cecalvo19@hotmail.com

CORRESPONDING AUTHOR: Josué Fernández Carnero
Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine.
Faculty of Health Sciences, Rey Juan Carlos University, Madrid, Spain.
Avda. Atenas s/n – 28922 Alcorcón — Madrid — Spain – Tel.: +34 914888949
Email: josuefernandezcarnero@gmail.com

hector.beltran@lasallecampus.es
ibai.uralde@gmail.com
josue.fernandez@urjc.es
roylatouche@lasallecampus.es

INTRODUCTION

Neck pain is a very common condition in clinical practice.[1-5] Recently, the International Neck Pain Task Force reported the impact of neck pain in social-related problems for families, work, health systems, and economies.[1-3] The prevalence of neck pain ranges between 30% and 50% in the general population of developed countries[3,4] and is more prevalent in women than men.[1,5] In 2010, 33.6 million people were affected worldwide, and neck pain was the 4th most frequent disability, with over 291 conditions studied.[5] The most common form of neck pain is non-specific chronic pain, which has a postural or mechanical basis and affects about two-thirds of people at some stage in their lives.[6,7]

Previous studies have shown an association between neck disability and chronic neck pain.[8-10] In addition, physical factors, such as active range of movement (ROM), and psychological factors, such as fear of movement, anxiety, or depression, are also associated with chronic neck pain.[8-10] To explain the relationship of neck pain with these factors, a "fear-avoidance model" may be used when the patient demonstrates avoidance-hypervigilance, which triggers a vicious cycle in which the patient is affected both physically and psychologically, leading to deconditioning.[8,10-12] Fear of motion may be correlated with neck kinematics, such as ROM or velocity. Also, The neck disability level may be partly related to ROM.[9] Furthermore, the pressure pain thresholds (PPT) of muscles, such as upper trapezius and tibialis anterior, have been widely used in order to evaluate local tenderness and central sensitization associated to chronic neck pain.[13]

Currently, no observational studies exist on non-specific chronic neck pain with different levels of disability, according to the neck disability index (NDI).[14,15]the Neck Disability Index (NDI The NDI is a clinical screening tool established for pathology-related neck pain.[16] The NDI has sufficient support in the literature and is the most commonly used self-report measure for neck pain.[17] There is a lack of observational studies that make it more difficult to classify this type of patient,[18] and classification could lead to a better therapeutic approach in the choice of treatment.

Therefore, the main aim of this study was to determine the kinesiophobia, active cervical range of movement (CROM), and PPT differences between different disability levels (mild, moderate, and severe) in subjects with non-specific chronic neck pain and asymptomatic subjects. Indeed, the pain intensity and chronicity influence were only established regarding NDI levels in patients with neck pain. As a secondary purpose, the association between these physical and psychological variables was analyzed in patients with non-specific chronic neck pain.

METHODS

Study design

A descriptive cross-sectional study was performed to assess differences in various physical and psychological outcomes of subjects with different levels of neck disability and asymptomatic subjects. The investigation was conducted according to the STROBE statement from November 2014 to November 2016,[19]which hampers the assessment of its strengths and weaknesses and of a study's generalisability. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE Before beginning the study, all participants were asked to read and sign an informed consent. Previously, the Ethics Committee for Clinical Research of the Hospital Universitario La Paz, Madrid, Spain (Registration number: PI-1241) approved the study.

Setting, evaluators and blinding

Subjects with chronic neck pain were recruited by referral from the primary health care center of Coslada (Madrid, Spain) and from an outpatient department of University Hospital La Paz (Madrid, Spain).

Two physiotherapists with over 5 years of experience in orthopedic manual therapy carried out the outcome measurement. A one-hour-long training session was scheduled to review how to perform measurement of the CROM and PPT protocols in the current study. In addition, they were responsible for collecting all outcome data without being aware of the subject's group, resulting in a single-blinded study.

Sample

A total sample of 128 subjects, 96 patients and 32 asymptomatic subjects, was recruited for the study. These subjects were classified by the NDI, [20] obtaining a final sample of 96 patients, divided into 3 disability groups: 32 patients (25 females, 7 males; mean ± SD age, 40.88 ± 11.31) with mild disability (MIL; NDI 5–14 scores), 32 patients (28 females, 4 males; 44 ± 14.64) with moderate disability (MOD; NDI 15–24 scores) and 32 patients (27 females, 5 males; 42,66 ±

11.90) with severe disability (SEV; NDI 25–34 scores). The symptomatic subjects were selected upon fulfilling the following inclusion criteria: aged between 18 and 65 years; proper understanding, writing, and speaking ability of the Spanish language; experienced neck pain for at least 12 weeks and complained of pain localized in the neck region. Patients were not considered if they reported any of the following conditions: neck pain associated with whiplash injuries, a reported red flag medical history (tumor, fracture, metabolic diseases, rheumatoid arthritis, osteoporosis), neck pain with cervical radiculopathy, neck pain associated with externalized cervical disc herniation, fibromyalgia syndrome (checked by a physician against the criteria established by the American College of Rheumatology), [21] previous neck surgery, neck pain accompanied by vertigo caused by vertebrobasilar insufficiency, or neck pain accompanied by non-cervicogenic headaches. People were also not considered if they were undergoing any type of pain treatment, or had received physical therapy in the previous 3 months.[8,13]

The control group consisted of 25 females and 7 males (mean ± SD age, 43.38 ± 10.67) recruited from family, friends, and the same environment as the patients' primary health center. The approach for this group was to ask the relatives of the patients if they wanted to participate in the study. All subjects of this group presented an age range between 18-65 years and were excluded if they had a history of cervical, upper limb, orofacial, or upper thoracic pain in the previous 12 months.

Outcome measurements

The main outcome measurement was the Tampa Scale of kinesiophobia (TSK-11). The secondary outcome measurements were the Visual Analogue Scale (VAS), PPT (trapezius and tibialis anterior), CROM (flexion, extension, rotation, and lateral inclination) and pain duration (months). The TSK-11, PPT, and CROM were assessed in patients and asymptomatic subjects. Nevertheless, VAS and pain duration were only measured in patients with non-specific chronic neck pain.

Self-report measures

Neck Disability Index (NDI): The NDI is a well-validated 10-item questionnaire, with each item rated on a 0 to 5-point scale. The sum of the 10 items gives a score between 0-50.[14] According to Vernon's NDI sub-classification,[14,15] this scale divides the sample into 5 groups of disability: scores of <4 indicate no disability, 5–14 mild disability, 15–24 moderate disability, 25–34 severe disability, and >35 complete disability. In the current study, the complete disability group was not taken into account due to the lack of sample in clinical practice. The NDI has sufficient support in the literature as the most commonly used instrument for reporting neck pain; [14,17] a Spanish validation of the index was used.[20]

Visual Analogue Scale (VAS): Pain intensity was measured via the VAS. A 100-mm horizontal line with pain descriptors marked "no pain" at the left side and "the worst pain imaginable" at the right side was used to measure pain intensity. Patients were asked to indicate their pain intensity at the time by marking the VAS with a perpendicular line. The VAS is a reliable and valid measurement of pain.[22,23]

Tampa Scale of Kinesiophobia (TSK): To evaluate the participants' pain-related fear of movement and (re)injury, a Spanish-validated Tampa Scale of Kinesiophobia (TSK) was used.[24]a Spanish version of the TSK has not been available, up to now. Thus, the aim of this study was to validate the Spanish version of the TSK in 2 different pain samples: A\u00a0heterogeneous chronic pain sample (n = 125 We used an 11-item version of it that has shown good psychometric reliability for chronic pain.[25] Each item is scored on a 4-point Likert scale, ranging from "strongly agree" to "strongly disagree." Total scores range from 11 to 44, with higher scores indicating more fear of movement and/or (re)injury.

Physical measures

Cervical range of movement (CROM): Active ROMs of the cervical spine was evaluated using the CROM, which consists of 3 inclinometers attached to a lightweight plastic frame secured with fastening straps. The protocol used was a sequence of 3 measurements, with an interval of 30 seconds between each measurement. The CROM has shown good intra-rater reliability for subjects with and without neck pain (ICC = 0.87 to 0.94 in asymptomatic subjects and ICC = 0.88 to 0.96 in neck pain subjects).[26] The following movements were measured by the CROM device (Figure 1): flexion and extension, right and left lateral flexion, and right and left rotation.

Pressure pain threshold (PPT): A digital algometer (FDX 25, Wagner Instruments, Greenwich, CT, USA), comprised of a rubber head (1 cm^2) attached to a pres-

sure gauge, was used to measure the PPT, which is defined as the amount of pressure at which the sense of pressure first changes to pain.[27]fibrositis, myalgic spots, activity of arthritis as well as assessment of sensitivity to pain can be diagnosed by PTM. This study therefore established standards for pressure threshold as well as the reproducibility and validity of measurement in 24 male and 26 female normal volunteers at 9 sites. Muscles frequently afflicted by trigger points were examined. The deltoid was chosen as a reference since it is rarely a site for trigger points. Comparison of corresponding muscles on opposite sides failed to demonstrate significant differences (except for 1 muscle in females The force was measured in kilograms (kg); therefore, thresholds were expressed in kg/cm^2. The protocol used

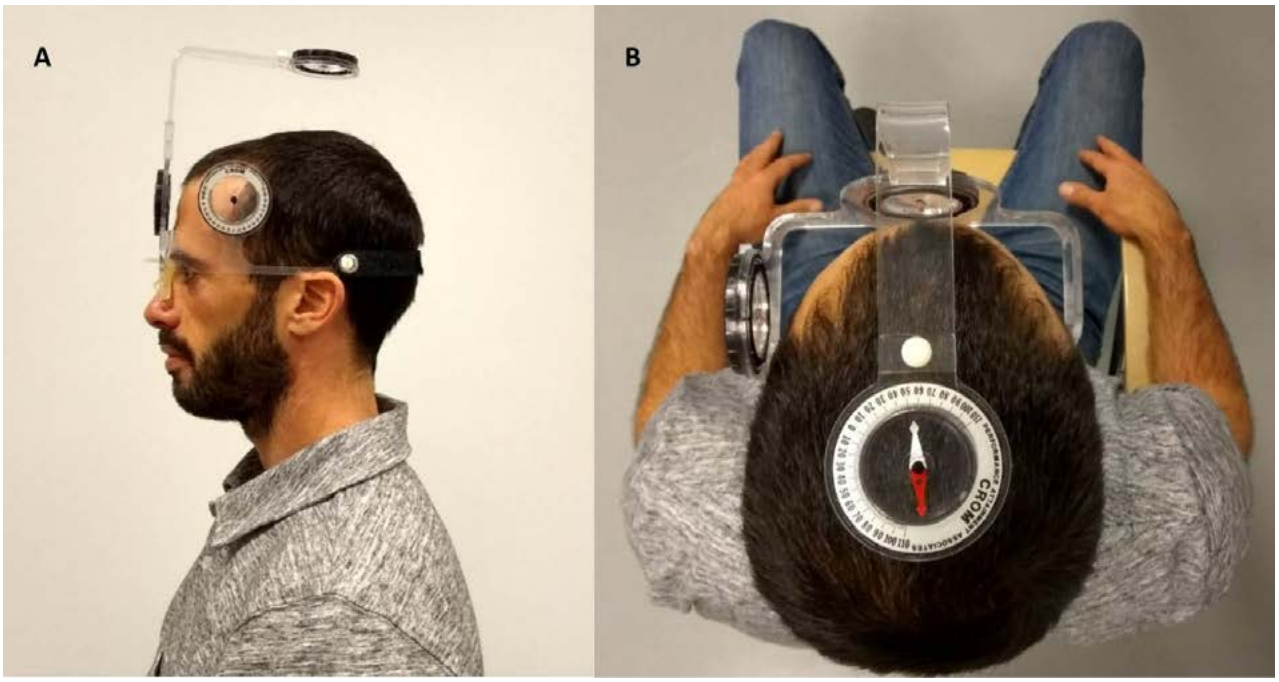


FIGURE 1. Lateral (A) and cranial (B) views for the CROM device use for active cervical movement measurement. Abbreviations: CROM, cervical range of movement.

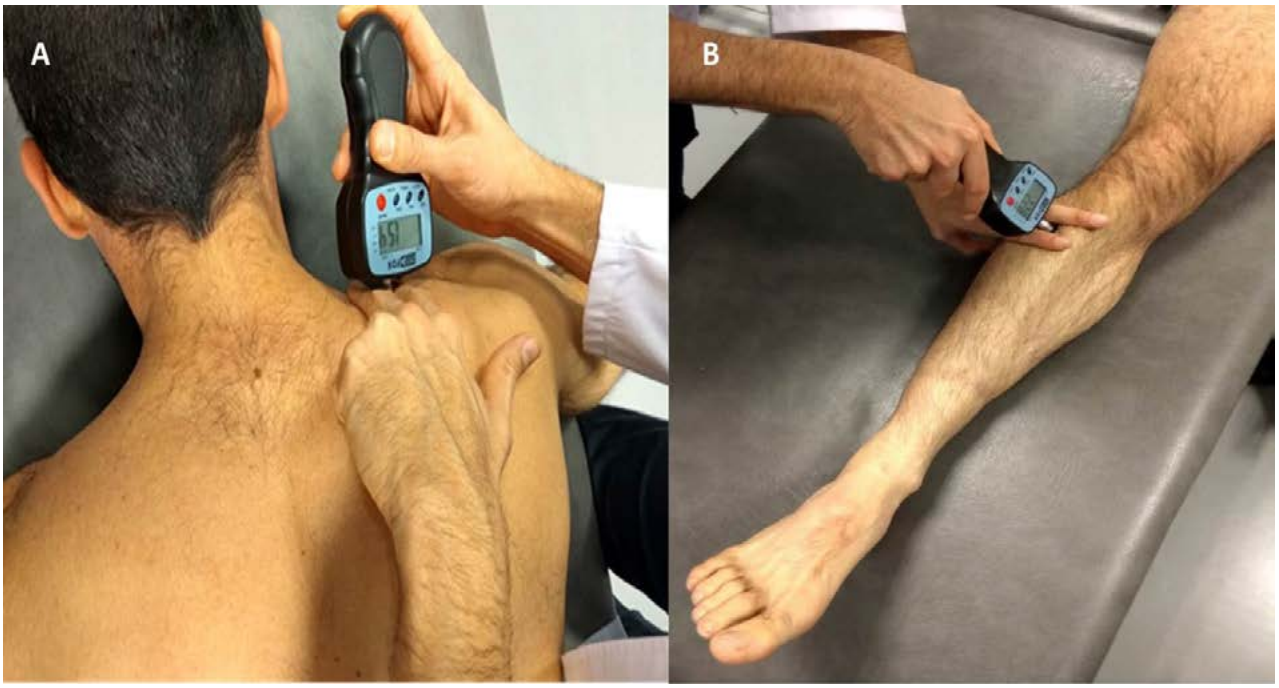


FIGURE 2. PPT assessment over the right upper trapezius muscle (A: midway between C7 and acromion) and the right tibialis anterior muscle (B: upper one-third of the muscle belly). Abbreviations: PPT, pressure pain threshold.

was a sequence of 3 measurements, with an interval of 30 seconds between each of them. The reliability of the pressure algometry was high (ICC = 0.91 [95% confidence intervals (CI): 0.82–0.97]. [28] At a rate of 5 Newtons (N) PPT was assessed over the right upper trapezius muscle (midway between C7 and acromion; Figure 2A) and the right tibialis anterior muscle (upper one-third of the belly muscle; Figure 2B). The upper trapezius muscle was chosen as the most common site of idiopathic neck pain, and the tibialis anterior was chosen as a remote distant site.

Procedure

The data collection was performed in a room in which only the assessor and patient were present. First, the measurement protocol was explained to the subject, then the informed consent was signed by the subject. Next, the questionnaires were filled out, and the patients' CROM and PTT measured, always in the same order. This study was conducted just before patients began treatment in their respective physiotherapy service. The asymptomatic subjects were healthy participants who accompanied the patients.

Sample size calculation

The sample size and power calculations were performed with appropriate software (G*Power 3.1).[29] To obtain 95% statistical power (1-β error probability) with an α error level probability of 0.05, a one-way fixed-effects analysis of variance (ANOVA) model and a large effect-size of 0.4 were used, generated for 4 groups and a total sample size of at least 112 participants (28 participants per group).

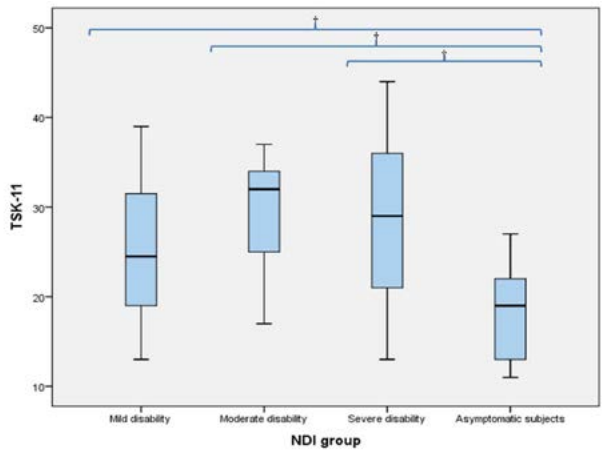


FIGURE 3. Box-plot to illustrate the TSK-11 differences between patients with different NDI level (mild, moderate and severe) and asymptomatic subjects. Abbreviations: NDI, neck disability index; TSK, Tampa Scale of Kinesiophobia. † $P < 0.01$ The rest of comparisons between groups did not show any statistically significant difference ($P > 0.05$).

Statistical methods

Data were analyzed using the *Statistical Package for the Social Sciences* (SPSS version 20.0; SPSS, Inc, Chicago, IL). Results are expressed as mean, standard deviation (SD), considering the 95% CI. The Z-score was assumed for all variables to follow a normal distribution based on the central limit theorem,[30,31] with 95% confidence intervals, and compute cost-effectiveness acceptability curves and confidence ellipses. Two alternative non-parametric methods for estimating INB are to apply the central limit theorem (CLT Differences in demographic and clinical features between all groups were compared using ANOVA for continuous data and the X^2 test of independence for categorical data. Quantitative data (i.e., VAS TSK-11, pain duration, CROM, and PPT) were analyzed with parametric tests. One-way ANOVA with post hoc Bonferroni correction was used to analyze the outcome differences. TSK-11, PPT and CROM were compared between patients with different NDI level (MIL, MOD and SEV) and asymptomatic subjects. However, VAS and pain duration were only analyzed between these disability levels in patients with non-specific chronic neck pain. Pearson's correlations were calculated separately for MIL, MOD and SEV groups and were also calculated for subjects with NDI scores between 5-34 (total sample with disability). The values of r for moderate or high correlation were considered between 0.50-0.70 and 0.70-0.90, respectively.[32] For all analyses, statistical significance was set at $P < 0.05$.

RESULTS

A total of 142 subjects were screened, out of which 128 (90.1%) were eligible and agreed to participate in the study. The mean age of all subjects was 42.67 ± 12.01 years, and 82.03% were female. There were no significant differences ($P > 0.05$) between groups in age (F = 0.379), gender (F = 0.467), height (F = 1.226), or weight (F = 1.797). All demographic data for each group are shown in Table 1.

Outcome measurements

The ANOVA results revealed a significant effect for the group factor [NDI (F = 278.198; $P < 0.001$); VAS (F = 24.61; $P < 0.001$); TSK-11 (F = 17.55; $P < 0.001$); Pain Du-

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE NDI GROUPS. VALUES ARE MEAN ± SD AND N (%).

	No disability (n = 32)	Mild (n = 32)	Moderate (n = 32)	Severe (n = 32)	P value of independent samples ANOVA or c2 test
Age (years)	43.38 ± 10.66	40.88 ± 11,31	44± 14.64	42.66 ± 11.9	0.768*
Gender, n female (%)	25 (78.1)	25 (78.1)	28 (87.5)	27 (84.4)	0.698†
Height (m)	1.65 ± 0.05	1.62 ± 0.08	1.63 ± 0.07	1.65 ± 0.07	0.303*
Weight (kg)	64.13 ± 7.43	61.81 ± 12.27	67.75 ± 11.97	65.5 ± 9.58	0.151*
NDI	N/A	10.19 ± 2.89	18.06 ± 2.42	29.22 ± 4.16	< 0.001*

Abbreviations: ANOVA, analysis of variance; N/A, not applicable; NDI, Neck Disability Index; SD, standard deviation. * ANOVA with independent samples was applied. † c2 test was applied.

TABLE 2. COMPARISONS BETWEEN GROUPS.

	Mean ± SD				Mean difference (95% CI);	
	Mild	Moderate	Severe	No Disability	a) Mild vs. Moderate b) Mild vs. Severe d) Moderate vs. Severe	c) Mild vs. No Disability e) Moderate vs. No Disability f) Severe vs. No Disability
VAS (mm)	50 ± 10.24	53.78 ± 10.7	69.34 ± 13.79	0 ± 0	a) -0.37 (-1.05 to 0.3) b) -1.93 (-2.61 to -1.25) † c) -1.55 (-2.23 to -0.87) †	d) N/A e) N/A f) N/A
Pain Duration (months)	72.53 ± 54.4	64.53 ± 48.54	211.41 ± 152.74	0 ± 0	a) 8 (-48.73 to 64.73) b) -138.87 (-195.61 to -82.14) † c) -146.87 (-203.61 to -90.14) †	d) N/A e) N/A f) N/A
TSK-11 (11-44)	25.25 ± 7.03	29.59 ± 5.52	28.72 ± 9	18.56 ± 4.8	a) -4.34 (-8.85 to 0.16) b) -3.47 (-8.1 to 1.15) c) 0.87 (-3.75 to 5.49)	d) 6.68 (2.18 to 11.20) † e) 11.03 (6.52 to 15.54) † f) 10.16 (5.54 to 14.78) †
Trapezius- PPT (kg/cm2)	2.74 ± 0.93	2.21 ± 0.59	1.37 ± 0.84	3.79 ± 0.84	a) 0.52 (-0.1 to 1.15) b) 1.36 (0.68 to 2.05) † c) 0.84 (0.16 to 1.52) †	d) -1.04 (-1.67 to -0.41) † e) -1.57 (-2.2 to -0.94) † f) -2.41 (-3.09 to -1.73) †
Tibialis- PPT (kg/cm2)	5.61 ± 1.83	4.75 ± 1.46	3.46 ± 1.59	5.79 ± 1.84	a) 0.85 (-0.28 to 2) b) 2.15 (0.8 to 3.5) † c) 1.29 (-0.05 to 2.64)	d) -0.17 (-1.32 to 0.96) e) -1.03 (-2.18 to 0.11) f) -2.32 (-3.67 to -0.97) †
Flexion	52.34 ± 8.63	49.06 ± 11.48	38.89 ± 13.94	58.65 ± 8.27	a) 3.28 (-3.82 to 10.38) b) 13.44 (5.77 to 21.12) † c) 10.16 (2.49 to 17.83) †	d) -6.31 (-13.41 to 0.78) e) -9.59 (-16.69 to -2.49) † f) -19.76 (-27.43 to -12.09) †
Extension	60.39 ± 18.47	54.03 ± 15.46	48.76 ± 19.66	72.07 ± 9.17	a) 6.35 (-4.34 to 17.06) b) 11.62 (0.69 to 23.18)* c) 5.26 (-6.29 to 16.82)	d) 11.68 (-22.38 to -0.98)* e) 18.04 (-28.74 to -7.34) † f) 23.31 (-34.87 to -11.75) †
Lateral Inclination	34.97 ± 7.41	33.46 ± 7.63	24.57 ± 16.51	40.42 ± 4.76	a) 1.51 (-5.25 to 8.29) b) 10.4 (3.63 to 17.18) † c) 8.89 (15.66 to 2.11) †	d) -5.44 (-12.21 to 1.32) e) 6.96 (-13.73 to -0.18)* f) 15.85 (-22.62 to -9.07) †
Rotation	58.17 ± 9.79	56.36 ± 12.32	39.13 ± 26.8	67.16 ± 7.6	a) 1.81 (-8.94 to 12.57) b) 19.04 (8.27 to 29.8) † c) 17.22 (6.46 to 27.99) †	d) 8.98 (-19.83 to 1.85) e) -10.8 (-21.65 to -0.04) f) -28.03 (-38.88 to -17.18) †

Abbreviations: CI, confidence interval; N/A, not applicable; PPT, pressure pain threshold; SD, standard deviation; TSK, Tampa Scale of kinesiophobia; VAS, Visual Analogue Scale. * P < 0.05. † P < 0.01

ration (F = 22.85; *P* < 0.001); Trapezius-PPT (F = 32.65; P < 0.001); Tibialis-PPT (F = 8.67; P < 0.001); Flexion (F = 16.85; P < 0.001); Extension (F =11.55; P < 0.001); Lateral flexion's (F = 13.55; P < 0.001); Rotations (F = 16.85; P < 0.001)]. In the comparisons between groups for the VAS, the differences between the MIL-SEV (*P* < 0.01) and MOD-SEV (*P* < 0.01) disability groups were statistically significant but not between MIL-MOD (*P* > 0.05). For the TSK, there were no statistically significant differences between these groups (*P* > 0.05). Figure 3 shows the box-plots to illustrate the TSK-11 differences between patients with different NDI level and asymptomatic subjects. Table 2 shows the values as the mean ± SD of each group and the means differences (95% CI) between them.

Correlations

The results for Pearson's correlations coefficients among the psychological and physical measures in each disability group are shown in Table 3. A mod-

TABLE 3. CORRELATIONS BETWEEN PSYCHOLOGICAL AND PHYSICAL MEASURES.

		Pain Duration	VAS	TSK-11
		Mild disability (5-14 NDI score)		
PPT				
	Trapezius	-0.099	-0.269	-0.026
	Tibialis	-0.083	-0.062	-0.275
ROM				
	Flexion	-0.308	-0.138	0.034
	Extension	0.152	-0.012	-0.042
	Lateral Flexion	-0.2	-0.183	-0.018
	Rotation	-0.19	-0.161	-0.18
		Moderate disability (15-24 NDI score)		
PPT				
	Trapezius	0.188	0.338	0.107
	Tibialis	0.172	0.11	-0.114
ROM				
	Flexion	-0.321	0.323	-0.033
	Extension	-0.45**	-0.121	-0.428*
	Lateral Flexion	-0.167	0.075	-0.387*
	Rotation	-0.244	0.011	-0.569**
		Severe disability (25-34 NDI score)		
PPT				
	Trapezius	-0.445*	-0.108	-0.078
	Tibialis	-0.199	-0.224	-0.364
ROM				
	Flexion	0.015	0.342	-0.040
	Extension	0.432*	-0.041	-0.124
	Lateral Flexion	-0.056	-0.423*	-0.099
	Rotation	0.015	-0.424*	-0.86
		Total sample with disability (5-34 NDI score)		
PPT				
	Trapezius	-0.425**	-0.357**	-0.161
	Tibialis	-0.265*	-0.281*	-0.385**
ROM				
	Flexion	-0.322**	-0.054	-0.209
	Extension	0.21	-0.165	-0.386**
	Lateral Flexion	-0.263**	-0.367**	-0.161
	Rotation	-0.262**	-0.454**	-0.212*

Abbreviations: NDI, Neck Disability Index; PPT, pressure pain threshold; ROM, range of motion; TSK, Tampa kinesiophobia Scale; VAS, Visual Analogue Scale. *p < 0.05; **p < 0.01

erate correlation was observed between TSK and Rotation (*r*= -0.569) in the MOD group. Considering the subjects with NDI scores between 5-34 (total sample with disability), a moderate correlation was observed between NDI and VAS (*r*= 0.566), as well as between NDI and Trapezius-PPT (*r*= -0.559).

DISCUSSION

This is the first study to show the differences between the psychological and physical variables according to different degrees of cervical disability using the NDI sub-classification described by Vernon[14,15]the Neck Disability Index (NDI in 1991. The number of studies on this topic proved to be very small. No studies were found on non-specific neck pain. On the other hand, the authors found a classification model for whiplash using Vernon's NDI (1996) but used another form of classification. [33,34]

For the VAS, differences between MIL-MOD were not statistically significant, but differences between the MIL-SEV and MOD-SEV were significant. Due to the lack of studies that use levels of disability as a means of classification, the authors compared their mean ± SD VAS scores for the MIL-MOD disability level to those in the literature, and VAS levels were very similar.[9,35] The SEV group had similar VAS levels to that of chronic whiplash patients. In the same article, MIL-MOD had different VAS scores, but this could be because the sample was comprised of recovering whiplash patients.[36] Emshoff et al.[37] reported that, for chronic pain, the cutoff for minimal detectable change for VAS was 11.5 - 28.5 mm, indicating that there are clinical differences between the MIL-SEV and MOD-SEV disability groups, but not between the MIL-MOD groups. According to Collins et al.[38], a VAS above 54 mm is considered severe, and over 30 mm moderate, indicating that the SEV group (69.34 mm) was different than MIL (50 mm) and MOD (53.78mm).

The kinesiophobia levels were higher in patients with disability in comparison to those without it, but there were no differences between groups with different levels of disability. Overall, the kinesiophobia levels were moderate, in agreement with a recent study in which the authors found a moderate (*r* = 0.46) correlation between TSK and NDI in patients with chronic neck pain; however, they included traumatic and non-traumatic neck pain disorders.[9]

In our results, TSK outcomes were between 25.25 ± 7.03 and 29.59 ±7.03 in all the patients with disability, and there were no statistically significant differences between the groups with different levels of disability. Our outcomes did not reach the kinesiophobia levels reported by Sarig Bahat et al. [9] (35.74 ± 5.71), possibly because they evaluated patients with different neck pain, such as traumatic neck pain or non-specific acute neck pain, and

used a larger version of the TSK (17-items). Saavedra-Hernández et al. reported similar levels of kinesiophobia to our study (25.4 ±6.5), but in patients with moderate disability.[8]

Regarding the PPT results, there were no statistically significant differences in the trapezius for MIL and MOD, but differences were statistically significant between the MIL-SEV and MOD-SEV groups. In addition, all groups had differences compared to the non-disabled group. For the right tibial anterior, differences were only found between the MIL-SEV and SEV-Control groups. These results are in agreement with La Touche et al.[39], who compared groups with moderate disability versus no disability subjects and had very similar PPT values in the trapezius and anterior tibial muscles and conclusions similar to ours. [39] Furthermore, PPT differences ranging from 123 kPa to 200 kPa (1.2–2 kg) are considered minimal detectable change differences[28,40-42] at two points on the trapezius muscles on each side and at the sternum as the only non-muscular site. The intratester repeatability of the PPT measurements was satisfactory or good (Intraclass correlation coefficient (ICC 0.78-0.93 Therefore, it can be suggested that, for trapezius-PPT, there are real differences between the SEV-MIL (1.37 kg/cm^2) and SEV-no disability (2.42 kg/cm^2) groups, but not between the SEV-MOD (0.84 kg/cm^2) or MOD-MIL (0.53 kg/cm^2) ones. This suggestion could be related to mechanical hyperalgesia.

In relation with ROMs, disability groups had significant differences with respect to the non-disabled group, which coincides with previous studies.[9,16,26,43] In addition, the SEV group has more differences from the other disability groups, especially in rotation movements. Sarig Bahat et al.[9] demonstrated that decreased CROM correlates with more kinesiophobia, more pain intensity, and a higher level of disability. This could explain our results, in which a higher level of disability obtained minor ROMs. Furthermore, the relationship between kinematics and fear of motion suggests that psychological fear may affect cervical motion control.[9,12,16,36,43]NDI and other questionnaires, whiplash and NDI and cervical range of motion and NDI. The NDI was shown to be a well validated and reliable self-reported questionnaire, especially when compared to other questionnaires, in both neck pain and whiplash (WAD This also justifies our results, in which all disability groups presented kinesiophobia and reduced ROMs.

Study limitations

This study has several limitations. First, the complete disability group (NDI between 35-50)[15]especially those involving the soft tissues, represent a significant source of chronic disability. Methods of assessment for such disability, especially those targeted at activities of daily living which are most affected by neck pain, are few in number. A modification of the Oswestry Low Back Pain Index was conducted producing a 10-item scaled questionnaire entitled the Neck Disability Index (NDI was not accounted for due to the lack of sample in clinical practice; this type of subject usually has polytrauma or accidents, and the access necessary to take certain measurements is limited. Second, because of the involvement of the psychological factor in chronic pain, we only measured kinesiophobia, but we should account for the measurement of depression, anxiety, and catastrophizing to observe if there are differences in different levels of neck disability. Third, the authors did not evaluate the reliability of the ROM and PPT measures, and this kind of clinical measure could be influenced by the skills of the rater. Another limitation is that this research was a cross-sectional study; hence, its results should be considered with caution because we do not know the outcomes of these patients over time. Thus, future studies should consider a longitudinal design and the implementation of linear regression analysis to establish a causal relationship per disability group.

Interpretation

Our findings suggest that there are differences between the different types of disability, which may have implications in both clinical practice and research. Having the NDI tool to classify disability in nonspecific neck pain will increase awareness of their differences and can be the key to selecting the best intervention for each patient. In research, nonspecific neck pain randomized controlled trials (RCT) are almost nonexistent when it comes to samples exclusively composed of severely disabled patients; most have a mild to moderate disability level.

Prospective and future studies

Future research could present different types of specific treatments for different levels of disability, but RCTs exclusive for patients with severe neck disability are needed, for they are not found in the current literature. According to this, pain education pro-

grams combined with multimodal treatments were shown to be beneficial for patients with chronic neck pain,[44] nevertheless the neck disability level should be related to the clinical course and treatment effectiveness.

CONCLUSIONS

Kinesiophobia may not be influenced by disability level in patients with chronic non-specific neck pain. Nevertheless, pain intensity and chronicity of patients with severe neck disability are increased with respect to mild and moderate disability indexes. In addition, patients with more disability showed higher local hyperalgesia, although differences in widespread hyperalgesia were only found when mild and severe disabilities were compared. Finally, the severe disability group showed more differences in ROM than the rest of the subgroups, especially in rotation movements.

RESUMO

CONTEXTO: *Até a data, não há estudos transversais considerando a influência do nível de incapacidade em pacientes com dor de garganta crônica não específica. Portanto, o objetivo principal deste estudo foi determinar a diferença entre os níveis de diminuição do colesterol cervical (Crom) e o limiar por dor de pressão (PPT) entre diferentes níveis de incapacidade (leve, moderada e grave) em indivíduos com dor crônica não específica no pescoço e sujeitos assintomáticos.*

MÉTODOS: *Estudo descritivo transversal. Os indivíduos foram recrutados de um centro de saúde primário e de um hospital do departamento ambulatorial. Uma amostra total de 128 indivíduos, 96 indivíduos com dor no pescoço crônica não específica e 32 indivíduos assintomáticos, foi recrutada. O NDI foi usado para dividir os indivíduos com dor no pescoço crônica em três grupos (incapacidade leve, moderada e grave). A principal medida de resultados foi a Tampa Scale of Kinesiophobia (TSK-11). As medidas de resultado secundário foram a Escala Analógica Visual (VAS), PPT (trapézio e tibial anterior), Crom (flexão, extensão, rotação e inclinação lateral) e duração da dor.*

RESULTADOS: *Nos resultados da Anova revelados nas comparações entre os grupos, diferenças estatisticamente significativas para o VAS foram observadas entre os grupos leve-grave (P<0,01) e moderado-grave (P<0,01), mas não entre os grupos moderado-moderado (P>0,05). Para o TSK, as diferenças não foram estatisticamente significativas (P>0,05).*

CONCLUSÃO: *A cinesiofobia pode não ser influenciada pelo nível de incapacidade em pacientes com dor no pescoço crônica não específica. No entanto, a intensidade da dor e a cronicidade de pacientes com deficiência grave do pescoço são aumentadas em relação ao índice de incapacidade leve e moderada.*

PALAVRAS-CHAVE: *Cervicalgia. Dor crônica. Avaliação da deficiência.*

ABREVIAÇÕES: *Faixa de movimento cervical (Crom); Índice de incapacidade do pescoço (NDI); Limiar da dor de pressão (PPT); Tampa Scale of Kinesiophobia (TSK-11); Escala Visual Analógica (VAS).*

REFERENCES

1. Haldeman S, Carroll L, Cassidy JD. Findings from the bone and joint decade 2000 to 2010 task force on neck pain and its associated disorders. J Occup Environ Med. 2010;52(4):424-7.
2. Carroll LJ, Hogg-Johnson S, van der Velde G, Haldeman S, Holm LW, Carragee EJ, et al. Course and prognostic factors for neck pain in the general population: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. J Manipulative Physiol Ther. 2009;32(2 Suppl):S87-96.
3. Hogg-Johnson S, van der Velde G, Carroll LJ, Holm LW, Cassidy JD, Guzman J, et al. The burden and determinants of neck pain in the general population: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. J Manipulative Physiol Ther. 2009;32(2 Suppl):S46-60.
4. Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population: a systematic critical review of the literature. Eur Spine J. 2006;15(6):834-48.
5. Hoy D, March L, Woolf A, Blyth F, Brooks P, Smith E, et al. The global burden of neck pain: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1309-15.
6. Binder AI. Neck pain. BMJ Clin Evid. 2008;2008. pii: 1103.
7. Bogduk N. Neck pain. Aust Fam Physician. 1984;13(1):26-30.
8. Saavedra-Hernández M, Castro-Sánchez AM, Cuesta-Vargas AI, Cleland JA, Fernández-de-las-Peñas C, Arroyo-Morales M. The contribution of previous episodes of pain, pain intensity, physical impairment, and pain-related fear to disability in patients with chronic mechanical neck pain. Am J Phys Med Rehabil. 2012;91(12):1070-6.
9. Sarig Bahat H, Weiss PL, Sprecher E, Krasovsky A, Laufer Y. Do neck kinematics correlate with pain intensity, neck disability or with fear of motion? Man Ther. 2014;19(3):252-8.
10. Hudes K. The Tampa Scale of Kinesiophobia and neck pain, disability and range of motion: a narrative review of the literature. J Can Chiropr Assoc. 2011;55(3):222-32.
11. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain. 2000;85(3):317-32.
12. Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. J Behav Med. 2007;30(1):77-94.
13. Sá S, Silva AG. Repositioning error, pressure pain threshold, catastrophizing and anxiety in adolescents with chronic idiopathic neck pain. Musculoskelet Sci Pract. 2017;30:18-24.
14. Vernon H. The Neck Disability Index: state-of-the-art, 1991-2008. J Manipulative Physiol Ther. 2008;31(7):491-502.
15. Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. J Manipulative Physiol Ther. 1991;14(7):409-15.
16. Howell ER. The association between neck pain, the Neck Disability Index and cervical ranges of motion: a narrative review. J Can Chiropr Assoc. 2011;55(3):211-21.

17. MacDermid JC, Walton DM, Avery S, Blanchard A, Etruw E, McAlpine C, et al. Measurement properties of the neck disability index: a systematic review. J Orthop Sports Phys Ther. 2009;39(5):400-17.

18. Borghouts JA, Koes BW, Bouter LM. The clinical course and prognostic factors of non-specific neck pain: a systematic review. Pain. 1998;77(1):1-13.

19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; Iniciativa STROBE. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Rev Esp Salud Publica. 2008;82(3):251-9.

20. Andrade Ortega JA, Delgado Martínez AD, Almécija Ruiz R. Validation of the Spanish version of the Neck Disability Index. Spine (Phila Pa 1976). 2010;35(4):E114-8.

21. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010;62(5):600-10.

22. Jensen MP, Turner JA, Romano JM, Fisher LD. Comparative reliability and validity of chronic pain intensity measures. Pain. 1999;83(2):157-62.

23. Katz J, Melzack R. Measurement of pain. Surg Clin North Am. 1999;79(2):231-52.

24. Gómez-Pérez L, López-Martínez AE, Ruiz-Párraga GT. Psychometric properties of the Spanish version of the Tampa Scale for Kinesiophobia (TSK). J Pain. 2011;12(4):425-35.

25. Roelofs J, Goubert L, Peters ML, Vlaeyen JW, Crombez G. The Tampa Scale for Kinesiophobia: further examination of psychometric properties in patients with chronic low back pain and fibromyalgia. Eur J Pain. 2004;8(5):495-502.

26. Fletcher JP, Bandy WD. Intrarater reliability of CROM measurement of cervical spine active range of motion in persons with and without neck pain. J Orthop Sports Phys Ther. 2008;38(10):640-5.

27. Fischer AA. Pressure algometry over normal muscles. Standard values, validity and reproducibility of pressure threshold. Pain. 1987;30(1):115-26.

28. Chesterton LS, Sim J, Wright CC, Foster NE. Interrater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. Clin J Pain. 2007;23(9):760-6.

29. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-91.

30. Nixon RM, Wonderling D, Grieve RD. Non-parametric methods for cost-effectiveness analysis: the central limit theorem and the bootstrap compared. Health Econ. 2010;19(3):316-33.

31. Mouri H. Log-normal distribution from a process that is not multiplicative but is additive. Phys Rev E Stat Nonlin Soft Matter Phys. 2013;88(4):042124.

32. Mukaka MM. Statistics corner: a guide to appropriate use of correlation coefficient in medical research. Malawi Med J. 2012;24(3):69-71.

33. Sterling M, Jull G, Vicenzino B, Kenardy J, Darnell R. Physical and psychological factors predict outcome following whiplash injury. Pain. 2005;114(1-2):141-8.

34. Vernon H. The neck disability index: patient assessment and outcome monitoring in whiplash. J Musculoskelatal Pain. 1996;4(4).

35. Leaver AM, Maher CG, McAuley JH, Jull GA, Refshauge KM. Characteristics of a new episode of neck pain. Man Ther. 2013;18(3):254-7.

36. Nederhand MJ, Ijzerman MJ, Hermens HJ, Turk DC, Zilvold G. Predictive value of fear avoidance in developing chronic neck pain disability: consequences for clinical decision making. Arch Phys Med Rehabil. 2004;85(3):496-501.

37. Emshoff R, Bertram S, Emshoff I. Clinically important difference thresholds of the visual analog scale: a conceptual model for identifying meaningful intraindividual changes for pain intensity. Pain. 2011;152(10):2277-82.

38. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain. 1997;72(1-2):95-7.

39. La Touche R, Fernández-de-Las-Peñas C, Fernández-Carnero J, Díaz-Parreño S, Paris-Alemany A, Arendt-Nielsen L. Bilateral mechanical-pain sensitivity over the trigeminal region in patients with chronic mechanical neck pain. J Pain. 2010;11(3):256-63.

40. Ylinen J, Nykänen M, Kautiainen H, Häkkinen A. Evaluation of repeatability of pressure algometry on the neck muscles for clinical use. Man Ther. 2007;12(2):192-7.

41. Sterling M, Jull G, Carlsson Y, Crommert L. Are cervical physical outcome measures influenced by the presence of symptomatology? Physiother Res Int. 2002;7(3):113-21.

42. Walton DM, Macdermid JC, Nielson W, Teasell RW, Chiasson M, Brown L. Reliability, standard error, and minimum detectable change of clinical pressure pain threshold testing in people with and without acute neck pain. J Orthop Sports Phys Ther. 2011;41(9):644-50.

43. Howell ER, Hudes K, Vernon H, Soave D. Relationships between cervical range of motion, self-rated disability and fear of movement beliefs in chronic neck pain patients. J Musculoskelet Pain. 2012;20(1):18-24.

44. Beltran-Alacreu H, López-de-Uralde-Villanueva I, Fernández-Carnero J, La Touche R. Manual therapy, therapeutic patient education, and therapeutic exercise, an effective multimodal treatment of nonspecific chronic neck pain: a randomized controlled trial. Am J Phys Med Rehabil. 2015;94(10 Suppl 1):887-97.

ORIGINAL ARTICLE

Assessment of quality of life in patients with advanced oral cancer who underwent mandibulectomy with or without bone reconstruction

Jose Roberto Netto Soares[1]
Fernando Luiz Dias[1]
Roberto Rego Monteiro de Araujo Lima[1]
Ullyanov Bezerra Toscano[1]
Ana Carolina Pastl Pontes[1]
Ruiter Diego Botinelly[1]
Fernanda Gonzalez Rocha Souza[1]
Vergilius José Furtado de Araujo Filho[2]
Leandro Luongo Matos[2]
Claudio Roberto Cernea[2]

1. Head and Neck Surgery Service - National Cancer Institute, Rio de Janeiro/RJ, Brasil
2. Discipline of Head and Neck Surgery, Faculty of Medicine, University of São Paulo, São Paulo/SP, Brasil

http://dx.doi.org/10.1590/1806-9282.64.08.710

INTRODUCTION: *Malignant neoplasms of the head and neck, due to its anatomical location, can cause significant alterations in vital functions related to feeding, communication and social interaction of the affected patients. Objective: To analyze the quality of life of patients with advanced malignant neoplasms of the oral cavity and submitted to radical operations with curative intent. Material and methods: 47 patients with oral cavity squamous cell carcinoma (SCC), in stages III and IV, underwent surgical treatment with segmental mandibulectomy and complementary radiotherapy. The patients were submitted to the quality of life questionnaires after a minimum time of six months after the surgical treatment. Results: Of the 183 patients, only 47 (25.7%) were able to answer the questionnaire and were included as the sample of the study. The majority of patients selected were male (39; 82.9%). The mean age was 64.4 years. The majority of the patients presented clinical stage IV (83%) and were submitted to adjuvant radiotherapy (95.4%). The mean score obtained after the questionnaires were applied was 64.6. The worst scores were found in swallowing and chewing. Conclusion: There were no statistically significant differences in the domains of quality of life between the two groups studied (with bone reconstruction versus no bone reconstruction). Patients interviewed 2 years or more after treatment presented higher scores (p = 0.02).*

KEY-WORDS: *Quality of life. Mouth neoplasms. Mandibular reconstruction. Carcinoma, squamous cell. Bone transplantation. Mandibular osteotomy.*

INTRODUCTION

Oral cancer can compromise important individual abilities and aspects, such as speech, breath, appearance, and swallowing; Radical surgery can incur in severe physical changes in the patient due to, mainly, the extension of the surgical treatment. A considerable number of patients feel mutilated, stigmatized, and bothered by people's reaction. This can lead to stress and social isolation, with a need for functional and psychosocial rehabilitation.[1,2] One of the biggest worries reported by patients is the disfigurement associated to the disease and extensive surgeries, in addition to the loss of major functions, especially those

DATE OF SUBMISSION: 08-Dec-2017
DATE OF ACCEPTANCE: 25-Dec-2017
CORRESPONDING AUTHOR: Leandro Luongo de Matos
Av. Dr. Enéas de Carvalho Aguiar, 255 – 8o andar – sala 8174 – CEP: 05403-000
São Paulo, SP, Brasil – Phone: +55-11-3069-6425; Fax: +55-11-3069-7506
E-mail: l.matos@fm.usp.br

jrnsoares2000@yahoo.com.br
fdiasmd@yahoo.com.br
rlimamd@uol.com.br; ullyanov@inca.gov.br
acpp@inca.gov.br; ruiterdb@inca.gov.br
fgrsouza@inca.gov.br
vergilius.filho@gmail.com
l.matos@fm.usp.br; cerneamd@uol.com.br

related to chewing and swallowing when there is the need of mandibular resection.[3,4]

Research on cancer patient's quality of life is essential to assess the areas affected by the disease and plan interventions to rehabilitate these patients. Thus, the purpose of this study was to assess the quality of life in patients with advanced malignant neoplasms in the oral cavity who underwent radical surgery with curative intent, comparing those who underwent functional reconstruction of the mandible to those who did not.

MATERIAL AND METHODS

This is a cross-sectional study that assesses the quality of life in oral cancer patients for a period of at least six months after ongoing surgical treatment. The study was approved by the Institutional Ethics Committee (protocol 058/2008), and all patients signed an Informed Consent Form.

Consecutive patients of both genders who were treated from 2004 to 2013 in a single tertiary institution were evaluated Those aged between 25 and 75 years, with stage III and IV squamous cell carcinoma of the oral cavity submitted to radical or reconstructive surgery were included. Patients who were actively sick at the moment when the questionnaires were applied were not included.

The Portuguese validated version of the University of Washington Quality of Life Questionnaire UW-QOL was used.[5] It comprises 12 questions related to specific functions of the head and neck, as well as others regarding activity, recreation, pain, mood, and anxiety. Each domain has three to five categories of answers, with scores varying from 0 (worst) to 100 (best), which were assessed in two ways: individually in each domain and the total score for all the domains, calculated as a composite score that is the average of all the 12 domains. There are also three generic questions that do not have a score of their own and are used as a basis for comparison between patients or groups of patients. The questionnaire was applied by a single trained evaluator.

Statistical analysis

A descriptive analysis of the selected population was performed using central tendency and dispersion for the continuous variables and frequency distribution for the categorical ones. All analyses were conducted with the help of the SPSS 20.0 software and a statistical significance of 5% ($p<0.05$) was adopted.

To assess the regular distribution of the outcome (quality of life score) and of the quantitative independent variables, the Kolmogorov-Smirnov was performed. A scatter plot was used to evaluate the linearity between the outcome and the independent variables. The Pearson correlation was used to test the collinearity of the qualitative independent variables.

The difference between each average score was calculated to assess the link between the independent variables and the quality of life scores, with the statistical difference obtained by means of analysis of variance. In order to identify the variables that would be included in the multiple linear regression model, a difference of seven points in the categories of each independent variable and/or the statistical significance were considered as clinically significant through the value of $p<0.20$.

RESULTS

Initially, 183 patients were selected who met the inclusion criteria. A total of 47 (25.7%) were submitted to an interview, thus forming the sample of the study.

At the time of the interview, the mean age was 61.8 ± 8.4 years, and the time between surgery and the time of the interview was 41.5 months. The most commonly affected place by the primary lesion was the floor of the mouth in 23 patients (49%), followed by gingival margin in 16 patients (34.0%). The patients who underwent combined surgery were reconstructed using myocutaneous flaps (72.3%) or free flaps (27.7%). Furthermore, 43 patients were classified as T4 (80.9%), and there was node metastasis in 21 patients (44.7%). The demographic and clinical characteristics of patients with advanced malignant neoplasms in the oral cavity included in this study are described in Table 1.

All the patients underwent mandibulectomy and were grouped according to the type of reconstruction used: in 34 patients (72.3%) closure by synthesis or soft tissue flap reconstruction were used (Group 1); bone flap reconstruction (Group 2) was used in 13 cases (27.7%).

The average score obtained after the assessment of the questionnaires was 64.6 (varying from 50 to 86.8). When stratified by type of reconstruction, the average was 65 in Group 1 and 63,1 in Group 2, both very similar.

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH MALIGNANT NEOPLASMS IN THE ORAL CAVITY (N=47)

Variable	Oral cavity (n=47) n (%)
Gender	
Men	39 (83.0)
Female	8 (17.0)
Formal education	
Up to 8 years	26 (55.3)
Over 8 years	21 (44.7)
Ethnicity	
White	29 (61.7)
Black and Brown skinned	18 (38.3)
Marital status	
With a spouse	25 (55.6)
Without a spouse	20 (44.4)
Unknown	2 (4.3)
Age at the time of the interview	
≤60 years	26 (55.3)
>60 years	21 (44.7)
Time between surgery and interview	
≤2 years	25 (53.2)
>2 years	22 (46.8)
T	
3	9 (19.1)
4	38 (80.9)
N	
0	26 (55.3)
1	9 (19.2)
2	10 (21.3)
3	2 (4.2)
Clinical Stage	
III	8 (17.0)
IV	39 (83.0)
Adjuvant radiotherapy	
No	2 (4.2)
Yes	42 (89.4)
Radiotherapy + Chemotherapy	3 (6.4)

TABLE 2. FREQUENCY OF THE OBJECTIVE DOMAINS OF THE UW-QOL

Domains	Categories	n (%)
Pain	Severe pain, uncontrolled by drugs	1 (2.1)
	Severe pain controlled by prescription drugs	1 (2.1)
	Moderate pain	7 (14.9)
	Mild pain	11 (23.4)
	Absence of pain	27 (57.4)
Appearance	Avoids social contact	1 (2.1)
	Feels disfigured and limited	10 (21.3)
	In slightly bothered, but active	16 (34.0)
	Slight change	15 (31.9)
	No change	5 (10.6)
Activity	Stays in bed and does not leave the house	0 (0.0)
	Barely leaves the house, inactive	1 (2.1)
	Slightly active, always tired	13 (27.7)
	Mostly active	18 (38.3)
	As active as always	15 (31.9)
Recreation	Does not leave the house, nothing is pleasant	1 (2.1)
	Severe limitation, stays home	8 (17.0)
	Would like to go out, but cannot	7 (14.9)
	Few limitations, but still leaves the house	9 (19.1)
	No limitations to leave the house	22 (46.8)
Swallowing	Cannot swallow	2 (4.3)
	Can only swallow liquids	17 (36.2)
	Can only swallow some solids	18 (38.3)
	Can swallow well	10 (21.3)
Chewing	Cannot chew anything	26 (55.3)
	Chews light food	20 (42.6)
	Chews light food and solids	1 (2.1)
Speech	Is not understood by others	1 (2.1)
	Is understood only by the family and a few others	5 (10.6)
	Slight difficulty to speak	34 (72.3)
	Same speech as always	7 (14.9)
Shoulder	Incapable of working	0 (0.0)
	Pain and weakness, affects work	9 (19.1)
	Hardened, does not affect activity	8 (17.0)
	No shoulder problems	30 (63.8)
Taste	Cannot taste anything	3 (6.4)
	Tastes some things	11 (23.4)
	Tastes most things	9 (19.1)
	Tastes everything	24 (51.1)
Saliva	No saliva	6 (12.8)
	Very little saliva	25 (53.2)
	Enough	5 (10.6)
	Normal saliva	11 (23.4)
Mood	Extremely depressed due to cancer	1 (2.1)
	Slightly depressed due to cancer	11 (23.4)
	Indifferent	7 (14.9)
	Good mood, only slightly affected due to cancer	13 (27.7)
	Excellent, unaffected due to cancer	15 (31.9)
Anxiety	Very anxious due to cancer	5 (10.6)
	Anxious due to cancer	3 (6.4)
	Slightly anxious due to cancer	18 (38.3)
	Not anxious due to cancer	21 (44.7)

The frequency of the objective domains in the UW-QOL questionnaire can be found in Table 2. The absence of pain was the most frequent answer for the pain domain (65.5%). As for appearance, oral cancer patients reported being slightly bothered but still remaining active (34%). Regarding activity, they reported being active most of the time (38.3%). For recreation, most patients reported not having limitations for leaving home (46.5%). The patients can only swallow some solid foods (38.3) and reported not being able to chew even light foods (55.3%). In relation to the speech domain, most patients reported a bit of difficulty in speaking (64.8%). Most patients reported no problems with the shoulder after the treatment (64.8%). Regarding the domain of mood, the patients reported being usually in an excellent mood, unaffected by cancer (45.8%). For the anxiety domain, most reported not being anxious as a result of cancer (59.2%).

The variable of age at the time of the interview showed clinical and statistical significance in the domain of pain (p=0.049), with patients over 60 years old reporting better scores than those younger at the time of the interview. The marital status was statistically associated with quality of life in the saliva

TABLE 3. AVERAGE FROM THE SCORES OF THE UW-QOL QUESTIONNAIRE DOMAINS, BY CLINICAL AND DEMOGRAPHIC VARIABLES OF PATIENTS WITH ADVANCED MALIGNANT NEOPLASMS IN THE ORAL CAVITY

Variable	Pain		Appearance		Activity		Recreation		Swallowing		Chewing		Speech	
	Average	P value	Average	P value	Average	P value	Average	P value	Average	P value	Average	P value	Average	P value
Gender														
Men	82.05	0.563	57.69	0.641	76.92	0.165	75.64	0.176	59.85	0.606	24.36	0.602	67.72	0.522
Female	87.50		53.13		65.63		59.38		54.13		18.75		62.75	
Age at the interview														
≤60 years	73.44	0.049*	60.94	0.431	78.12	0.466	73.44	0.929	58.37	0.932	25.00	0.777	71.06	0.300
>60 years	87.90		54.84		73.39		72.58		59.13		22.58		64.71	
Formal education														
Up to 8 years	79.81	0.318	58.65	0.599	76.92	0.488	75.96	0.450	57.69	0.753	23.08	0.928	66.85	0.992
Over 8 years	86.90		54.76		72.62		69.05		60.33		23.81		66.90	
Ethnicity														
White	81.03	0.486	56.90	0.995	75.00	1.000	75.00	0.553	64.38	0.089	25.86	0.439	66.90	0.992
Black and Brown skinned	86.11		56.94		75.00		69.44		50.00		19.44		66.83	
Marital status														
With a spouse	80.00	0.300	52.00	0.082	73.00	0.488	70.00	0.416	61.32	0.469	24.00	0.631	64.24	0.334
Without a spouse	87.50		65.00		77.50		77.50		55.00		20.00		70.15	
Clinical Stage														
III	81.25	0.825	71.88	0.061	81.25	0.358	93.75	0.034*	66.87	0.383	25.00	0.858	71.13	0.509
IV	83.33		53.85		73.72		68.59		57.23		23.08		66.00	
Site		0.139		0.033*		0.285		0.068		0.537		0.818		0.128
Tongue	87.07		62.93		77.59		79.39		60.90		24.14		63.41	
GIngival margin	76.39		47.22		70.83		72.50		55.61		22.22		72.44	
Time of surgery/interview														
≤2 years	76.00	0.032*	52.00	0.150	73.00	0.489	64.00	0.034*	60.00	0.773	28.00	0.222	61.52	0.046*
>2 years	90.91		62.50		77.27		82.95		57.59		18.18		72.95	
Reconstruction				0.580						0.334				
Myocutaneous flap/no	82.81	0.287	51.56		67.19	0.119**	70.31	0.696	54.13		25.00	0.958	69.00	0.823
Free flap	75.00		59.62		75.00		69.23		53.92		23.08		64.31	

TABLE 3 - CONTINUED AVERAGE FROM THE SCORES OF THE UW-QOL QUESTIONNAIRE DOMAINS, BY CLINICAL AND DEMOGRAPHIC VARIABLES OF PATIENTS WITH ADVANCED MALIGNANT NEOPLASMS IN THE ORAL CAVITY

Variable	Shoulder		Taste		Saliva		Mood		Anxiety		Composite score	
	Average	P value	Average	P value	Average	P value	Average	P value	Average	P value	Average	P value
Gender												
Men	80.33	0.497	75.23	0.102	52.03	0.073	67.95	0.330	74.46	0.348	66.00	0.142
Female	87.50		54.00		28.88		56.25		62.63		57.54	
Age at the interview												
≤60 years	85.44	0.482	75.06	0.617	58.25	0.134	70.31	0.489	75.13	0.686	67.04	0.413
>60 years	79.55		69.84		42.84		63.71		71.06		63.28	
Formal education												
Up to 8 years	82.08	0.884	79.50	0.071	53.73	0.199	66.35	0.924	75.73	0.441	66.12	0.426
Over 8 years	80.90		61.86		41.10		65.48		68.38		62.62	
Ethnicity												
White	81.59	0.992	68.93	0.490	51.59	0.336	68.10	0.547	73.66	0.747	65.74	0.492
Black and Brown skinned	81.50		75.94		42.44		62.50		70.50		62.65	
Marital status												
With a spouse	76.00	0.075	74.68	0.530	38.48	0.045*	61.0	0.208	72.12	0.970	62.20	0.248
Without a spouse	90.00		68.30		58.25		72.50		71.75		67.47	
Clinical Stage												
III	83.38	0.836	70.75	0.937	49.88	0.870	78.13	0.220	79.25	0.516	71.04	0.176
IV	81.18		71.79		47.72		63.46		71.05		63.23	
Site		0.473		0.424		0.014*		0.906		0.740		0.121
Tongue	79.31		74.72		57.31		66.38		73.69		67.20	
GIngival margin	85.17		66.61		33.22		65.28		70.44		60.31	
Time of surgery/interview												
≤2 years	75.96	0.129	60.00	0.009*	49.16	0.816	59.00	0.097	61.48	0.011*	60.01	0.023*
>2 years	87.91		84.82		46.86		73.86		84.91		69.73	
Reconstruction												
Myocutaneous flap/no	81.50	0.932	77.78	0.393	51.72	0.632	68.06	0.860	72.33	0.472	67.95	0.464
Free flap	79.46		74.38		51.16		67.96		64.31		63.06	

*Corresponds to values with clinical significance (a difference of 7 points in score and p< 0.05).

domain (p=0.045) and clinically associated with the appearance and shoulder domains. Patients in clinical stage III presented better clinical scores than those in stage IV, showing statistical significance in the field of recreation (p=0.034). Patients with over two years of difference between the time of the interview and the time of the surgery presented better quality of life scores than those with less than 2 years of difference, with statistical significance for the domains of pain (p=0.032), recreation (p=0.034), speech (p=0.046), taste (p=0.009), anxiety (p=0.011), and composite score (p=0.023). The average from the scores of the UW-QOL questionnaire domains, by clinical and demographic variables of patients with advanced malignant neoplasms in the oral cavity, can be found in Table 3.

The only variable of the composite quality of life score included in the linear regression model was time between surgery and interview, with those with under two years presenting a lower composite score (coefficient of -9.73, 95% CI -18.016 -1.435, p=0.023). The model expressed a score of 9% for quality of life in that population (r2=0.091).

DISCUSSION

Advanced malignant neoplasms of the head and neck and its extensive treatments, associated with adjuvant radiotherapy, may result in significant dysfunction, such as in chewing, swallowing and speech. Our results show that these individuals have an epidemiological profile similar to those present in other Brazilian studies.[6] The average age of the population studied was over 50 years, and most individuals were men, with low levels of formal education, white, who lived with their spouses, presented clinical stage level IV, and underwent radiotherapy.

Still regarding the studies by Vartanian and Kowalski[6], advanced stage patients, with over 5 years of survival, reported good quality of life, a result compatible with the one found in this study. Patients with survival over 12 months who took the questionnaire presented higher scores. This finding can be due to a greater time to adapt to the repercussions of treatment.

Studies with positive results for quality of life in patients who underwent mandible reconstruction with fibula were conducted in patients with benign disease, for which treatment required resection with less damage to the soft tissues[3], unlike the cases in this study.

As for the global parts of the questionnaire, 47.2% of patients considered their quality of life to be good overall, and 57.8% considered their health to be the same or better than it was before the treatment. These results differ from those found by Vartanian and Kowalski[6], in which 59.3% of the patients considered their quality of life to be from good to excellent ,and 74.0% to be the same or better. This study included a broader variety of sites and stages of the disease, which might have affected the results.

As for the comparative questions, it was found that quality of life was the same (31.9%) when compared to a time prior to the disease or slightly better (38.3%) after the treatment. In general, patients considered their quality of life to be from average (23.4%) to good (48.9%).

There is no data indicating if cultural aspects influenced these results. However, according to Vartanian and Kowalski[6], patients from developing countries and with difficult access to healthcare are usually more grateful to doctors and try not to disappoint them, despite the assured confidentiality. That might explain the high level of satisfaction present in the global questions.

This study followed the guidelines of Weymuller et al.[7] for researches in a single institution, with the recommendation of cross-sectional studies in which the survivors can be assessed in a single application of the questionnaire and also in a cohort that represents the majority of cases in the institution.

During the screening of eligible cases, out of the total 183 oral cancer patients, 47 were alive after less than five years. In a similar study[8]. it was found that even with surgical treatment and adjuvant radiotherapy, only the minority of patients were cured and less than 30% survived after five years. It was not possible to include more patients, which might have had a negative influence on the results. However, a small number was also reported in an American retrospective study over 25 years that found only 26 patients alive, out of which only 26 could be assessed.[9]

No link was found between any of the UW-QOL domains and the type of reconstruction undergone by the advanced oral cancer patients, contrary to what was initially expected. The impossibility of bone reconstruction generates the greater functional and aesthetic defect. The sample size might have affected these results, a difficulty also reported by similar studies.[9]

According to the findings of Vartanian and Kowalski[10], patients under 60 years old reported worse scores and increased complaints about pain when compared to those younger, which was inconsistent to the finding of another Spanish study, in which individuals under 60 years old had better results in the early stages group of patients.[11] Stage III individuals showed better scores than those in stage IV, in line with the findings of the same study by López-Jornet et al.[11] In the recreation domain, stage IV patients presented greater difficulties in leaving the house and having contact due to greater aesthetic-functional sequelae.

In view of the results discussed, it is evident that the incorporation of quality of life analysis in clinical practice is of great relevance, for it allows for the assessment of treatments and its sequelae. Its adoption in everyday practice and the presence of a qualified and cohesive multidisciplinary team allows for the thorough care of patients and their family. Furthermore, the knowledge of the most affected domains makes t possible to have a proper approach to the needs of the patients, allowing them a better quality of life.

The fact that the study was conducted using a homogeneous population from a single institution with data collected by a single researcher increases its internal validity since it minimizes selection and measurement biases of both outcome and independent variables. However, due to the characteristics previously mentioned, the applicability of these data in other populations with a different profile is arguable. Nonetheless, our results were similar to those found in literature.[12]

A limitation of the cross-sectional study is its use of the surviving population, for its results may not be representative of the entire population subject to the treatment. Even though the measurement of quality of life after the treatment can be considered limiting, for these individuals could present a lower score at the moment of diagnosis, the author who validated the questionnaire affirms that this is the best way to apply it in cross-sectional studies.[7]

In conclusion, there was no statistically significant difference among domains of quality of life between both groups studied (with bone reconstruction versus without bone reconstruction). Patients interviewed at least two years after the treatment presented higher scores on quality of life. Our results were able to describe general aspects of quality of life in this population, which can be used to plan and assess strategies used in patients who undergo oral cancer treatment.

RESUMO

INTRODUÇÃO: *As neoplasias malignas de cabeça e pescoço, pela própria localização anatômica, podem acarretar alterações significativas em funções vitais relacionadas à alimentação, comunicação e interação social dos indivíduos afetados.*

OBJETIVO: *Analisar a qualidade de vida dos pacientes com neoplasias malignas avançadas de cavidade oral, submetidos a operações radicais com intenção curativa.*

MATERIAL E MÉTODOS: *47 pacientes portadores de carcinoma espinocelular de cavidade oral, em estádios III e IV, foram submetidos ao tratamento cirúrgico com mandibulectomia segmentar e radioterapia complementar. Os pacientes foram submetidos ao teste de qualidade de vida após o tempo mínimo de seis meses do tratamento cirúrgico.*

RESULTADOS: *Dos 183 pacientes, com apenas 47 (25,7%) foi possível a realização da entrevista, compondo estes a amostra para o estudo. A maioria dos pacientes do grupo selecionado era do sexo masculino, total de 39 homens (82,9%). A idade média foi de 64,4 anos. A maioria dos pacientes apresentava estadiamento clínico IV (83%), sendo submetidos à radioterapia adjuvante (95,4%). A média do escore obtido após a avaliação dos questionários foi de 64,6. Os piores escores foram encontrados nos quesitos deglutição e mastigação.*

CONCLUSÃO: *Não houve diferenças estatisticamente significativas nos domínios de qualidade de vida entre os dois grupos estudados (com reconstrução óssea versus sem reconstrução óssea). Pacientes entrevistados dois anos ou mais após o tratamento apresentaram escores superiores (p=0,02).*

PALAVRAS-CHAVE: *Qualidade de vida. Neoplasias bucais. Reconstrução mandibular. Carcinoma de células escamosas. Transplante ósseo. Osteotomia mandibular.*

REFERENCES

1. Nemoto RP, Victorino AA, Pessoa GB, Cunha LL, Silva JA, Kanda JL, et al. Oral cancer preventive campaigns: are we reaching the real target? Braz J Otorhinolaryngol. 2015;81(1):44-9.
2. Rigoni L, Bruhn RF, De Cicco R, Kanda JL, Matos LL. Quality of life impairment in patients with head and neck cancer and their caregivers: a comparative study. Braz J Otorhinolaryngol. 2016;82(6):680-6.
3. Li X, Zhu K, Liu F, Li H. Assessment of quality of life in giant ameloblastoma adolescent patients who have had mandible defects reconstructed with a free fibula flap. World J Surg Oncol. 2014;12:201.
4. Lin CS, Oliveira Santos AB, Silva EL, Matos LL, Moyses RA, Kulcsar MA, et al. Tumor volume as an independent predictive factor of worse survival in patients with oral cavity squamous cell carcinoma. Head Neck. 2017;39(5):960-4.

5. Vartanian JG, Carvalho AL, Furia CLB, Castro Jr G, Rocha CN, Sinitcovisky IML, et al. Questionários para a avaliação de Qualidade de Vida em pacientes com câncer de cabeça e pescoço validados no Brasil. Rev Bras Cir Cabeça Pescoço. 2007;36(2):108-15.

6. Vartanian JG, Kowalski LP. Acceptance of major surgical procedures and quality of life among long-term survivors of advanced head and neck cancer. Arch Otolaryngol Head Neck Surg. 2009;135(4):376-9.

7. Weymuller EA, Yueh B, Deleyiannis FW, Kuntz AL, Alsarraf R, Coltrera MD. Quality of life in patients with head and neck cancer: lessons learned from 549 prospectively evaluated patients. Arch Otolaryngol Head Neck Surg. 2000;126(3):329-35.

8. Sanabria A, Carvalho AL, Vartanian JG, Magrin J, Ikeda MK, Kowalski LP. Factors that influence treatment decision in older patients with resectable head and neck cancer. Laryngoscope. 2007;117(5):835-40.

9. Thomas L, Moore EJ, Olsen KD, Kasperbauer JL. Long-term quality of life in young adults treated for oral cavity squamous cell cancer. Ann Otol Rhinol Laryngol. 2012;121(6):395-401.

10. Vartanian JG, Carvalho AL, de Araújo Filho MJ, Junior MH, Magrin J, Kowalski LP. Predictive factors and distribution of lymph node metastasis in lip cancer patients and their implications on the treatment of the neck. Oral Oncol. 2004;40(2):223-7.

11. López-Jornet P, Camacho-Alonso F, López-Tortosa J, Palazon Tovar T, Rodríguez-Gonzales MA. Assessing quality of life in patients with head and neck cancer in Spain by means of EORTC QLQ-C30 and QLQ-H&N35. J Craniomaxillofac Surg. 2012;40(7):614-20.

12. Silveira A, Gonçalves J, Sequeira T, Ribeiro C, Lopes C, Monteiro E, et al. Head and neck cancer: health related quality of life assessment considering clinical and epidemiological perspectives. Rev Bras Epidemiol. 2012;15(1):38-48.

ORIGINAL ARTICLE

Analysis of survival in patients with brain metastases treated surgically: Impact of age, gender, oncologic status, chemotherapy, radiotherapy, number and localization of lesions, and primary cancer site

José Marcus Rotta[1]
Daniella Brito Rodrigues[1]
Juliete Melo Diniz[1]
Bianca Medeiros de Abreu[1]
Fernanda Kamimura[1]
Ulysses Oliveira Sousa[1]
Ricardo Vieira Botelho[1]
Matheus Fernandes de Oliveira[1]

1. Neurosurgery Service of the Public Servant's Hospital of the State of São Paulo (HSPE-SP), São Paulo/SP, Brasil

http://dx.doi.org/10.1590/1806-9282.64.08.717

SUMMARY

OBJECTIVE: *To evaluate the survival of patients with brain metastases treated surgically according to the potentially involved factors.*

METHODS: *71 patients treated surgically were analyzed with the diagnosis of brain metastases during the period from January 2011 to November 2014, totaling 47 months of follow-up. The Kaplan-Meier curve method was used for survival analysis. Results: We evaluated 71 patients with brain metastases treated surgically, 44 female and 27 male, mean age of 60.1 years. According to the Karnofsky scale, 44 patients were classified with Karnofsky greater than or equal to 70 and 27 patients with Karnofsky inferior to 70. Lung was the primary site most commonly found. Death occurred in twenty patients (28%), and lung tumors were responsible for the most deaths. Twelve patients had supra and infratentorial metastases, fifty-nine only had supratentorial lesions, and lesions were multiple in twenty-eight patients and single in forty-three. Thirty patients were also treated with chemotherapy, eighteen with chemotherapy and radiation therapy, while only three received just radiotherapy. Survival analysis by Kaplan-Meier curve showed no statistical significance regarding age, histological type, location, Karnofsky, chemotherapy, and radiotherapy. There was statistical significance regarding gender.*

CONCLUSION: *The factors analyzed did not change survival rates, except for gender. This fact may probably be explained due to the systemic and diffuse behavior of cancer.*

KEYWORDS: *Neoplasm metastasis. Survival analysis. Neoplasms. Prognosis.*

INTRODUCTION

Brain metastases are the most common type of intracranial tumors in adults, accounting for more than half of all cases. Typically, they are related to cancer stage but can also be the first manifestation of an undiagnosed malignancy. Brain metastases occur in 10 to 30% of adults with disseminated tumors[1-15]. The presence of brain metastases implies an adverse shift in the course of the primary systemic disease due to its impact on survival and quality of life and to the development of potentially disabling symptoms[1-10].

DATE OF SUBMISSION: 05-Dec-2017
DATE OF ACCEPTANCE: 07-Jan-2018
CORRESPONDING AUTHOR: Matheus Fernandes de Oliveira
Address: Rua Loefgren, 700, apt, Vila Clementino,
São Paulo/SP, Brasil – 04040-000
E-mail: mafernoliv@yahoo.com.br

josemarcusrotta@gmail.com
danibrito@gmail.com,
julietemelodiniz@yahoo.com.br
biancaabreu@yahoo.com.br,
fernandakamimura@gmail.com,
ulyssesguimar@yahoo.com.br
bitbot@uol.com.br

Surgical resection of brain metastases is often indicated for the local control of cancer and may have impacts on the symptoms and course of the disease[10-15]. Considering the importance of brain metastases and their impact on morbidity and mortality in patients with cancer, this study was designed to evaluate the survival of patients with brain metastases treated surgically and elucidate potential factors involved in progression.

METHODS

The study sample consisted of patients with cerebral metastasis consecutively admitted to Public Servant's Hospital of the State of São Paulo (HSPE) from January 2011 to November 2014. Patients enrolled in the study were then followed during treatment.

The study was observational and retrospective; all patients who received surgical treatment for a diagnosis of brain metastases during the period of interest were analyzed.

Inclusion criteria

Patients undergoing surgery as the first treatment strategy for brain metastases from systemic tumors were eligible for inclusion.

Criteria for surgery

Criteria used to indicate surgery for brain metastases were: in patients with single lesions, the presence of symptoms or lesion size >2 cm; in patients with multiple lesions, the presence of symptoms and larger lesions. Patients in palliative care and/or with very low functional status (Karnofsky score <40) were not considered candidates for surgery.

Survival analysis

Survival time was extracted from the HSPE registry of patient data. In questionable cases or when information was not available in the registry, direct telephone contact with family members was established.

Analyzed factors

The factors considered potentially related to survival were age, gender, histology, Karnofsky score, preoperative location (supratentorial versus infratentorial), number of lesions (single versus multiple), and adjuvant chemotherapy and radiotherapy (RT).

For the analysis of survival in relation to a general condition, patients were divided into two groups based on Karnofsky score (<70 and ≥ 70).

Statistical analysis

Numerical data were presented as a mean and standard deviation. Relative frequencies were described as percentages. Kaplan–Meier curves were plotted for evaluation of survival, and the log-rank test was used for univariate analysis. Multivariate analysis was performed with Cox regression. The level of significance was set at $p<0.05$. All analyses were carried out in SPSS 20.0.

RESULTS

Demographic data

We evaluated 71 patients (44 female and 27 male), with a mean age of 60.1 ± 10.2 years (range, 40 to 85 years). The mean age was 58.8 ± 9.8 years for women and 62.2 ± 11.9 years for men, with no significant difference between both groups.

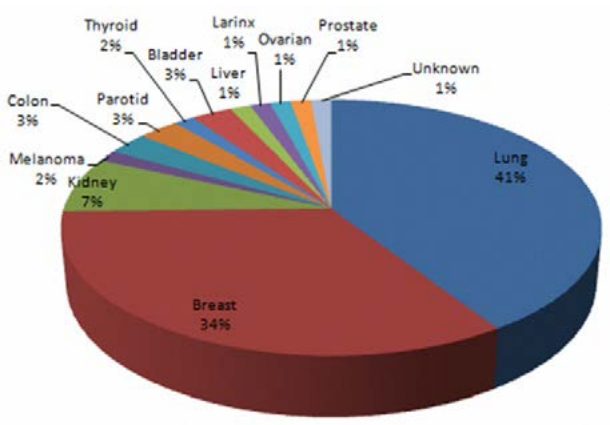
Clinical status

Regarding functional status, 44 patients were assigned a Karnofsky score greater than or equal to 70 (62%), while 27 patients had a Karnofsky score below 70 (38%).

Primary site of the tumor

The most common primary site for cancer was the lung (n = 29), followed by breast (n = 24), kidney (n = 5), colon (n = 2), bladder (n = 2), and parotid gland (n = 2). There was one case each of melanoma, liver, laryngeal, thyroid, ovarian, and prostate cancers, and one cancer of unknown primary site (Figure 1).

FIGURE 1. TUMOR TYPES.



Follow-up

The mean length of follow-up was 30.5 ± 13.62 months (range, 1 to 47 months).

Mortality

At the end of the follow-up, 20 patients had died (28%). Lung tumors accounted for most deaths (n = 11), followed by breast (n = 3) and kidney tumors (n = 3). One parotid tumor, one prostate tumor, and one cancer of unknown primary site were responsible for the other three deaths.

Site and number of lesions

Twelve patients had both supra- and infratentorial metastases (17%); the remaining 59 (83%) had supratentorial lesions only. No patients presented exclusively infratentorial lesions. Lesions were isolated in 43 patients (60.6%) and multiple in 28 (39.4%).

TABLE 1. SURVIVAL ACCORDING TO ANALYZED PARAMETER.

Parameter	Subgroup	Number of patients	Survival (months)	p
Age	< 60	37	18.9	>0.05
	= or > 60	34	14.8	
Gender	Female	44	19.2	<0.05*
	Male	27	12.9	
Karnofsky	<70	27	13.4	>0.05
	= or > 70	44	18.3	
Chemotherapy	Yes	30	14.3	>0.05
	No	41	18.6	
Radiotherapy	Yes	22	14.5	>0.05
	No	49	17.7	
Number of lesions	Single	42	16.7	>0.05
	Multiple	29	16.8	
Lesion site	Supratentorial	59	19.9	>0.05
	Supra and infratentorial	12	16.1	
Tumor site	Lung	29	17.7	>0.05
	Breast	24	18.6	
	Other	18	12.2	

*: statistically significant when p< 0.05.

Adjuvant treatment

Thirteen patients received adjuvant chemotherapy alone, 18 received both chemotherapy and radiotherapy, and four received radiotherapy alone.

UNIVARIATE ANALYSIS (TABLE 1)

Survival × Age

Patients were divided into two groups: < 60 years (n = 37) and ≥ 60 years (n = 34). The average survival after diagnosis of brain metastases was 18.9 months in patients aged < 60 years and 14.8 months in those aged ≥ 60. This difference was not statistically significant (p = 0.16).

Survival × Gender

The average survival after diagnosis of brain metastases was 19.2 months in women and 12.9 in men, a statistically significant difference (p = 0.008) (Figure 2).

Survival × Karnofsky score

Patients were divided into two groups: Karnofsky score < 70 (n = 27) and ≥ 70 (n = 44). The mean survival after diagnosis of brain metastasis was 13.44 months in patients with a Karnofsky score < 70 and 18.34 months in those with a score ≥ 70. The difference was not statistically significant (p = 0.84).

Survival × Chemotherapy

Median survival after diagnosis was 14.36 months in patients who underwent chemotherapy (n = 31) and 18.62 months in those who did not (n = 40). The difference was not significant (p = 0.18).

Survival × Radiotherapy

Median survival after diagnosis was 14.57 months in patients who received radiotherapy (n = 22) and 17.75 months in those who did not (n = 49). Again, the difference was not significant (p = 0.14).

Survival × Number of lesions

Mean survival after diagnosis of intracranial metastasis was 16.85 months in patients with multiple metastases (n = 29) and 16.76 months in those with single metastasis (n = 42). There was no statistical significance (p = 0.91).

Survival × Lesion site

Mean survival after diagnosis of metastasis was

19.9 months in patients with supratentorial metastases (n = 59) and 16.15 months in patients with both supratentorial and infratentorial lesions (n = 12). The difference was not significant (p = 0.44).

Survival × Primary cancer site

Median survival after diagnosis of brain metastases was 17.7 months in patients with lung cancer (n = 29), 18.6 months in patients with breast cancer (n = 24), and 12.2 months in patients with other primary sites (n = 18). The differences were not significant (p = 0.34).

Multivariate analysis

Multivariate analysis confirmed the results of the univariate analysis. The only variable with a significant impact on the survival curve was gender (p=0.02).

DISCUSSION

In adults, the primary tumors most often responsible for brain metastases are lung, breast, kidney, colorectal, and melanoma[1,4]. Nevertheless, up to 10% of metastases have an unknown primary source[2,3].

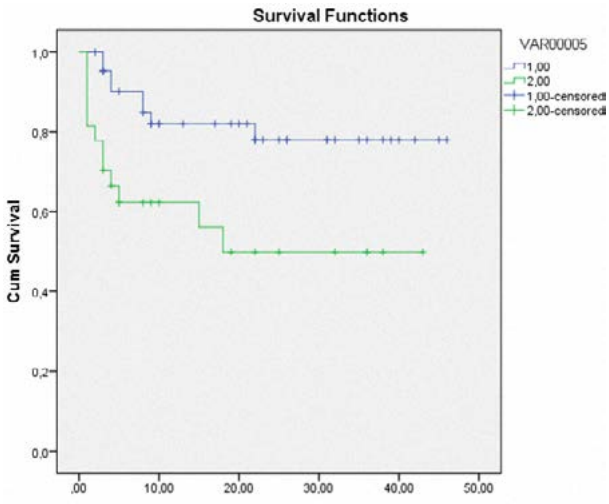
Metastatic tumors are a heterogeneous group with potentially varied treatment responses and survival rates. However, the presence of brain metastasis is understood to be indicative of poor prognosis and is considered the end stage of systemic malignancy. This is true not only because of the impact of such metastases on the central nervous system and their potentially disabling symptoms but also due to a change in the biological behavior of the tumor, suggesting an aggressive state of invasiveness and spread, including a higher risk of metastases to other organs[1-10].

Thus, it is important to consider various factors affecting the prognosis of these patients prior to therapeutic decision making[1-14]. A review showed that the benefit of surgical resection is to increase local recurrence-free time, with no impact on the duration of survival compared to non-surgical treatment. Previous studies have shown four factors associated with improved survival: Karnofsky score of 70 or higher, primary tumor type, age < 60 years, and metastasis limited to the brain. Patients with all favorable characteristics might have a survival prognosis of 200 days in 52% of cases, whereas those without any of the favorable factors had an expected survival of 1.8 months[1-8].

Neurosurgical resection of such lesions is associated with a mean survival of 11 months (range, 6 to 16 months) and 1-year survival in 42% of patients (range, 22 to 63%). Additionally, Patchell et al.[2] reported a median survival of 16 months after surgery and RT compared to only 6 months after RT alone[7-10]. However, proper selection of candidates for surgical resection is crucial. Some factors have been proposed as criteria for a surgical indication: imaging pattern (number, size, and site of lesions), histological type, radiosensitivity, and, especially, the stage of systemic disease[10-15].

In our sample, lung and breast cancers were those most commonly implicated in the pathogenesis of metastatic tumors. This is consistent with the current literature[1-13].

FIGURE 2. SURVIVAL BY GENDER.



INFERENCES

Our study revealed that survival after surgical resection of brain metastases is highly variable, with an average of 16.6 months, ranging from less than 1 month to 46 months. Upon comparing survival curves according to the potential factors involved, the only variable associated with a significant difference was patient gender. None of the other factors (age, Karnofsky score, chemotherapy, radiotherapy, number of lesions, lesion location, and primary site) were associated with a difference in survival.

However, comparison of survival in patients with Karnofsky < 70 (18.34 months) versus > 70 (13.44 months) shows that the survival rate was higher in

patients with a better clinical condition. Similarly, comparison of survival among patients aged < 60 years (18.4 months) versus those aged > 60 (14.8 months) shows that the survival rate was higher in younger patients. These findings suggest that patients with a better clinical condition at baseline also have a better prognosis, which may have clinical, but not statistical, significance.

In our sample, all patients with infratentorial lesions had supratentorial tumors as well. Overall, patients with infratentorial lesions had worse survival than those with supratentorial lesions, but the difference was not significant. These findings may suggest infratentorial tumors are associated with greater odds of multiple lesions, hydrocephalus, and increased risk of intracranial hypertension and death.

We did not disclose any significant impact of primary tumor site on survival time. This clearly suggests that, although primary tumors may behave differently due to distinct biological features in their original target organs, all share a similar aggressiveness curve once they become emboligenic and metastatic.

Predictably, the resection of brain metastases can treat brain diseases but does not alter the progression of the disease outside the nervous system. Failure to identify factors associated with prognosis suggests that the extent of the primary disease has a greater impact on survival than the assessed factors. Thus, resection of cerebral metastases may change acute survival curves due to the control of intracranial hypertension and improve quality of life by removing symptomatic masses. Nevertheless, systemic disease progression will be the determinant death cause. In other words, a patient with brain metastases should not die because of brain lesions if properly treated but will probably die as a result of the natural course of cancer itself.

The identification of gender as a factor related to survival probably reflects intrinsic differences between genders, such as hormonal aspects, the prevalence of specific cancers, and habits related to risk factors, such as smoking, alcoholism, and delay in diagnosis and initiation of cancer treatment. However, as these factors were not specifically studied, we can only conjecture as to their potential role.

Although our study is not comparative, the overall survival of the patients (16.6 months) suggests that neurosurgical resection of brain metastasis should continue to be performed.

LIMITATIONS

Interpretation of our results is limited by the retrospective nature of the study, nonrandomized design, and analysis restricted to surgical patients, which introduces selection bias. Data collection and analysis biases are also a concern. Another relevant limitation of our study was the small number of patients who received adjuvant therapy (13 receiving chemotherapy alone, four receiving RT alone, and 18 receiving both RT and chemotherapy). Although we do not know the precise reasons for this low adherence to adjuvant therapy, we believe it is due to loss of adequate oncology follow-up and, mainly, the unavailability of timely adjuvant treatment within the Brazilian public health care system.

Our study did not include an evaluation of surgical complications, which may impair but not invalidate our findings. Additionally, scales of postoperative life quality were not applied or described. We understand that life quality is as important as survival. However, our analyses were restricted to survival.

The lack of statistical significance may be explained by the fact that the analyzed factors do not capture the systemic nature of malignancy. Systemic disease may actually have as much or more impact on survival as cerebral metastatic disease.

CONCLUSION

Patients with cerebral metastases have approximately 16 months of survival after surgery. Survival is mainly defined by the systemic status of the disease and thus, except for gender, no evaluated variable impacted in survival curves.

Ethical statement:

- Funding: No funding source was used in this paper.
- Conflict of Interest: Authors declare no conflicts of interest
- Ethical approval: The current study was approved by HSPE Ethics and Research Committee.
- Informed consent: If necessary, all informed consent are available.

RESUMO

OBJETIVO: *Avaliar a sobrevivência de pacientes com metástases cerebrais tratados cirurgicamente de acordo com os fatores potencialmente envolvidos. Métodos: 71 pacientes tratados cirurgicamente foram analisados com o diagnóstico de metástases cerebrais durante o período de janeiro de 2011 a novembro de 2014, totalizando 47 meses de seguimento. A curva de Kaplan-Meier foi utilizada para análise de sobrevivência. Resultados: Avaliamos 71 pacientes com metástases cerebrais atendidas cirurgicamente, 44 do sexo feminino e 27 do sexo masculino, idade média de 60,1 anos. De acordo com a escala de Karnofsky, 44 pacientes foram classificados com Karnofsky maior ou igual a 70 e 27 pacientes com Karnofsky com menos de 70. O pulmão era o local mais comum. A morte ocorreu em 20 pacientes (28%) e os tumores pulmonares são responsáveis pela maioria das mortes. Doze pacientes apresentavam metástases supra e infratentoriais, 59 apresentavam apenas lesões supratentoriais, e as lesões eram múltiplas em 28 pacientes e isoladas em 43. Trinta pacientes também foram tratados com quimioterapia, 18 foram tratados com quimioterapia e radioterapia, enquanto que apenas três receberam apenas radioterapia. A análise de sobrevivência pela curva de Kaplan-Meier não mostrou significância estatística de acordo com a idade, tipo histológico, localização, Karnofsky, quimioterapia e radioterapia. Houve significância estatística em relação ao gênero. Conclusão: Os fatores analisados não alteraram a sobrevivência, exceto o gênero. Este fato provavelmente pode ser explicado devido ao comportamento sistêmico e difuso do câncer.*

PALAVRAS-CHAVE: *Metástase neoplásica. Análise de sobrevida. Neoplasias. Prognóstico.*

REFERENCES

1. Muacevic A, Wowra B, Siefert A, Tonn JC, Steiger HJ, Kreth FW. Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. J Neurooncol. 2008;87(3):299-307.
2. Patchell RA, Regine WF, Loeffler JS, Sawaya R, Andrews DW, Chin LS. Radiosurgery plus whole-brain radiation therapy for brain metastases. JAMA. 2006;296(17):2089-90.
3. Suki D, Abouassi H, Patel AJ, Sawaya R, Weinberg JS, Groves MD. Comparative risk of leptomeningeal disease after resection or stereotactic radiosurgery for solid tumor metastasis to the posterior fossa. J Neurosurg. 2008;108(2):248-57.
4. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol. 1993;33(6):583-90.
5. Bertolini F, Spallanzani A, Fontana A, Depenni R, Luppi G. Brain metastases: an overview. CNS Oncol. 2015;4(1):37-46.
6. Venur VA, Ahluwalia MS. Prognostic scores for brain metastasis patients: use in clinical practice and trial design. Chin Clin Oncol. 2015;4(2):18.
7. Gorovets D, Rava P, Ebner DK, Tybor DJ, Cielo D, Puthawala Y, et al. Predictors for long-term survival free from whole brain radiation therapy in patients treated with radiosurgery for limited brain metastases. Front Oncol. 2015;5:110.
8. Nieder C, Mehta MP. Prognostic indices for brain metastases: usefulness and challenges. Radiat Oncol. 2009;4:10.
9. Tevlin R, Larkin JO, Hyland JM, O'Connell PR, Winter DC. Brain metastasis from colorectal carcinoma: a single cancer centre experience. Ir J Med Sci. 2015;184(3):673-5.
10. Shen Q, Sahin AA, Hess KR, Suki D, Aldape KD, Sawaya R, et al. Breast cancer with brain metastases: clinicopathologic features, survival, and paired biomarker analysis. Oncologist. 2015;20(5):466-73.
11. Li Z, Zhang X, Jiang X, Guo C, Sai K, Yang Q, et al. Outcome of surgical resection for brain metastases and radical treatment of the primary tumor in Chinese non-small-cell lung cancer patients. Onco Targets Ther. 2015;8:855-60.
12. Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol. 2011;29(2):134-41.
13. Willett A, Wilkinson JB, Shah C, Mehta MP. Management of solitary and multiple brain metastases from breast cancer. Indian J Med Paediatr Oncol. 2015;36(2):87-93.
14. Soon YY, Tham IW, Lim KH, Koh WY, Lu JJ. Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. Cochrane Database Syst Rev. 2014;(3):CD009454.
15. Arita H, Narita Y, Miyakita Y, Ohno M, Sumi M, Shibui S. Risk factors for early death after surgery in patients with brain metastases: re-evaluation of the indications for and role of surgery. J Neurooncol. 2014;116(1):145-52.

ORIGINAL ARTICLE

Diagnosis and management of systemic hypertension due to renovascular and aortic stenosis in patients with Williams-Beuren syndrome

Erika Arai Furusawa, MD, PhD[1]
Camila Sanches Lanetzki Esposito, MD[1]
Rachel Sayuri Honjo, MD, PhD[2]
Lisa Suzuki, MD, PhD[3]
Gabriela Nunes Leal, PhD[3]
Chong Ae Kim, MD, PhD[2]
Benita Galassi Soares Schvartsman, MD, PhD[1]

1. Pediatric Nephrology Unit, Institute of Children, Hospital das Clínicas, Faculty of Medicine, University of São Paulo, São Paulo, Brasil.
2. Genetics Unit, Institute of Children, Hospital das Clínicas, Faculty of Medicine, University of São Paulo, São Paulo, Brasil.
3. Radiology Unit, Institute of Children, Hospital das Clínicas, Faculty of Medicine, University of São Paulo, São Paulo, Brasil.

http://dx.doi.org/10.1590/1806-9282.64.08.723

SUMMARY

AIM: *To describe the incidence, diagnosis, and management of systemic arterial hypertension related to renal artery stenosis in patients with Williams-Beuren syndrome.*

METHODS: *Sixty-five patients with Williams-Beuren syndrome were evaluated for hypertension. Enrolled patients underwent Doppler sonography of the renal arteries and Doppler echocardiography. Those with Doppler sonography-detected lesions or with normal Doppler sonography but severe hypertension underwent computed tomography or gadolinium-enhanced magnetic resonance angiography of the aorta and renal vessels. Patients needing vascular therapeutic intervention underwent conventional angiography.*

RESULTS: *Systemic arterial hypertension was diagnosed in 21/65 patients with Williams-Beuren syndrome (32%; 13 male) with a mean age of 13.9 years (5mo-20yrs). In 8/21 patients renovascular hypertension was detected. Angioplasty was unsuccessful in five patients with renal artery stenosis, requiring additional treatment. Doppler echocardiography showed cardiac abnormalities in 16/21 (76%) hypertensive patients.*

CONCLUSION: *Cardiac abnormalities and hypertension in patients with Williams-Beuren syndrome are common. Thus, thorough evaluation and follow-up are necessary to reduce cardiovascular risks and mortality of these patients*

KEYWORDS: *children, hypertension, renal artery stenosis, Williams-Beuren syndrome*

INTRODUCTION

Williams-Beuren syndrome (WBS) is a genetic disorder characterized by facial dysmorphisms, congenital heart defects, growth retardation, infantile hypercalcemia, renal and vascular abnormalities, and intellectual disability[1]. Clinical diagnosis is usually performed during childhood when the typical facial changes and cognitive profile become more apparent[1] (Figure 1). Genetic confirmation can be carried out using FISH[2] (fluorescence in situ hybridization) [or] MLPA[3] (multiplex ligation-dependent probe amplification), or microarray tests for identification of the causal microdeletion at 7q11.23. Urinary tract system abnormalities in WBS have been described in approximately 18% of patients[4,5,6] and include renal

DATE OF SUBMISSION: 18-Nov-2016
DATE OF ACCEPTANCE: 20-Nov-2016
CORRESPONDING AUTHOR: Erika Furusawa
Hospital das Clínicas, Av. Dr. Eneas de Carvalho Aguiar, 647
05403-000, Cerqueira Cesar, São Paulo, Brasil
E-mail: erika.f@hc.fm.usp.br

ectopia, hydronephrosis, renal agenesis or hypoplasia, vesicoureteral reflux, and voiding dysfunction. Nephrocalcinosis, proteinuria, and chronic renal failure have also been reported in some cases series[4,5,6]

Cardiovascular abnormalities are also quite common in patients with WBS and have been observed in more than 80% of cases[7,8]. Supravalvular aortic stenosis (SVAS) is the most frequent abnormality, with an estimated incidence of 64%[9,10]. Systemic arterial abnormalities include localized or diffuse narrowing of the thoracic or abdominal aorta, coronary, renal and other visceral arteries[11,12]. According to Lacolley et al.[13] vascular injury in patients with WBS may be associated with reduced elastin synthesis and increased proliferation of vascular smooth muscle cells.

Arterial hypertension arterial (SAH) is also observed with high prevalence in WBS[14]. In a minority of patients, renal artery stenosis, diffuse narrowing of the aorta, aortic coarctation or a combination of these abnormalities have been implicated[4,5]. Renal artery stenosis is usually found at the origin of the renal arteries[7] (Figure 2). Nonetheless, there are few reports about the origin and management of SAH in WBS, and the diagnosis is often not made.

This study aimed to describe the incidence of hypertension among 65 patients with WBS, as well as the diagnosis and management of hypertension due to renovascular or aortic stenosis.

METHODS

Sixty-five patients who were being treated from 1993 to 2010 at the Pediatric Nephrology and Genetics Units at the Institute of Children, Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo were included in this study. All patients were diagnosed with WBS based on clinical findings and had the presence of the 7q11.23 microdeletion confirmed by the FISH (2) or MLPA test (with a specific kit for WBS) [3].

Patients with blood pressure (BP) values at or above the 95th percentile for age, gender, and height confirmed on 3 different occasions[15] were included in the study and followed prospectively. Clinical and laboratory parameters such as the age of onset of hypertension, associated symptoms, baseline BP, fundus examination, microalbuminuria/creatinine[16] and calcium/creatinine ratio[17] in spot urine samples, estimated creatinine clearance[18], and serum ionized calcium were evaluated.

All enrolled patients were initially investigated by Doppler echocardiography(DE) and renal ultrasound (RU) with color-flow Doppler sonography of the renal arteries (DS). Those with findings of renal artery stenosis[19] or hypertension stage II[15] with a normal DS underwent computed tomographic angiography (CTA)[20] and/or gadolinium-enhanced magnetic resonance angiography (MRA) of the aorta and renal vessels[21]. Patients with unclear diagnosis by CTA and/or MRA or who required vascular therapeutic intervention (angioplasty) underwent conventional angiography (CA).

RESULTS

Of the 65 patients with WBS included in this study, 21 (32%; mean age of 13.9 years, range: 5 months to 20 years, 13 males) had hypertension and

FIGURE 1: Female patient, at age 9y4m, with facial characteristics of WBS: periorbital fullness, short nose, malar hypoplasia, long philtrum, and thick lips.

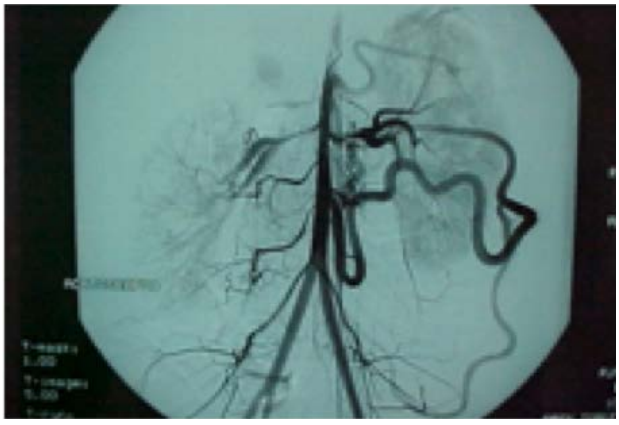


FIGURE 2: Digital subtraction angiography demonstrates discreet stenosis of the abdominal aorta anda severe stenosis of the left and right renal arteries. Also note several collateral arteries from the aorta on the left side

were submitted to further imaging studies. In this group, the mean age at WBS diagnosis was 5.2 years (ranging from 8 months to 12 years). All patients were asymptomatic, and hypertension was detected by active investigation during routine medical visits.

The evaluation of the renal arteries by DS was normal in 12/21 patients. Of these, five patients did not undergo a CTA or MRA scan because of a low clinical suspicion of hypertension due to renovascular or aortic stenosis. In these five patients, BP was adequately controlled with one or two medications, and none had secondary involvement of target organs during follow-up. Of the 12 patients with normal DS results, seven had persistent severe hypertension and were therefore submitted to further testing. Two of them had findings consistent with SAH associated with vascular stenosis, as detected by CTA and conventional arteriography (one had abdominal aorta narrowing, and the other had right renal artery stenosis), indicating that DS resulted in false negative results for these patients. The remaining five patients had normal CTA results.

Nine patients with DS suggesting renal artery stenosis were also submitted to CTA or MRA, and only six patients had vascular lesions confirmed by one of these methods. In three patients, the DS yielded false positive results. Of the 21 hypertensive patients, 16 underwent DS followed by complementary renal and aortic vascular investigation with CTA or MRA. The DS showed discordant results when compared with CTA or MRA in five of those patients (31%).

TABLE 1: RENAL AND AORTIC VASCULAR LESIONS IN 8/21 PATIENTS WITH WILLIAMS-BEUREN SYNDROME AND SYSTEMIC ARTERIAL HYPERTENSION.

	Patients	Type of lesion
Renal artery stenosis	6	unilateral 2 / bilateral 4*
Aorta coarctation	1	thoracic
Diffuse aorta narrowing	1	descendent and abdominal

*One patient also had aortic stenosis.

TABLE 2: ECHOCARDIOGRAPHIC FEATURES IN THE 21 WBS PATIENTS WITH SYSTEMIC ARTERIAL HYPERTENSION.

Echocardiographic features	n (%)
Supravalvular aortic stenosis	10 (47.6%)
Mitral valve prolapse	6 (28.6%)
Normal	5 (24%)

Hypertension associated with renal or aortic lesions was confirmed in 8/21 patients (Table 1), corresponding to 12% of the cases of WBS and 38% of patients with arterial hypertension. Renal artery stenosis was detected in six patients (28.6%), aortic coarctation in one patient, and diffuse narrowing of the aorta in another one. One patient with renal artery stenosis also had aortic stenosis.

Percutaneous transluminal balloon angioplasty was performed in five patients with renal artery stenosis, and it was unilateral in two and bilateral in three patients. In one patient with bilateral stenosis, a stent was placed in the renal arteries. All four patients who underwent angioplasty had treatment failure, and two of them required surgical intervention for stenosis correction. An aortorenal graft was performed in one patient. For another patient who had stenosis of both renal arteries and of the aorta, an iliac renal graft, as well as a graft of the descending aorta to the infrarenal abdominal aorta, were inserted. Two patients who did not undergo surgical intervention continued with conservative treatment with antihypertensive medications (amlodipine, carvedilol, hydralazine, and diuretic). Two patients with lesions of the aorta underwent surgical correction.

All patients underwent DE at the initial examination, and the alterations found are described in Table 2. SVAS was the most prevalent malformation (46%). Two patients underwent surgical correction of SVAS and had mitral valve regurgitation, eccentric left ventricular hypertrophy, and left ventricular systolic dysfunction. Three patients with mitral valve prolapse also had eccentric left ventricular hypertrophy and left ventricular systolic dysfunction.

Hypercalciuria was found in four patients, and hypercalcemia was diagnosed in one patient. Estimated creatinine clearance and albuminuria at the beginning of the study are shown in Table 3. One patient had hypertension after clinically presenting hemolytic uremic syndrome. Unilateral pyelocalyceal dilatation was observed in 2/21 patients submitted to renal sonography.

In this series, three patients died during follow-up due to heart failure: one patient with surgically corrected SVAS, one with both bilateral renal artery and aortic stenosis who had been submitted to angioplasty and iliac-renal and aortic grafts, and one with SVAS who died following heart transplantation.

TABLE 3: LABORATORY FEATURES (MEAN; RANGE) IN 21 PATIENTS WITH WBS AND ARTERIAL HYPERTENSION.

Laboratory features	Mean; range n
Serum ionized calcium Hypercalcemia[a]	1.23 (1.1-1.4) mmol/L 1
Urinary calcium Hypercalciuria[b]	0.15 (0-0.94) mg/mg creatinine 4
eGFR[c] CKD class II	118.23 (68-183) ml/min/1.73m^2 3
Albuminuria Microalbuminuria [d]	13.31 (3.55-36.79) mg/g creatinine 1

a serum ionized calcium >1.4mmol/L ; **b** calcium /creatinine ratio of random spot urine > 0.21 mg/mg [17]; **c** glomerular filtration rate estimated by serum creatinine[18] , **d** albumin/creatinine ratio of random urine >30 mg/g creatinine[16]; CKD: chronic kidney disease[22]

DISCUSSION

WBS is a congenital multisystem disease affecting the cardiovascular system, nervous system, and connective tissues that often involves hypertension, although the etiology of this symptom is not fully understood. Possible explanations include disorganization of the elastic layer and hypertrophy of smooth muscle cells and collagen fibers. As a result, diffuse or localized progressive narrowing of the arterial wall leads to increased arterial stiffness and sympathetic activity[23]. The prevalence of hypertension in WBS is widely variable[4,5,6,8,14] (5 to 70% in series including all ages and 5 to 46% in children). It can appear as early as infancy, but the average age of diagnosis varies from 6.5 to 38 years. In the present study, the incidence of hypertension was 32%, with a mean age of diagnosis of 13.9 years (range: 5 months to 20 years). As observed by other authors[8], we confirmed that patients with WBS are initially asymptomatic for hypertension, which highlights the need for health professionals to actively measure BP in these children in all routine visits.

In the present study, which included only children and adolescents, systemic arterial hypertension associated with vascular stenosis was observed in 8/21 hypertensive patients (38%), which included renal artery stenosis (28.6%) and aortic lesions. In the literature; the frequency of arterial stenosis is variable across case series (e.g., 2 to 70%)[5,8,12,14,22].

Renal DS is usually indicated as an initial diagnostic method for screening of arterial stenosis. It is a non-invasive, relatively inexpensive test that is available in most centers but may have a high rate of technical failure (approximately 30%)[24] because it is an operator-dependent method that also requires patients' cooperation. In our study, we found a similar failure rate for DS (31%). The main difficulties are the detection of intra-renal and bilateral stenosis, the presence of obesity and the inadequate preparation of the patient. In WBS, psychomotor and behavioral disorders (agitation and anxiety) may represent additional complications[1]. The sensitivity and specificity of DS in the detection of vascular stenosis have been shown to be between 60 and 98% and between 62 and 98%, respectively[24;25]. It should be emphasized that the current sample was too small, since we conducted further imaging tests only on severely hypertensive patients, hindering this type of analysis.

Computed tomographic angiography or MRA is commonly used in patients with WBS, but these techniques are not always available and require sedation or general anesthesia in children. MRA has high sensitivity (64-93%) and specificity (72-97%)[25,26] but may overestimate renal arterial lesions or underdiagnose intra-renal lesions. On the other hand, CTA requires the use of iodinated contrast and ionizing radiation. Most of our patients underwent CTA because of the limited availability of the MRA equipment at our unit. However, we were unable to establish the accuracy of these methods in our study, because only some of the patients who received MRA or CTA also underwent CA, which is considered the gold standard in the diagnosis of arterial stenosis[21].

Angioplasty was performed in five patients with stenosis of the renal artery but was unsuccessful, as observed by other authors[26,27]. Patients with aortic coarctation or stenosis were treated with surgical correction, with graft insertion in severe cases.

Other causes of hypertension such as hypercalcemia, renal scarring secondary to recurrent urinary infections, obesity, and essential hypertension may also be involved in hypertension in WBS. Hypercalcemia is frequently described in WBS [29] and occurred transiently in one patient in this study. It may manifest early or later in life, and patients should, therefore, be periodically monitored for possible calcium disturbances[1,6,9]. Broder et al.[30] found a higher incidence of hypertension in patients with infantile hypercalcemia, but to date, no direct links between hypertension and hypercalcemia have been established.

Congenital cardiovascular abnormalities are prevalent in patients with WBS and can occur in about 75% of cases[7,8]. SVAS is the most prevalent disease, and is also present in up to 75% of cases[9,14,30]. Mitral valve prolapse, bicuspid aortic valve, and coronary abnormalities have also been described[10,11,12]. SVAS

may be severe in up to 30% of patients[30], and surgical correction is necessary in such cases[27]. Consistent with earlier reports[10,12,23], the most common cardiovascular abnormality observed in our study was SVAS, and it was severe in two patients who required surgical intervention.

CONCLUSION

Hypertension is a common finding in children with WBS and should be tested and investigated routinely as early as possible in this population. We recommend that CTA or MRA be used whenever possible for cases of severe hypertension.

RESUMO

OBJETIVO: *Descrever a incidência, o diagnóstico e o tratamento da hipertensão arterial sistêmica relacionada com estenose da artéria renal em pacientes com síndrome de Williams-Beuren.*

MÉTODOS: *Sessenta e cinco pacientes com síndrome de Williams-Beuren foram avaliados quanto à presença de hipertensão. Os pacientes foram submetidos à ultrassonografia com Doppler das artérias renais e ecocardiograma Doppler. Aqueles com suspeita de hipertensão renovascular foram submetidos à tomografia computadorizada ou angiografia por ressonância magnética da aorta e vasos renais ou angiografia convencional.*

RESULTADOS: *A hipertensão arterial sistêmica foi diagnosticada em 21/65 pacientes com síndrome de Williams-Beuren (32%, 13 do sexo masculino), com idade média de 13,9 anos (5 meses-20 anos). Em 8/21 pacientes foi detectada a hipertensão renovascular. Angioplastia não teve sucesso em cinco pacientes com estenose da artéria renal, necessitando de tratamento adicional. O ecocardiograma Doppler mostrou anormalidades cardíacas em 16/21 (76%) pacientes hipertensos.*

CONCLUSÃO: *As anormalidades cardíacas e hipertensão arterial em pacientes com síndrome de Williams-Beuren são muito frequentes, sendo necessários uma avaliação minuciosa e seguimento para diminuir o risco cardiovascular e a morbimortalidade desses pacientes*

PALAVRAS-CHAVE: *Criança. Hipertensão. Estenose de artéria renal. Síndrome de Williams-Beuren.*

REFERENCES

1. American Academy of Pediatrics: Health care supervision for children with Williams syndrome. *Pediatrics* 2001; 107: 1192–204.
2. Borg I, Delhanty JD, Baraitser M. Detection of hemizygosity at the elastin locus by FISH analysis as a diagnostic test in both classical and atypical cases of Williams syndrome. *J Med Genet* 1995; 32: 692–696.
3. Dutra RL, Pieri Pde C, Teixeira AC, Honjo RS, Bertola DR, Kim CA. Detection of deletions at 7q11.23 in Williams– Beuren syndrome by polymorphic markers. *Clinics* (Sao Paulo) 2011; 66: 959–964.
4. Sugayama SM, Koch VH, Furusawa EA, Leone C, Kim CA. Renal and urinary findings in 20 patients with Williams–Beuren syndrome diagnosed by fluorescence in situ hybridization (FISH). *Rev Fac Med Hosp Clin Sao Paulo* 2004; 59: 266–272.
5. Pankau R, Partsch CJ, Winter M, Gosch A, Wessel A. Incidence and spectrum of renal abnormalities in Williams-Beurens syndrome. *Am J Med Genet* 1996; 63: 301–304.
6. Pober BR, Lacro RV, Rice C, Mandell V, Teele RL. Renal finding in 40 individuals with Williams syndrome. *Am J Med Genet* 1993; 46: 271–274.
7. Donnai D, Karmiloff-Smith A. Williams syndrome. From genotype through to the cognitive phenoype. *Am J Med Genet* 2000; 97: 164–171.
8. Bouchired K, Boyer O, Bonnet D, Brunelle F, Decramer S, Landthaler G et al. Clinical features and management of arterial hypertension in children with Williams–Beuren syndrome. *Nephrol Dial Transplant* 2010; 25: 434–438
9. Morris CA. Williams Syndrome. 1999 Apr 9 [Updated 2013 Jun 13]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1249/
10. Vernant P, Corone P, Rossignol AM, Bielman C. 120 cases of the Williams and Beuren syndrome. *Arch Mal Coer Vaiss* 1980; 73: 661–666.
11. Bernand Y, Didier D, Bozio A, Champsaur G, Renaud JC, Maurat JP. Coronary anomalies associated with the Williams–Beuren syndrome. Apros of 2 cases. *Arch Mal Coeur Vaiss* 1985; 78: 791–795.
12. Zalzstein E, Moes CA, Musewe NN, Freedom RM. Spectrum of cardiovascular anomalies Williams–Beuren syndrome. *Pediatr Cardiol* 1991; 12: 219–223.
13. Lacolley P, Boutouyrie P, Glukhova M, Daniel Lamaziere JM, Plouin PF, Bruneval P et al. Disruption of the elastin gene in adult Williams syndrome is accompanied by a paradoxical reduction in arterial stiffness. *Clin Sci* (Lond) 2002; 103: 21–29.
14. Honjo RS, Dutra RL, Furusawa EA, Zanardo EA, Costa LSA, Kulikowski LD, Bertola DR, Kim AE. Williams-beurens syndrome: A clinical study of 55 brazilian patients and the diagnosis use of MLPA. Biomed Res Int. 2015:903175
15. National High Blood Pressure Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004; 114: 555–576.
16. Karalliedde J, Vibert G. Microalbuminuria and cardiovascular risk. *Am J Hypertens* 2004; 17(10): 989-93
17. Butani L, Kalia A. Idiopathic hypercalciuria in children-how valid are the existing diagnostic criteria? Pediatric Nephrol 2004; 19: 577-582.
18. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976; 58:259-263.
19. Granata A, Fiorinin E, Andrulli S, Loggias F, Gallieni M, Sicurezza E et al. Doppler ultrasound and renal artery stenosis: An overview. *J Ultrasound* 2009; 12: 133–143.
20. Kurian J, Epelman M, Darge K, Meyers K, Nijs E, Hellinger JC. The role of CT angiography in the evaluation of pediatric renovascular hypertension. *Pediatr Radiol* 2013; 43: 490–501.
21. O'Neill WC, Bardelli M, Yevzlin AS. Imaging for renovascular disease. *Se-2min Nephrol* 2011; 31(3): 272-282.
22. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3:1-150.
23. Collins RT 2nd, Kaplan P, Somes GW, Rome JJ. Long-term outcomes of patients with cardiovascular abnormalities and Williams syndrome. *Am J Cardiol* 2010; 105: 874–878.
24. Wessel A, Pankau R, Kececioglu D, Ruschewski W, Bursch JH. Three decades of follow up of aortic and pulmonary vascular lesions in the Williams–Beuren syndrome. *Am J Med Genet* 1994; 52: 297–301.
25. Conkbayir I, Yucesoy C, Edguer T, Yanik B, Yasar AU, Hekimoglu B. Doppler sonography in renal artery stenosis. An evaluation of intrarenal and extrarenal imaging parameters. *Clin Imaging* 2003; 27: 256–260.
26. Rountas C, Vlychou M, Vassiou K, Liakopoulos V, Kapsalaki E, Koukoulis G

et al. Imaging modalities for renal artery stenosis in suspected renovascular hypertension: prospective intraindividual comparison of color Doppler US, CT angiography, GD–enhanced MR angiography, and digital subtraction angiography. *Ren Fail* 2007; 29: 295–302.

27. Actis Dato GM, La Torre M, Caimmi P, Actios Dato A Jr., Centofanti P, Ottino GM et al. Williams-Beuren syndrome. Long-term results of surgical treatments in six patients. *J Cardiovasc Surg* (Torino) 1997; 38: 125–129.

28. Kumada Y, Yasuda H, Sasaki E, Murakawa S, Mori Y, Hirose H. Reoperation for diffuse supravalvar aortic stenosis with Williams syndrome–extended path aortoplasty and extra–anatomic bypass from the ascending aorta to the descending aorta in a median sternotomy. *J Thorac Cardiovasc Surg* 1998; 46: 1061–1064.

29. Udwin O. A survey of adults with Williams syndrome and idiopathic infantile hypercalcaemia. *Dev Med Child Neurol* 1990; 32: 129–141.

30. Broder K, Reinhardt E, Ahern J, et al. Elevated ambulatory blood pressure in 20 subjects with Williams syndrome. *Am J Med Genet* 1999; 83: 356-360

ORIGINAL ARTICLE

Clinical, ultrasonographic and histological findings in varicose vein surgery

Moacir de Mello Porciunculla[1]
Dafne Braga Diamante Leiderman[2]
Rodrigo Altenfeder[1]
Celina Siqueira Barbosa Pereira[1]
Alexandre Fioranelli[1]
Nelson Wolosker [2,3]
Valter Castelli Junior[1]

1. Medical Science Faculty of the Santa Casa of São Paulo, São Paulo/SP, Brasil
2. Hospital Israelita Albert Einstein, São Paulo/SP, Brasil
3. Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo, São Paulo/SP, Brasil

http://dx.doi.org/10.1590/1806-9282.64.08.729

SUMMARY

OBJECTIVE: *This study aims to correlate the demographic data, different clinical degrees of chronic venous insufficiency (CEAP), ultrasound findings of saphenofemoral junction (SFJ) reflux, and anatomopathological findings of the proximal segment of the great saphenous vein (GSV) extracted from patients with primary chronic venous insufficiency (CVI) submitted to stripping of the great saphenous vein for the treatment of lower limb varicose.*

METHOD: *This is a prospective study of 84 patients (110 limbs) who were submitted to the stripping of the great saphenous vein for the treatment of varicose veins of the lower limbs, who were evaluated for CEAP clinical classification, the presence of reflux at the SFJ with Doppler ultrasonography, and histopathological changes. We study the relationship between the histopathological findings of the proximal GSV withdrawal of patients with CVI with a normal GSV control group from cadavers.*

RESULTS: *The mean age of the patients was higher in the advanced CEAPS categories when comparing C2 (46,1 years) with C4 (55,7 years) and C5-6(66 years), as well as C3 patients (50,6 years) with C5-6 patients. The normal GSV wall thickness (mean 839,7 micrometers) was significantly lower than in the saphenous varicose vein (mean 1609,7 micrometers). The correlational analysis of reflux in SFJ with clinical classification or histopathological finding did not show statistically significant findings.*

CONCLUSIONS: *The greater the age, the greater the clinical severity of the patients. The GSV wall is thicker in patients with lower limb varicose veins, but those histopathological changes are not correlated with the disease's clinical severity or reflux in the SFJ on a Doppler ultrasound.*

KEYWORDS: *Varicose veins. Ultrasonography. Histology.*

INTRODUCTION

Amongst chronic vascular diseases, the chronic venous insufficiency (CVI) of the lower limbs (LLS) is the most prevalent.[1] In Brazil, the prevalence ranges from 35% to 50% of the adult population.[2,3]As for socioeconomic impact, according to the Ministry of Health, CVI occupies the 14th position among the 50 top diseases to cause temporary or permanent leave from work, resulting in the payment of benefits to those ensured by the Brazilian social security system and still of working age.[4]

Histological performed on varicose veins have demonstrated contradictory findings of the structural changes in the smooth muscle of the venous wall.[5] Some researchers have reported an increase in that

DATE OF SUBMISSION: 120-Dec-2017
DATE OF ACCEPTANCE: 24-Dec-2017
CORRESPONDING AUTHOR: Dafne Braga Diamante Leiderman
Rua Dr. Cesário Motta Junior, 61 - Vila Buarque, São Paulo - SP, Brasil – 01221-020
Phone: (11) 21515423 – Fax: (11) 38855361
E-mail: dah.diamante@gmail.com

mmporc@uol.com.br
dah.diamante@gmail.com
roaltenfeder@terra.com.br
celina.pereira@yahoo.com.br
alexpa@terra.com.br
nwolosker@yahoo.com.br
vacastell@uol.com.br

muscle's quantity or activity[6], while others have observed reduced amounts of smooth muscle associated to the replacement of connective tissue.[7,8] It has also been suggested that the segregation of muscle cells by fibrous infiltration could interfere on the performance of those cells as a whole, resulting in alterations of the venous wall and, consequently, abnormal dilation.[9] However, other studies were not able to demonstrate any differences between varicose veins and normal veins regarding muscle content of the venous wall.[8]

In the Brazilian national literature, there are no studies on the correlation of histopathological findings relating to the trunk of the great saphenous vein (GSV) with anamnesis of physical examination data. There are also no sufficiently conclusive reports regarding the thickness alterations of the GSV wall on lighter or more advanced classes of the CEAP clinical classification to explain whether there is any difference in the response of the venous wall thickness in the comparison amongst patients who have undergone surgery multiple times.

OBJECTIVE

The objective of this study is to correlate demographic data and the different clinical levels of chronic venous insufficiency (CEAP) with ultrasound findings of reflux in the saphenofemoral junction and anatomopathological findings of the proximal segment of the great saphenous vein extracted from patients with chronic venous insufficiency who underwent stripping of the great saphenous vein to correct lower limb varicose.

METHODOLOGY

A total of 84 consecutive patients were prospectively studied with a mean age of 51.2 ± 11.9 years, ranging from 21 to 74 years, out of which 63.6% were females, with CVI who underwent surgical treatment for varicose of 110 lower limbs and total unilateral stripping of the greater saphenous vein (58 patients) or bilateral (26 patients), over a period of three years in the Santa Casa de Misericórdia of São Paulo. The study was approved by the Research Ethics Committee (CEP) (235/06).

We used the CEAP clinical classification to standardize the physical assessment of patients. The clinical classification (C) is described below:

C0: No visible or palpable signs of venous disease

C1: Telangiectasies and reticular veins

C2: Varicose veins

C3: Edema

C4a: Brown pigmentation (ochre dermatitis) and/or eczema

C4b: Lipodermatosclerosis or athrophie blanche

C5: Healed venous ulcer

C6: Active venous ulcer

The inclusion criteria were: the presence of primary symptomatic varicose veins; absence of obstructions of the deep venous system (DVT); limbs with GSV at thigh level with reflux in the Doppler ultrasound (reflux criteria used >0.5 seconds) and with CEAP clinical categories C2 to C6.

All information was collected using an specific form that included anamnesis, the clinical examination using the CEAP categories, ultrasound data (reflux of the great saphenous vein with or without saphenofemoral junction reflux), surgical data, and the anatomopathological study of the proximal portion of the great saphenous vein arch removed during surgery, the segment between the surgical ligation of the saphenous vein at the saphenofemoral junction and a second segment 1 cm below it, where the GSV is attached to the vein stripper.

The venous segments were removed for analysis and put in a 10% formalin solution for no longer than 48 hours. Cross-sections were made, which were included in the paraffin and stained with hematoxylin and eosin and the Masson's trichrome in order to measure the thickness of the vessel, the only parameter selected for histopathological assessment in this study. The pieces were analyzed in an optical microscope with a magnification of 50x, and the images captured with an attached camera to digitally measure the greater thickness of the vessel, from the tunica intima to the adventitia.

For the anatomopathological analysis, a control group was created in which normal great saphenous veins were removed from five corpses with the same mean age, death unrelated to vascular diseases, and absence of clinical signs of reports of chronic venous disease and upon consent of family members. A total of 10 samples of the great saphenous vein were collected with the same procedure conducted for in vivo samples. The samples were submitted to the same preparation procedures and anatomopathological analysis, and the maximum thickness of the venous wall of the great saphenous vein found was consid-

ered the control. Bearing in mind that the thickness is not the uniform around the vessel, we used the biggest measurement for the analysis.

We analyzed and correlated demographic data, clinical findings with the CEAP classification, the presence of pathological reflux of the SFJ detected by color Doppler ultrasound, and histological changes in the thickness of the GSV arch wall upon optical microscopy. Lastly, we compared the average of the greatest GSV wall thickness at the arch in patients with CVI who underwent varicose surgical treatment with the healthy great saphenous vein obtained from cadavers (control group).

The statistical study considered data expressed in frequencies and means, averages and standard deviations. The chi-square test was applied for frequency comparison; the Student's t-test was used to compare means and standard deviations; and the Pearson's r coefficient for correlations between dependent and independent variables. To analyze the null hypothesis, a probability of 95% ($p<0.05$) was adopted.

RESULTS

Analyzing the relationship between the different CEAP clinical categories and patient gender, we found that most cases ($x^2 = 79.3089$; $p<0.0001$) were in the CEAP category C3 (60.0%) for both genders. The relationship between CEAP classification and patient gender and age is presented in Table 1.

The patient age distribution was similar in different CEAP clinical classifications. Regarding the different clinical categories and patient age, we observed that the older the patient, the greater the severity of the varicose veins ($r=0.3268$; $p<0.05$). We found a statistical difference when comparing CEAP C2 patients with CEAP categories C4 ($p=0.0035$) and C5-6 (0.027), as well as when comparing CEAP C3 patients with C5-6 ($p=0.0374$).

Reflux in the SFJ was found in 81.8% of GSVs, with reflux at the thigh. No statistical difference was found in the analysis comparing the average age of patients with reflux (51.7 years) and without reflux (49 years) at the arch of the GSV, with $p=0.3621$. The relationship between the CEAP clinical classification and the presence of reflux in the SFJ is shown in Table 2.

No relationship was found between CEAP clinical categories and the presence of reflux in the SFJ (Table 3). Most cases that presented reflux in the SFJ were in category 3, with a higher frequency of that clinical category in the general sample.

The thickness of the normal GSV (ranging from 401-1.175, mean of 839.7+-243 micrometers) was significantly lower ($p<0.0001$) than in the GSV varicose

TABLE 1 – RELATIONSHIP BETWEEN CEAP CLINICAL CATEGORIES AND PATIENT GENDER AND AGE DISTRIBUTION FOR EACH CATEGORY

CEAP (C)	Male (n=40)		Female (n=70)		Total		Age	
	n	%	n	%	n	%	Mean (Min-Max)	
2	7	17.5	13	18.6	20	18.2	46.1 (31-71)	X^2= 2.9728
3	21	52.5	45	64.3	66	60.0	50.6 (21-74)	p=0.3958
4	11	27.5	10	14.3	21	19.1	55.7 (37-71)	
5	0	-	2	2.8	2	1.8	66.0 (62-74)	
6	1	2.5	0	-	1	0.9		

TABLE 2 – RELATIONSHIP BETWEEN CEAP CLINICAL CATEGORIES AND THE PRESENCE OF REFLUX IN THE SFJ

CEAP Category (C)	Present (n=88)		Reflux Absent (n=20)			Total (n=110)	Statistics
	n	%	n	%	n	%	
2	13	14.5	7 ^	35	20	18.2	
3	58	64.4	8	40	66	60.0	
4	171	18.9	4	20	21	19.1	
5	1	1.1	1	5	2	1.8	
6	1	1.1	0	-	1	0.9	x^2=6.635; p= 0.1564

veins (ranging from 802-2.663, mean of 1,609+,7-376). There was no relationship between gender and age distribution and GSV thickness.

The analysis of the varicose GSV thickness with the CEAP classification, the presence of reflux at the GSV arch, uni- or bilateral involvement, and family history are shown in Table 3.

The relationship was demonstrated between thickness and the CEAP classification, the presence of reflux at the GSV arch, and uni- or bilateral involvement. We found that 95.5% of patients reported a family history of CVI, and in 32.7% of cases, there was a previous family history of LLS surgery. Such influence has not been proven during the statistical analysis of the cases.

The images of the lowest, average, and highest values recorded during the measuring of GSV wall thickness in the control and study groups are presented in Figure 1.

DISCUSSION

Our study group consists of patients with symptomatic varicose veins and GSV insufficiency at the thigh who sought help at a large public hospital in the city of São Paulo and, after the recommendation of conventional surgery, were consecutively included in the study. These patients are mostly aged between 30-50 years (48.8%), with a greater proportion of males (63.6% females and 36.4% males) than in other published studies, 3 to 6 women for 1 man.[1,10,11] This discrepancy with the literature is not explained by the CVI severity in our study, since, despite previously published works having included less advanced categories of the disease with a bigger aesthetic problem, the advanced clinical categories (C4, C5, and C6) have the same distribution for both genders. Although the evidence of genetic predisposition for varicose veins is still not highly conclusive, a family history of CVI was reported by 95.5% of the patients in this study.

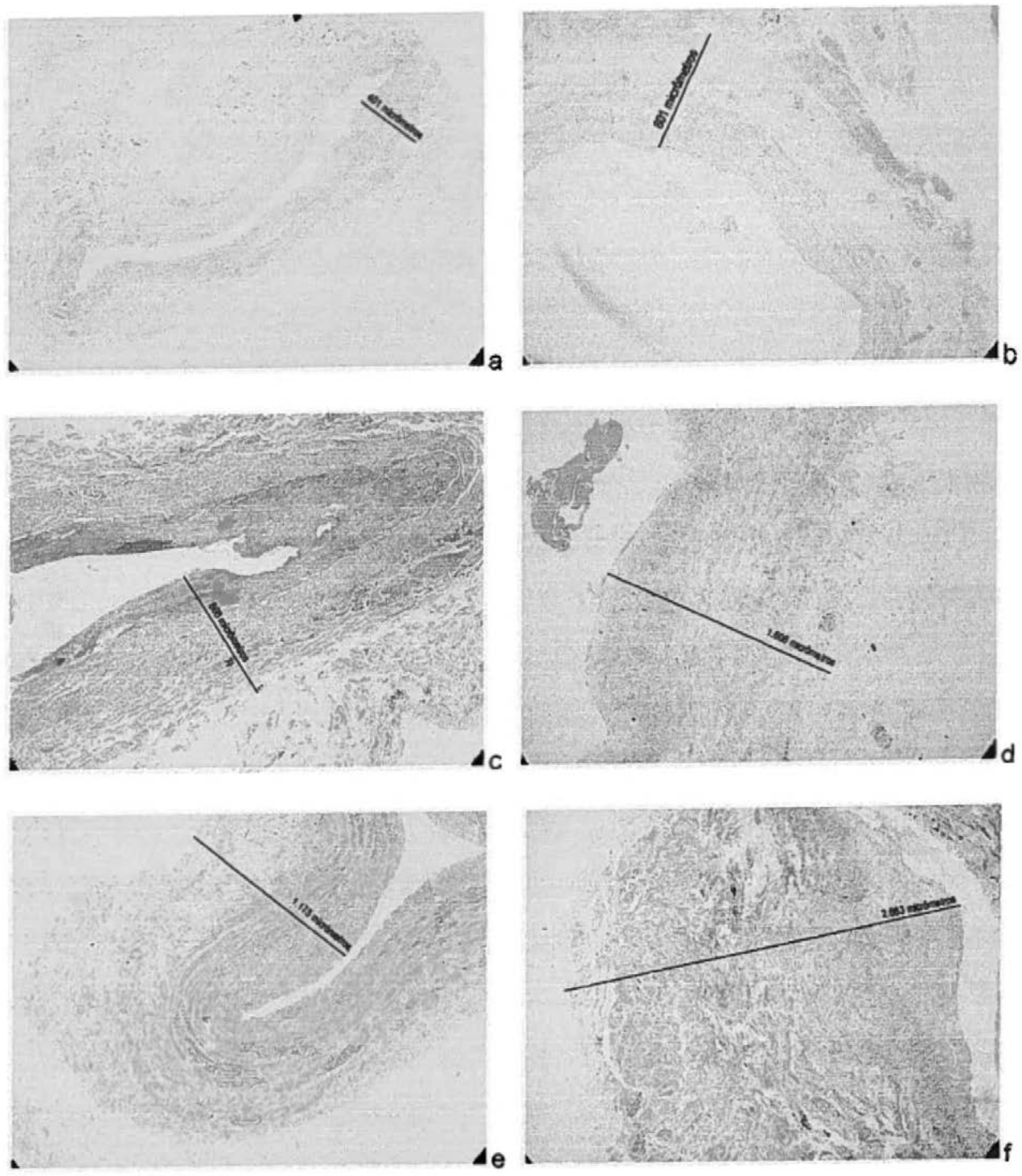
TABLE 3 – RELATIONSHIP BETWEEN THE VARICOSE GSV THICKNESS AND THE CEAP CLASSIFICATION, THE PRESENCE OF REFLUX AT THE GSV ARCH, FAMILY HISTORY, AND UNI- OR BILATERAL INVOLVEMENT

Variables		Thickest Average	Measurement Standard deviation	Statistics
CEAP	2 3 4 5 and 6	1,648 1,596 1,599 1,711	351 384 344 718	p> 0.05
Altered reflux	Present Absent	1,629.6 1,520.2	385.5 324.3	p=0.2411
Family history	Present Absent	1,618 1,434.4	381 202	p=0.2882
Family members who underwent surgery	Present Absent	1,601.4 1,613.7	369 382	p=0.8734
Type of involvement	Unilateral Bilateral	1,661.2 1,552.2	379.4 367.5	p=0.1295

The CEAP clinical classification for assessing the level of patient compromise due to chronic venous disease of the lower limbs was elaborated in the American Venous Forum held in 1994, and its adoption as a universal language was helpful to a more homogeneous understanding of the venous disease, allowing for the use of such classification in scientific studies.12 In this study, 21.8% of members had advanced CVI, categorized as CEAP C$, 5, or 6, in which there is a greater technical difficulty in surgery and worse outcomes due to lipodermatofibrosis, eczema, and active or healed ulcers, in addition to higher recurrence rates.[13,14] In this study, all patients were submitted to conventional surgery, during which samples of the GSV arch segment were collected. The effectiveness of conventional varicose surgery and its low recurrence rates are undeniable,[15,16] which makes this technique the gold standard for varicose vein treatment. Despite the increase in the use of modern techniques of venous thermal ablation and the fact that its effectiveness is comparable to conventional surgery, Mendes et al.[17] demonstrated, in a randomized study, that if patients are not told the technique used, they cannot differentiate the conventional surgery from the radiofrequency ablation.

We found a clear progression of the clinical classification of the disease with increasing age when comparing early clinical classifications C2 (average age of 46.1 years) and C3 with the advanced classifications C4 and C5-6, with a statistically significant difference despite the lower number of C5-6 patients (three patients, average age of 66 years). The low number of C5-6 patients is the result of the inclusion of consecutive patients who met the research inclusion criteria associated with a lower frequency of the advanced classifications of the disease in the general population. The clinical deterioration with increasing age reveals the natural history of the disease, illustrating that the complications and severity of CVI increase over the years in patients with no definitive treat-

FIGURE 1: (A) Lowest value recorded in the control group: 401 micrometers; (b) Smaller value recorded in the study group: 801 micrometers; (c) Value closest to the average value of the control group: 866 micrometers; (d) Value closest to the average value of the study group: 1,606 micrometers; (e) Highest value recorded in the control group: 1,175 micrometers; (f) Highest value recorded in the study group: 2,663 micrometers.



ment, and that there may be a lack of information among the population regarding the evolution of the chronic venous disease and its complications when there is no early treatment, evidencing the need for awareness campaigns.

In our study, we included patients with GSV reflux in the thigh, and reflux in the saphenofemoral junction was the ultrasound factor studied, since one of the sources of proximal GSV reflux, an important cause for varicose recurrence, direct-

ly interferes in the surgical approach and the postoperative results. The abnormal reflux in the saphenofemoral junction is considered the cause for 60% to 80% of all primary varicose vein cases.18 In line with some other studies,18,19 we found altered reflux in the saphenofemoral junction in 81.8% of the limbs analyzed with GSV reflux in the thigh. Seidel et al.[10] studied the association between CVI symptoms, visible varicose veins, and GSV reflux, grouping patients in three different groups (asymptomatic with varicose veins, symptomatic with no varicose veins, and symptomatic with varicose veins) and concluded that GSV reflux was more frequent in symptomatic patients with visible varicose veins, however they did not study the relevance of SFJ insufficiency on symptoms and on the level of varicose veins visible during the physical examination. Even though the presence of altered SFJ reflux is a relevant parameter for surgical recommendation[20] and predictor of CVI,[19] the presence of such reflux presented no correlation with the clinical classification of CVI (CEAP) in this study, i.e. Patients with saphenofemoral junction reflux did not present a more advanced clinical stage than patients with SFJ and no pathological reflux. Yamaki et al.[21] also did not find an association between the presence of superficial venous reflux or isolated perforator insufficiency and the early (CEAP C1-3) or advanced (CEAP C4 to 6) CVI clinical categories. However, the maximum reflux speed and maximum volume of reflux in the great saphenous vein, saphenofemoral and saphenopopliteal junctions, and deep venous system are higher in patients with advanced CEAP.

Even though alterations in the composition of the venous wall are considered the basic dysfunction for all CVI[8] and are related to GSV insufficiency,[10] our study did not show any relationship between an increased thickness of the GSV wall and the presence of SFJ reflux.

Amongst possible structural alterations in the varicose GSV, the focus of our study was the thickness of the GSV wall in SFJ. Santos Ferreira[22,23] found the thickening of the venous walls, especially in distal positions and in the tunica intima, to be the main and most frequent histological alteration in varicose veins. Silveira[24] found thicker walls in varicose veins than in normal veins in all three tunicas. In our study we also found thicker walls in varicose veins than in normal veins obtained from cadavers with no history of venous disease, but found no correlation between such increased thickness and clinical and ultrasound data, thus confirming the findings of Santos Ferreira and the observations of Garrido et al.[22,23]

CONCLUSIONS

The findings in this study confirm that the clinical classification of CVI is more severe with increased patient age. However, the thickness of the arch of the great saphenous vein is bigger in patients with varicose veins of the lower limbs, and these alterations do not correlate to the clinical classification of the disease or the presence of pathological reflux in the SFJ identified by Doppler ultrasound.

RESUMO

OBJETIVO: *Este estudo tem como objetivo correlacionar os dados demográficos, os diferentes graus clínicos da insuficiência venosa crônica (Ceap), com achados ultrassonográficos de refluxo da junção safenofemoral (JSF) e os achados anatomopatológicos do segmento proximal da veia safena magna (VSM) extraído de pacientes com insuficiência venosa crônica (IVC) primária submetidos à safenectomia magna para correção de varizes dos membros inferiores.*

MÉTODO: *Estudo prospectivo de 84 pacientes e 110 membros submetidos à safenectomia magna para o tratamento de varizes de membros inferiores, correlacionando a sua classificação clínica Ceap, presença de refluxo na JSF ao ultrassom Doppler e alterações histopatológicas. Comparamos ainda os achados histopatológicos da VSM proximal retirada dos pacientes com IVC com grupo controle de VSM normal retirada de cadáveres.*

RESULTADOS: *Média de idade dos pacientes foi maior nos Ceaps avançados quando comparado Ceap C2 (46,1 anos) com C4 (55,7 anos) e C5-6 (66 anos), e pacientes C3 (50,6 anos) com C5-6. A espessura da parede da VSM normal (média de 839,7 micrômetros) foi significativamente menor do que das VSM varicosas (média de 1.609,7 micrômetros). As análises de correlação da presença do refluxo em JSF com a classificação clínica ou achado histopatológico não demostraram ser estatisticamente significativas.*

CONCLUSÕES: *Quanto maior a idade, mais avançada é a classificação clínica da IVC dos pacientes. A espessura da parede da crossa da VSM é maior nos pacientes com IVC e essas alterações não se correlacionam com a classificação clínica da doença ou com a presença de refluxo na JSF ao ultrassom Doppler.*

PALAVRAS-CHAVE: *Varizes. Ultrassonografia. Histologia.*

REFERENCES

1. Hobson J. Venous insufficiency at work. Angiology. 1997;48(7):577-82.
2. Cabral ALS. Insuficiência venosa crônica de membros inferiores: prevalência, sintomas e marcadores preditivos [Tese de doutorado]. São Paulo: Universidade Federal de São Paulo, Escola Paulista de Medicina; 2000. p.140.
3. Maffei FH, Magaldi C, Pinho SZ, Lastoria S, Pinho W, Yoshida WB, et al. Varicose veins and chronic venous insufficiency in Brazil: prevalence among 1755 inhabitants of a country town. Int J Epidemiol. 1986;15(2):210-7.
4. Mallick R, Lal BK, Daugherty C. Relationship between patient-reported symptoms, limitations in daily activities, and psychological impact in varicose veins. J Vasc Surg Venous Lymphat Disord. 2017;5(2):224-37.
5. Abramson DI. Diseases of the veins: pathology, diagnosis and treatment. JAMA. 1988;260(24):3680.
6. Obitsu Y, Ishimaru S, Furukawa K, Yoshihama I. Histopathological studies of the valves of varicose veins. Phlebology. 1990;5(4):245-54.
7. Rose SS, Ahmed A. Some thoughts on the aetiology of varicose veins. J Cardiovasc Surg (Torino). 1986;27(5):534-43.
8. Jacobs BN, Andraska EA, Obi AT, Wakefield TW. Pathophysiology of varicose veins. J Vasc Surg Venous Lymphat Disord. 2017;5(3):460-7.
9. Wali MA, Dewan M, Eid RA. Histopathological changes in the wall of varicose veins. Int Angiol. 2003;22(2):188-93.
10. Seidel AC, Campos MB, Campos RB, Harada DS, Rossi RM, Cavalari Junior P, et al. Associação entre sintomas, veias varicosas e refluxo na veia safena magna ao eco-Doppler. J Vasc Bras. 2017;16(1):4-10.
11. Seidel AC, Mangolim AS, Rossetti LP, Gomes JR, Miranda Jr F. Prevalência de insuficiência venosa superficial dos membros inferiores em pacientes obesos e não obesos. J Vasc Bras. 2011;10(2):124-30.
12. Venous Forum Annual Meeting, Royal Society of Medicine, London, 14 October 1994. Phlebology. 2016;10(2):79-85.
13. Kokkosis AA, Schanzer H. Anatomical and clinical factors favoring the performance of saphenous ablation and microphlebectomy or sclerotherapy as a single-stage procedure. Phlebology. 2015;30(9):627-31.
14. van der Velden SK, Pichot O, van den Bos RR, Nijsten TE, De Maeseneer MG. Management strategies for patients with varicose veins (C2-C6): results of a worldwide survey. Eur J Vasc Endovasc Surg. 2015;49(2):213-20.
15. Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, et al. Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVeS Study). J Vasc Surg. 2003;38(2):207-14.
16. Siribumrungwong B, Noorit P, Wilasrusmee C, Attia J, Thakkinstian A. A systematic review and meta-analysis of randomised controlled trials comparing endovenous ablation and surgical intervention in patients with varicose vein. Eur J Vasc Endovasc Surg. 2012;44(2):214-23.
17. Mendes CA, Martins AA, Fukuda JM, Parente JB, Munia MA, Fioranelli A, et al. Randomized trial of radiofrequency ablation versus conventional surgery for superficial venous insufficiency: if you don't tell, they won't know. Clinics (Sao Paulo). 2016;71(11):650-6.
18. Engelhorn CA, Engelhorn AL, Cassou MF, Salles-Cunha SX. Patterns of saphenous reflux in women with primary varicose veins. J Vasc Surg. 2005;41(4):645-51.
19. Konoeda H, Yamaki T, Hamahata A, Ochi M, Sakurai H. Quantification of superficial venous reflux by duplex ultrasound-role of reflux velocity in the assessment the clinical stage of chronic venous insufficiency. Ann Vasc Dis. 2014;7(4):376-82.
20. Ciostek P, Michalak J, Noszczyk W. Improvement in deep vein haemodynamics following surgery for varicose veins. Eur J Vasc Endovasc Surg. 2004;28(5):473-8.
21. Yamaki T, Nozaki M, Fujiwara O, Yoshida E. Comparative evaluation of duplex-derived parameters in patients with chronic venous insufficiency: correlation with clinical manifestations. J Am Coll Surg. 2002;195(6):822-30.
22. Maffei FHA, Lastoria S, Yoshida WB, Rollo HA. Doenças vasculares periféricas. 3rd ed. Rio de Janeiro: Medsi; 2002.
23. Garrido M, Santos Ferreira C, Sales EA. Varizes de membros inferiores: Patologia. In: Maffei FHA, Lastória S, Yoshida WB, Rollo HA. Doenças vasculares periféricas. 3ª. ed. Rio de Janeiro; Medsi; 2002. Volume 2. p. 1511-20
24. Silveira PRM. Estudo estrutural da veia safena magna normal e varicosa [Tese de doutorado]. São Paulo: Escola Paulista de Medicina; 1992.

ORIGINAL ARTICLE

Characterization of post-surgical critical patients with infections associated with healthcare after prolonged perfusion of remifentanil

José Luis Bonilla García[1]
Manuel Cortiñas Sáenz[2]
Esperanza del Pozo Gavilán[3]

1. FEA Anestesiología y Reanimación. Complejo Hospitalario Universitario de Huelva, Huelva, Huelva, Spain
2. FEA Anestesiología y Reanimación. Hospital Torrecárdenas de Almería, Almería, Almería, Spain
3. Departamento de Farmacología e Instituto de Neurociencias. Facultad de Medicina, Universidad de Granada, Granada, Spain

http://dx.doi.org/10.1590/1806-9282.64.08.736

SUMMARY

INTRODUCTION: *Healthcare associated infections (HAI) are the most frequent complication of hospitalized patients. The aim of this study was to describe the clinical and epidemiological characteristics of critically ill post-surgical patients with a diagnosis of healthcare associated infections, after a pattern of sedoanalgesia of at least 4 days.*

METHODS: *All patients over 18 years of age with a unit admission of more than 4 days were consecutively selected. The study population was the one affected by surgical pathology where sedation was based as analgesic the opioid remifentanil for at least 96 hours in continuous perfusion. Patients who died during admission to the unit and those with combined analgesia (peripheral or neuroaxial blocks) were excluded. Data analysis was performed using the statistical package Stata version 7.0.*

RESULTS: *The patients admitted to the Post-Surgical Critical Care Unit (PCU) during study were 1789 and the population eligible was comprised of 102 patients. 56.86% of patients suffered IACS. The most frequent IACS was pneumonia associated with mechanical ventilation (30.96 per 1000 days of mechanical ventilation), Pseudomonas aeruginosa being the most frequently isolated germ. The germs with the greatest involvement in multiple drug resistance (MDROs) were enterobacteria, mainly Klebsiella pneumoniae resistant to extended-spectrum beta-lactamases (ESBL).*

CONCLUSIONS: *Pneumonia associated with mechanical ventilation is the most prevalent HAI and Pseudomonas aeruginosa is the main etiological agent. The groups of antibiotics most frequently used were cephalosporin and aminoglycosides. It is necessary to implement the prevention strategies of the different HAI, since most of them are avoidable.*

KEYWORDS: *Analgesics, opioid. Cross infection. Immunosuppression. Critical care. Piperidines/administration & dosage.*

INTRODUCTION

Healthcare Associated Infections (HAI), formerly known as nosocomial or in-hospital, are those infections that did not manifest nor were incubated at the time of admission and the patient acquired it during treatment for any medical or surgical condition. It is necessary that they occur after 48 hours of hospitalization[1].

HAI are the most frequent complication of hospitalized patients. In Spain, according to the data provided by the EPINE Project[2], prevalence of HAI is estimated at around 7.5-8% in the last 4 years, with a recovery in 2015 compared to the previous years. This prevalence increases to 23.52% in critically ill patients, with intensive care units being the most prevalent areas.

DATE OF SUBMISSION: 08-Jan-2018
DATE OF ACCEPTANCE: 13-Jan-2018
CORRESPONDING AUTHOR: Mr. Jose Luis Bonilla-Garcia
Ronda exterior norte s/n, Huelva, Huelva, Spain - 21005
E-mail: joseluisbonilla86@gmail.com
mcortinassaenz@gmail.com
edpozo@ugr.es

The development of infections is associated with multiple causes, including, but not limited to, the use of medical devices, post-surgical complications, transmission between patients and healthcare personnel, and the outcome of frequent antibiotic treatment. On the other hand, we must also consider different host conditions that predispose to HAI acquisition, among them, immunosuppression, either by pre-existing or drug-induced comorbidities[3].

Among the drugs administered to the seriously ill patient, different combinations of pain killers and hypnotics are essential to ensure their comfort, care and safety[4]. However, inappropriate use of these drugs may increase morbidity and mortality, mechanical ventilation time, and length of hospital stay.

Sedoanalgesia alters immune function, but its real clinical importance is unknown. Several animal and human studies have demonstrated the immunosuppressive effects of opioids,[5] consequently associating the administration of opioids with increased susceptibility to certain bacterial and viral infections[6]. Morphine is associated with decreased lymphoproliferative processes, Natural killer (NK) lymphocyte activity and the production of interferon-γ and IL-2[7].

Several animal studies suggest that the withdrawal of opioids induces a state of immunosuppression that would increase the risk of infection[8] and therefore, the modification of immunomodulation by certain drugs may be responsible for part of the HAI complications in critical medicine. In this sense, the study by Nseir et al.[9] shows that the discontinuation of the remifentanil opioid in perfusion in critical post-surgical patients represents an independent risk factor for the development of HAI.

The objective of this study is to describe the clinical, demographic and epidemiological characteristics of critical post-surgical patients diagnosed with healthcare-associated infection with admission to the Post-Surgical Resuscitation Unit (URP) for two years, whose sedation was based on association of a hypnotic with remifentanil as a pain killer in continuous perfusion for at least 96 hours, based on the hypothesis, with increase of HAI on withdrawal of the opioid remifentanil.

MATERIAL AND METHODS

Following the approval of the Hospital Ethics Committee, a prospective and observational study of a historical court was conducted in a Post-Surgical Resuscitation Unit with 6 beds during the years 2010-2012.

All patients aged over 18 years with admission to the unit over 4 days were consecutively selected. The study population was the one affected by surgical pathology from any source in which sedation was based on any hypnotic and as pain killer, the opioid remifentanil for at least 96 hours in continuous infusion. Patients who died during admission to the unit and patients with combined analgesia (peripheral or neuroaxial block) were excluded.

Doses of midazolam, propofol, and remifentanil are described in the unit sedoanalgesia protocol, following the Guidelines of the Society of Critical Care Medicine[10]. Initially, remifentanil was administered at a dose of 0.05-0.20 µg/kg/min. If the ideal Ramsay level was not achieved, propofol was associated at 0.5-4 mg/kg/h, if the patient remained hemodynamically stable, or otherwise, midazolam at 0.05-0.20 mg/kg/h. Ketamine hydrochloride was administered if the desired goal was not achieved. The deprivation syndrome is treated within the strategy of sequential sedation.

The main variable of our study was the number of infections associated with healthcare acquired in the URP during the days of hospitalization. We also considered incidence density, defined as the number of infections acquired in the unit per 1000 days of hospitalization.

The cut-off point between early and late HAI was established as 6 days before and after remifentanil cessation.

There is a HAI surveillance system with systematic and routine detection of multiresistant germs. Only the infections confirmed by the Microbiology Service were considered for this study. The different HAI were defined according to the definitions of the Centres for Disease Control and Prevention (CDC)[11].

Other variables collected were: age, gender, APACHE II rating (Acute Physiology and Chronic Health Evaluation II), ASA index (American Society of Anaesthesiologists), McCabe score, number and type of comorbidity, cause of hospitalization, number of surgical reinterventions, previous treatment with antibiotics, stay in the Ramsay URP, ratio of use of central and arterial venous catheters, closed system urinary catheters and mechanical ventilation, number of reintubations, tracheostomy, duration and type of antimicrobial agent, dose of remifentan-

il, midazolam and propofol, use of neuromuscular blocking drugs and mortality.

For the empirical treatment of infectious processes the recommendations were used based on the therapeutic guidelines of the *Sociedade Espanhola de Anestesiologia y Reanimación* (Spanish Society of Anaesthesiology and Reanimation) adjusted for the local epidemiology of bacterial resistance of our critical unit[12].

In patients with sepsis on admission, vigorous resuscitation measures with fluid and instauration of hemodynamic support measures by vasopressors were initiated if there was hypotension or lactate> 4 mmol/L, low-dose corticosteroids in patients with septic shock, mechanical invasive ventilation of pulmonary protection, glycaemia control between 150-180 mg/dl, assessment of need for surgical intervention or percutaneous drainage, culture and beginning of empirical antimicrobial treatment based on Surviving Sepsis Campaign guidelines[13].

Data analysis was performed using the statistical package Stata version 7.0. The results are presented as number of percentages for the categorical variables and mean with their standard deviation for the quantitative variables.

RESULTS

The number of patients admitted to the URP during the study period was 1,072. After applying the inclusion and exclusion criteria, the eligible population consisted of 102 patients whose analgesic protocol was carried out by intravenous infusion of remifentanil for at least 96 hours. 56.86% of patients had HAI.

The main demographic data, associated comorbidity conditions, rate of use of medical devices and drugs applied in the sedoanalgesia of the study cohort that developed HAI are presented in Tables 1, 2 and 3. The age was 68.37 ± 10.79 years old. The mean length of stay in the URP was 19.87 ± 14.29 days, with total hospital stay of 40.39 ± 27.53 days. Mean APACHE II on admission was 18.27 ± 8.15. 53.44% (31 cases) of admissions to the unit that were emergencies.

The mean infusion rate of remifentanil was 11.4 µg kg-1 h-1. 64% simultaneously received sedation with midazolam, 31% with propofol, and the rest did not receive sedative drugs, only remifentanil. The remifentanil infusion was during the study period of 14.93 ± 11.35 days. The mean medical remifentanil infusion per day of study and in relation to the hypnotic administered is shown in figure 1.

Figure 2 shows the number of HAI in temporal relation to the administration and removal of intravenous remifentanil. We did not observe statistically significant differences in its incidence in relation to discontinuation of remifentanil, using the Mann-Whitney U test (p = 0.19).

The most frequent HAI was pneumonia associated with mechanical ventilation (30.96 per 1000 days of mechanical ventilation), with Pseudomonas aeruginosa being the most frequently isolated germ. The incidence density of primary and/or secondary bacteraemia and urinary tract infection was 23.87 and 9.67 per 1000 days of risk factor, respectively. The germs most involved in multidrug resistance (MDROs) were enterobacteria mainly Klebsiella pneumoniae resistant to extended spectrum betalactamases (ESBL).

The most commonly used antibiotic groups were cephalosporin and aminoglycosides (figure 3). Fungicides were used in 15 cases.

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION ADMITTED TO THE URP

VARIABLES.	IN. (n = 58).
Age	68.37 ± 10.79
Gender (Male)	26 (44)
ASA> 2	44 (75)
Score McCabe. Good prognostic Poor prognostic Fatal prognostic Death expectations	13 15 20 10
Basal Comorbidity Hemodynamic Respiratory Renal Hepatic Neoplasia Immunosuppression Diabetes mellitus	31 (53) 27 (46) 16 (27) 10 (17) 43 (74) 32 (55) 25 (43)
Number of Comorbidities ≤ 2 > 2	22 (37) 36 (62)
APACHE II	18.27 ± 8,15
Days of admission to URP	19.87 ± 14.29
Days of admission to hospital Pre-URP Post-URP Global	4.25 ± 4.10 16.10 ± 21.76 40.39 ± 27.53
Mortality UCC Post-URP	18 (31) 12 (20)
Type of Surgery Scheduled Emergency	27 (46) 31 (53)
Reintubation	2 (37)

DISCUSSION

HAI are the most frequent complication of hospitalized patients. According to data provided by the National Survey of Nosocomial Infection Surveillance in Intensive Care Services (ENVIN) of 2015[14], in postoperative patients, the most frequent HAI are related to ventilator-associated pneumonia (VAP), catheter-related urinary tract infection (UTI) and bacteraemia of unknown origin associated with the catheter. This data is consistent with those of our cohort, since ventilator-associated pneumonia was the most frequent cause, with a DI of 30.96 per 1000 days of mechanical ventilation followed by primary and/or secondary bacteraemia, and urinary tract infection with ID 23.87 and 9.67 per 1,000 days of risk factor, respectively.

The main microbiological causes of the different HAI have not undergone major changes in recent years. In relation to our cohort, Pseudomonas aeruginosa is the most frequently isolated in VAP, E. coli in urinary infections, and Staphylococcus epidermidis in bacteraemia, these results being comparable to those presented in several epidemiological studies on HAI in critical patients[15].

The fact that Pseudomonas aeruginosa is the most frequent pathogen associated with VAP could be justified because this microorganism is related to late VAPs. This circumstance in our study is favoured by the prolonged duration of mechanical ventilation in our patients.

A growing concern in the intensive units is the appearance of multidrug resistant germs, which complicate both the prognosis and the management and evolution of patients, which increases the consumption of resources in the units[16]. In our case, the germs most involved in multidrug resistance (MDROs) were enterobacteria, especially Klebsiella pneumoniae resistant to beta-lactamases (ESBL), which showed, however, a good sensitivity for carbapenems. The low incidence of methicillin-resistant Staphylococcus aureus (MRSA) and the absence of Clostridium difficile carriers are noteworthy. These organisms are identified in national studies as multidrug resistant pathogens[14].

The causes of these strains of Vancomycin-Resistant Enterococcus (VRE) may be multifactorial. Among these factors are the progressive increase of elderly patients with higher comorbidity, the current economic crisis leading to increased workloads for healthcare professionals and it is associated with a higher risk of infection by MRSA and ERV[17], or an incorrect antibiotic policy.

In our cohort, antibiotic therapy was adjusted according to SEDAR recommendations, adjusted to our local ecology. The use of antimicrobials in an early

FIGURE 1. AVERAGE INFUSION OF REMIFENTANIL PER STUDY DAYS IN RELATION TO THE HYPNOTIC USED.

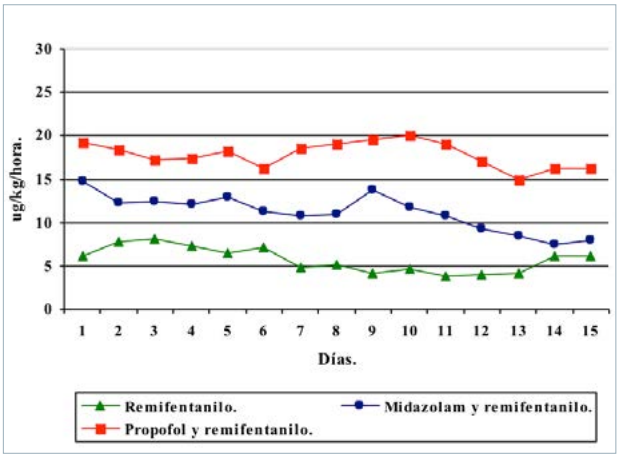


FIGURE 2. TIME RELATION BETWEEN HEALTHCARE-ASSOCIATED INFECTIONS (HAI) AND INTRAVENOUS REMIFENTANIL ANALGESIA IN A POST-ANESTHESIA CARE UNIT

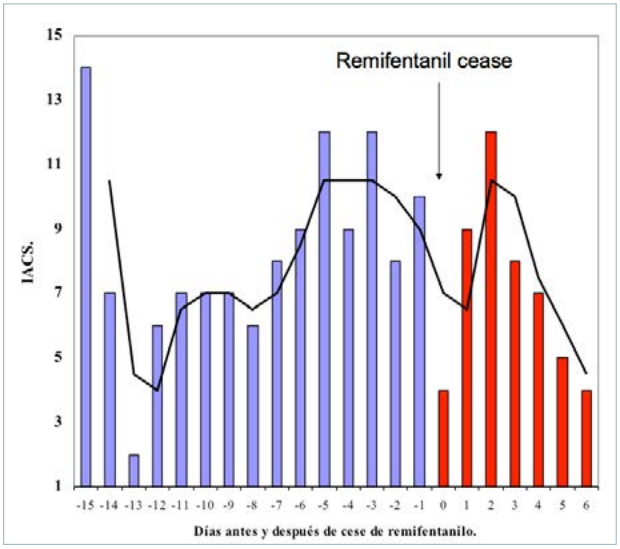


FIGURE 3. ANTIMICROBIAL USED IN URP

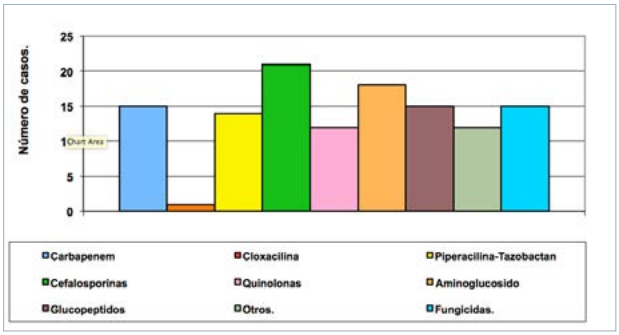


TABLE 2. USE OF MEDICAL DEVICES BY THE STUDY POPULATION ADMITTED TO THE URP AND TREATED WITH REMIFENTANIL FOR AT LEAST 96 HOURS.

VARIABLES	IN (n = 58)
CVC	57 (98)
Days of CVC	22.62 ± 16.68
VMI	58 (100)
Days of VMI	13.20 ± 11.04
Tracheostomy	22
Days of Tracheostomy	10.81 ± 4.66
SU	58 (100)
Days of SU	23.56 ± 19.23

TABLE 3. DRUGS USED IN THE COHORT SEDOANALGESIA

VARIABLES	IN (n = 58)
Remifentanil	3 (5)
Days of Remifentanil	14.93 ± 11.35
Midazolam and Remifentanil	37 (64)
Days of Midazolam.	15.21 ±13.44
Propofol and Remifentanil	18 (31)
Days of Propofol	8.16 ± 2.70

and adequate manner has been shown to reduce the morbidity and mortality of critically ill patients. The employees of our series are in accordance with what has been published in the literature[18].

In our study we observed that the factors that may have contributed to the emergence of infections by multidrug resistant microorganisms are the advanced age of our cohort as well as the high comorbidity. In our area there is a bacterial resistance surveillance system, but it is probably necessary to introduce and/or potentiate other strategies, such as the molecular typing of isolates, intensification of hygiene measures control, regrouping or cohorting of patients, rotation and restriction in the use of antibiotics, and a rigorous follow-up of patients infected and/or colonized by resistant germs[19].

Another element to be considered in our study as a factor favouring HAI is the use of prolonged sedoanalgesia based on the use of remifentanil, associated or not with propofol or midazolam hypnotics, to achieve an optimal level of sedation. The transcendence of prolonged use in sedation of critically ill patients may be relevant but there are no clinical studies demonstrating that the specific use of any analgesic or hypnotic drug has an impact on patient survival. Several animal studies suggest that withdrawal of opioids after a variable time of administration induces a state of immunosuppression that would increase the risk of infection[8,20]. In this sense, the effect of certain drugs on immunomodulation could increase the risk of acquiring infections associated with healthcare in intensive units.

Sedation in our work was performed using the midazolam or propofol hypnotics according to the protocol attached. In patients with greater severity, sedoanalgesia was based on the midazolam-remifentanil binomial. Although some studies[21] have suggested the importance of choosing this in immunocompromised patients with a high risk of infection, we have not found that the applied hypnotic correlates with an increase in HAI when adjusted for severity, medical device utilization ratio and hospital stay.

On the other hand, our study shows that the acute use and the interruption of opioid remifentanil is an independent risk factor for nosocomial infection, unlike the results presented by the Nseir et al.[9] group. This study showed, after a logistic regression analysis, that there is a high incidence of nosocomial infections during the 4 days after the cessation of analgesia based on opioid remifentanil. In our study, it was observed that patients belonging to the HAI group require more days of sedoanalgesia with remifentanil, with longer exposure to extrinsic factors of infection, such as mechanical ventilation, central venous catheters and urinary catheter exposing them to a higher HAI risk. These data could explain the differences of our results with those obtained in the work of Nseir et al.[9]. Our findings are consistent with the study by Cronin et al.[22], which shows that infusion of fentanyl has no effect on cellular immune function in healthy volunteers.

For preventing these infections, the implementation of strategies to prevent the different HAI is necessary, since it is possible to prevent most of them and therefore, to put all the resources at our disposal to avoid them. Thus, it is possible to implement both measures common to different HAI and specific ones, depending on the area that presents the greatest needs (training, reduction of risk factors, and adherence to clinical guidelines for the prevention of infection)[23].

The study has a number of limitations. First, the sample size is limited and extracted from a single intensive unit. Second, the bias of hypnotic choice depending on the hemodynamic instability of the

subject. Third, the existence of possible periods of infrasedation or oversedation, with the possible immunological and infectious repercussions that could derive from those, which were not tabulated in this study.

In conclusion, HAI are the most frequent complication of hospitalized patients. VAP is the most prevalent nosocomial infection and *Pseudomonas aeruginosa* is the most frequently isolated germ. The germs most involved in multidrug resistance (MDROs) are mainly enterobacteria, mainly Klebsiella pneumoniae resistant to extended spectrum beta-lactamases (ESBL). It is necessary to implement prevention strategies for the different HAI, since most of them can be avoided. The statement that remifentanil discontinuation is associated with a high incidence of HAI was not verified in our study.

Given the importance of the topic and areas of uncertainty, it could be of interest to carry out multicentre, controlled, and larger series studies to elucidate all factors related to HAI in critically ill postoperative patients, as it influences their prior immunological status, among others.

ACKNOWLEDGMENTS

The results of this publication are part of the José Luis Bonilla García Doctoral Thesis, entitled "Relationship between infection rate associated with healthcare in a Post-surgical Critical Unit and suspension of treatment with remifentanil", attached to the Program of Doctorate in "Clinical Medicine and Public Health" from the University of Granada. Thanks to the Andalusian Public Foundation for the Oriental Andalusian Biosanitary Research - Alejandro Otero de Almería for his invaluable help in the study and statistical analysis.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

RESUMO

INTRODUCCIÓN: *Las infecciones asociadas a cuidados de salud (IACS) constituyen la complicación más frecuente de los pacientes hospitalizados. El objetivo de este estudio es describir las características clínicas y epidemiológicas de los pacientes críticos postquirúrgicos con diagnóstico de infección asociada a cuidados de salud, tras una pauta de sedoanalegia de al menos 4 días.*

MÉTODOS: *Se seleccionaron de manera consecutiva todos los pacientes mayores de 18 años con un ingreso en la Unidad de Reanimación Postquirúrgica (URP) superior a 4 días. La población de estudio fue aquella afectada por patología quirúrgica de cualquier origen donde la sedación se basó en cualquier hipnótico y como analgésico el opioide remifentanilo durante al menos 96 horas en perfusión continua. Se excluyeron los pacientes que fallecieron durante su ingreso en la unidad y aquellos pacientes con analgesia combinada (bloqueos periféricos o neuroaxiales). El análisis de los datos se realizó con paquete estadístico Stata versión 7.0.*

RESULTADOS: *El número de pacientes que ingresaron en la URP durante el periodo de estudio fueron de 1789. Tras aplicar los criterios de inclusión y exclusión, la población elegible quedó constituida por 102 pacientes. Un 56,86% de pacientes padecieron IACS. La IACS más frecuente fue la neumonía asociada a ventilación mecánica (30,96 por 1000 días de ventilación mecánica) siendo* Pseudomona aeruginosa *el germen más frecuentemente aislado. Los gérmenes con mayor implicación en las multirresistencias (MDROs) fueron las enterobacterias, principalmente Klebsiella pneumoniae resistente a betalactamasas de espectro extendido (BLEE).*

CONCLUSIONES: *La neumonía asociada a ventilación mecánica es la IACS más prevalente y* Pseudomona aeruginosa *es el principal agente etiológico. Los grupos de antibióticos más frecuentemente empleados fueron cefalosporinas y aminoglucósidos. Es necesario implementar las estrategias de prevención de las distintas IACS, ya que la mayoría de ellas son evitables.*

PALABRAS CLAVE: *Analgésicos opioides. Infección hospitalaria. Inmunosupresión. Cuidados críticos. Piperidinas/administración & dosificación.*

REFERENCES

1. CDC/NHSN Identifying healthcare-associated infections (HAI) for NHSN Surveillance. (Accessed Sept 5, 2016) Available from: http://www.cdc.gov/nhsn/PDFs/pscManual/2PSC_IdentifyingHAIs_NHSNcurrent.pdf
2. Sociedad Española de Medicina Preventiva, Salud Pública e Higiene, European Centre for Disease Prevention and Control. Estudio EPINE-EPPS 2015. Informe Global de España (resumen provisional). (Accessed Sept 5, 2016). Available from: http://hws.vhebron.net/epine/Descargas/EPINE%202015%20INFORME%20GLOBAL%20DE%20ESPA%C3%91A%20RESUMEN.pdf
3. Pujol M, Limón E. General epidemiology of nosocomial infections. Surveillance systems and programs. Enferm Infec Microbiol Clin. 2013;31(2):108-13.
4. Chamorro C, Romera MA, Silva JA. Importancia de la sedoanalgesia en los pacientes en ventilación mecánica. Med Intensiva 2003;1(Suppl):2-4.
5. Eisenstein TK, Hilburger ME. Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations. J Neuroimmunol. 1998;83(1-2):36-44.
6. Risdahl JM, Khanna KV, Peterson PK, Molitor TW. Opiates and infections. J Neuroimmunol. 1998;83(1-2):4-18.
7. Garcia JBS, Cardoso MGM, Dos-Santos MC. Los opioides y el sistema inmunológico: relevancia clínica: Rev Bras Anestesiol. 2012;62(5):1-6.
8. Feng P, Wilson QM, Meissler JJ Jr, Adler MW, Einstein TK. Increased sensitivity to Salmonella enterica serovar Typhimurium infection in mice undergoing withdrawal from morphine is associated with suppression of interleukin-12. Infect Immun. 2005;73(12):7953-9.

9. Nseir S, Hoel J, Grailles G, Soury-Lavergne A, Di Pompeo C, Mathieu D, et al. Remifentanil discontinuation and subsequent intensive care unit-acquired infection: a cohort study. Crit Care. 2009;13(2):R60.

10. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, et al; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med. 2002;30(1):119-41.

11. CDC/NHSN surveillance definitions for specific types of infections. (Accessed Sept 5, 2016). Available from: http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf

12. Guiraoa X, Ariasa J, Badía JM, García-Rodríguez JA, Mensa J, Alvarez-Le rma F, et al. Recommendations in the empiric anti-infective agents of intra-abdominal infection. Cir Esp. 2010;87(2):63-81.

13. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock 2012. Crit Care Med. 2013;41(2):580-637.

14. Sociedad Española de Medicina Intensiva Crítica y Unidades Coronarias, Grupo de Trabajo de Enfermedades Infecciosas y Sepsis. Estudio Nacional de Vigilancia de Infección Nosocomial en Servicios de Medicina Intensiva (ENVIN) 2015. (Accessed Sept 5, 2016). Available from: http://www.semicyuc.org/sites/default/files/envin-uci_informe_2015.pdf

15. Olaechea PM, Insausti J, Blanco A, Luque P. Epidemiology and impact of nosocomial infections. Med Intensiva. 2010;34(4):256-67.

16. Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. Ann Intern Med. 2001;134(4):298-314.

17. Warren DK, Liao RS, Merz LR, Eveland M, Dunne WM Jr. Detection of methicillin-resistant Staphylococcus aureus directly from nasal swab specimens by a real-time PCR assay. J Clin Microbiol. 2004;42(12):5578-81.

18. Amador JS, Carrasco JP, Morales AA, Cortes CP. Therapeutic evaluation of prolonged infusions of β-lactam antibiotics in the treatment and management of critically ill patients. J Pharm Pharmacogn Res. 2017;5(2):88-95.

19. Therre H. *National policies for preventing antimicrobial resistance*: the situation in 17 European countries in late 2000. Euro Surveill. 2001;6(1):5-14.

20. Feng P, Truant AL, Meissler JJ Jr, Gaughan JP, Adler MW, Eisenstein TK. Morphine withdrawal lowers host defense to enteric bacteria: spontaneous sepsis and increased sensitivity to oral Salmonella enterica serovar Typhimurium infection. Infect Immun. 2006;74(9):5221-6.

21. Helmy SA, Al-Attiyah RJ. The immunomodulatory effects of prolonged intravenous infusion of propofol versus midazolam in critically ill surgical patients. Anaesthesia. 2001;56(1):4-8.

22. Cronin AJ, Aucutt-Walter NM, Budinetz T, Bonafide CP, DiVittore NA, Gordin V, et al. Low-dose remifentanil infusion does not impair natural killer cell function in healthy volunteers. Br J Anaesth. 2003;91(6):805-9.

23. Palomar M, Rodríguez P, Nieto M, Sancho S. Prevention of nosocomial infection in critical patients. Med Intensiva. 2010;34(8):523-33.

REVIEW ARTICLE

Anthracycline-associated cardiotoxicity in adults: systematic review on the cardioprotective role of beta-blockers

Roberto Ramos Barbosa[1]
Taissa Borges Bourguignon[1]
Luíza Dias Torres[1]
Lorenza Silveira Arruda[1]
Tiago de Melo Jacques[1]
Renato Giestas Serpa[1]
Osmar de Araujo Calil[1]
Luiz Fernando Machado Barbosa[1]

1. School of Sciences of Santa Casa de Misericórdia de Vitoria, Vitória, ES, Brasil

http://dx.doi.org/10.1590/1806-9282.64.08.745

SUMMARY

OBJECTIVES: *This study aimed at assessing the role of beta-blockers on preventing anthracycline-induced cardiotoxicity in adults.*

METHODS: *A systematic review was performed on electronic databases, including relevant studies that analysed beta-blockers as cardioprotective agents before the use of anthracyclines by adult oncologic patients.*

RESULTS: *After application of eligibility and selection criteria, eight articles were considered as high quality, complying with the proposed theme; all eight clinical trials, four of them placebo-controlled, with a total number of 655 patients included. From this sample, 281 (42.9%) used beta-blocker as intervention, and carvedilol was the most frequent (167 patients – 25.5%). Six studies were considered positive regarding the cardioprotection role played by beta-blockers, although only four demonstrated significant difference on left ventricle ejection fraction after chemotherapy on groups that used beta-blockers compared to control groups. Carvedilol and nebivolol, but not metoprolol, had positive results regarding cardioprotection. Other beta-blockers were not analysed in the selected studies.*

CONCLUSIONS: *Despite the potential cardioprotective effect of beta-blockers, as demonstrated in small and unicentric clinical trials, its routine use on prevention of anthracycline-associated cardiotoxicity demands greater scientific evidence.*

KEYWORDS: *Cardiotoxicity. Anthracyclines. Heart failure. Heart diseases/prevention & control.*

INTRODUCTION

Anthracyclines (doxorubicin, daunorubicin, epirubicin and idarubicin) are chemotherapeutic drugs that act as potent antineoplastic agents. After its introduction into the therapeutic arsenal of oncology, survival rates of cancer patients increased from 30% to 70%[1]. Unfortunately, despite its effectiveness, one of its consequences is cardiac failure[1,2]. As the replacement of anthracyclines by other chemotherapeutic agents are often infeasible from a therapeutic perspective, the deprivation of this drug could negatively influence the prognosis of the tumour and the patient survival.

Among the mechanistic hypotheses of induction of cardiotoxicity by anthracyclines are apoptosis,

DATE OF SUBMISSION: 31-Dec-2017
DATE OF ACCEPTANCE: 07-Jan-2018
CORRESPONDING AUTHOR: Roberto Ramos Barbosa
Rua Dr. Jairo de Matos Pereira, 780, ap. 1001, Praia da Costa - 29101-310 - Vila Velha, ES – Brasil – Tel: +55 27 99961-4907
E-mail:roberto.b@cardiol.br

taissabourguignon@gmail.com
luiza_dtorres@gmail.com
lorenza.arruda@gmail.com
tiagomj@cardiol.br
jrserpa@terra.com.br
osmarcalil@uol.com.br
uip@terra.com.br

mitochondrial dysfunction, activation of the metalloproteinases matrix and formation of oxygen free radicals.[2,3] The main cardiotoxic effects of anthracyclines are related to higher cumulative doses, however, higher doses lows can also be harmful. Left ventricular diastolic dysfunction is usually seen in cumulative doses of 200 mg/m², while systolic dysfunction is seen at cumulative doses above 400mg/m².[4] The intracellular biochemical mechanisms of anthracycline-induced cardiotoxicity are illustrated in Figure 1.

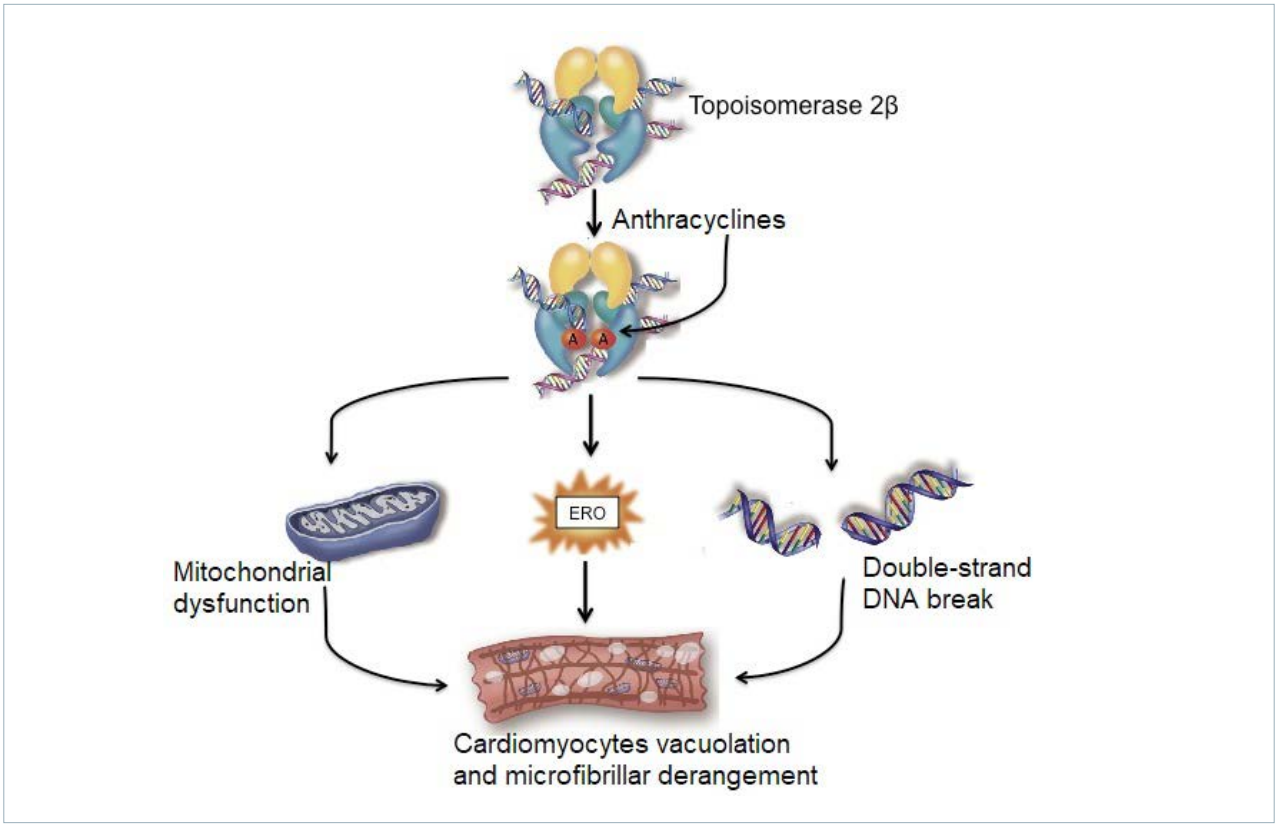
The use of potent antiemetic agents and granulocyte colony stimulating factors decreased the occurrence of the most common adverse effects, which resulted in the use of higher doses of anthracyclines in treatments, predisposing to the cardiac damages known today[5]. Both the symptomatic phase and the asymptomatic phase of heart failure induced by chronic cardiotoxicity of doxorubicin are associated with a worse prognosis, with a mortality rate of up to 50% in one year.[6,7]

Beta-blockers promote neurohumoral regulation in the presence of cardiac dysfunction, leading to positive remodelling of the left ventricle, which reduces mortality in heart failure.[8] Some have antioxidant and free radical removal function.[7] Their pharmacological mechanism suggests a cardioprotective function, however, there are still no recommendations for their use in prevention of anthracycline-induced cardiotoxicity. The objective of this study was to conduct a systematic review of the cardioprotective role of beta-blockers in preventing anthracycline-induced cardiotoxicity in adults.

METHODS

A descriptive study was carried out, consisting of a systematic review of the literature. The research was carried out in the databases MedLine/PubMed, Embase, ISI Web of Knowledge, Latin American and Caribbean Literature in Health Sciences (Lilacs) and Scientific Electronic Library Online (SciELO), in which several combinations of terms related to the topic were used, including derivations. The filter *humans* was used to limit the search, excluding experimental animal studies and in vitro tests. Articles listed in the references have also been identified and reviewed. The search strategy used for the MedLine/PubMed database and replicated to the other databases is in Appendix 1.

FIGURE 1



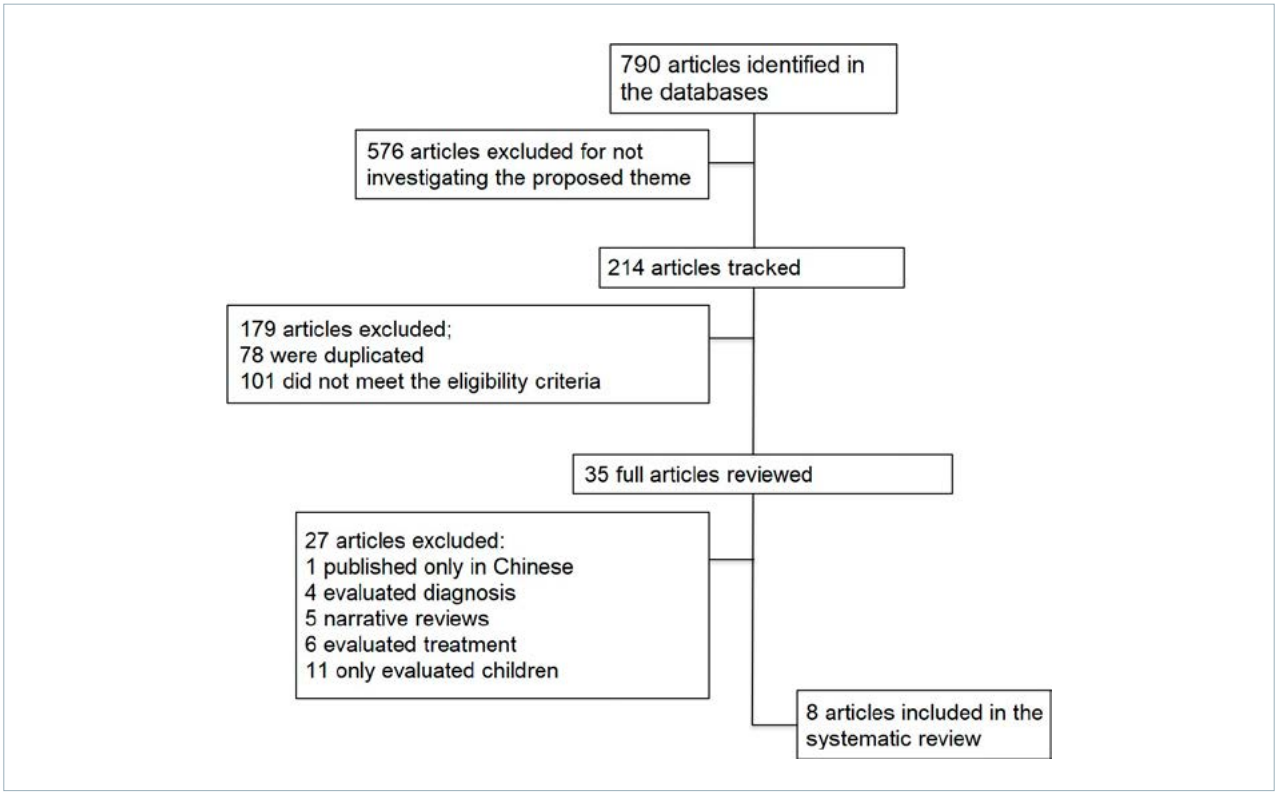
Studies could include, in addition to adults, paediatric populations. However, studies with only patients younger than 18 years old were excluded. Studies focusing on the diagnosis or treatment of anthracycline-induced cardiotoxicity, rather than on its primary prevention, were also excluded, as well as studies analysing non-beta-blocking drugs as a strategy to prevent anthracycline cardiotoxicity. Studies that included other chemotherapeutics in their analysis could be included in the review, provided that an anthracycline had also been analysed. The included studies could be clinical trials, cohort studies, historical cohorts or case-control studies, originally published in any language, provided they also had a publication in the English or Spanish language. There was no restriction of publication date. Articles published up to April 10, 2017 (date of search) could be included. Articles such as Simple Revision/Narrative, Editorial, Letter to the Editor, Short Communication, Preliminary Communication or Case Report were excluded. Since this was a systematic review, it did not require approval from the institution's Research Ethics Committee.

For the analysis and selection of the articles to be included in the review, the articles titles were initially evaluated based on the search strategy in the electronic databases, with a subsequent evaluation of the studies abstracts that contemplated the subject. The articles considered pertinent to the subject were read in full, to be then excluded the articles considered outside the topic or with a design out of the inclusion criteria. In this process, two reviewers participated independently, reaching a consensus when there was disagreement. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma) criteria was used in the eligibility of articles found for inclusion in the systematic review.[9] No meta-analysis was performed. The results of the studies were described in a descriptive way by drugs of the beta-blockers. Biases were considered and analysed individually for each study included.

RESULTS

From the keywords used in the search strategy, 790 articles were found. Delimiting the topic from the title, 576 articles were excluded (different population, different chemotherapeutics or different intervention medications), and 214 articles were then screened. Of these, after reviewing the abstract, 78 articles were excluded due to duplication in the electronic databases search, and 101 articles because they

FIGURE 2



did not meet the eligibility criteria (case reports, case series, experimental studies, animal studies, treatment research, chemotherapy not including anthracyclines), leaving 35 articles for full analysis. After reading the complete text, 27 were excluded because they did not fit the inclusion criteria regarding the design, research proposal and quality of evidence, remaining eight articles that met the inclusion criteria and were included in the systematic review.[10-17] Relevant articles were screened and analysed according to the flowchart contained in Figure 2.

The eight articles selected consist of unicentric randomized clinical trials, four of them being placebo-controlled trials (Kalay et al.[10], Kaya et al.,[12] Tashakori Beheshti et al.,[15] Gulati et al.[17]), and four with control group without placebo or any other intervention (Georgakopoulos et al.,[11] Bosch et al.,[13] Jhorawat et al.,[16] and Elitok et al[14]). The study by Bosch et al.[13] analyzed the intervention with two combined drugs (carvedilol and enalapril), and Georgakopoulos et al.[11] also evaluated two drugs: metoprolol and enalapril, but in separate groups, compared to the control group. The study by Gulati et al.[17] evaluated the use of metoprolol and candesartan, in combination and separately (associated with placebo), and included a control group that received two placebos. The other five studies compared one group with administration of a beta-blocker to a control group with or without placebo.

A total of 655 research participants were included in the eight studies, of which 281 (42.9%) used a beta-blocker drug, while 115 (17.5%) used placebo and 184 (28.1%) did not receive medication as intervention or placebo (control group without placebo). The remaining 75 patients (11.4%) used another drug to be evaluated as cardioprotective intervention: 43 (6.5%) used enalapril and 32 (4.9%) used candesartan.

Among the patients who received beta-blockers, 27 (4.1%) used nebivolol, 87 (13.3%) used metoprolol, 30 (4.6%) used metoprolol in combination with candesartan, 167 (25.5%) used carvedilol and 45 (6.9%) used carvedilol in combination with enalapril.

In the eight articles included, the primary outcome consisted of changes in echocardiographic parameters, mainly left ventricular ejection fraction (LVEF) and left ventricular systolic and diastolic diameters. Two of the studies performed longitudinal strain and left ventricular myocardial strain rate analysis using tissue Doppler, including those findings at the primary outcome (Tashakori Beheshti et al.[15] and Elitok et al.[14]). Another study (Bosch et al.[13]) evaluated, in addition to the echocardiogram, troponin I and brain natriuretic peptide (BNP) values, and cardiac magnetic resonance imaging.

Two studies also evaluated mortality as a secondary outcome (Jhorawat et al.[16] and Kalay et al.[10]), in which, respectively, 22.2% and 4.0% of carvedilol patients died at follow-up, while mortality in the control group was 18.5% and 16.0%, with no statistically significant difference for this comparison in the two studies. In both, however, there was no differentiation of the cause of the deaths, and it was not possible to distinguish the cardiovascular mortality from that occurred by the neoplasia or its complications. The study by Georgakopoulos et al.[11] did not describe the mortality among the outcomes analysed, but it describes, in the results, that no patient died or stopped chemotherapy due to cardiotoxicity.

The beta-blockers used in the included articles were administered under different therapeutic regimens at different doses, always before the start of chemotherapy. Clinical follow-up was performed for up to 31 months in the study by Georgakopoulos et al.,[11] with great heterogeneity regarding the follow-up time in the sample analysed. In the study by Tashakori Beheshti et al.,[15] the follow-up time was not explained, despite description of the protocol of four consecutive cycles of chemotherapy, with a duration of 21 days each. In the other studies included, clinical follow-up was done for six months.

Six studies analysing beta-blockers as cardioprotective agents in anthracycline chemotherapy were positive, with superiority of medication use over placebo or no medication. In two of these (Tashakori Beheshti et al.[15] and Elitok et al.[14]), there was no difference in relation to LVEF between the intervention and control groups, but the studies were considered positive by changes in strain parameters in all walls (Tashakori Beheshti et al.[15]) or most of the ventricular walls (Elitok et al. [14]), observed in the control group compared to the intervention group. Thus, in the four studies that showed a difference in the mean final LVEF between the intervention and control groups, the differences were, in percentage points, 17.4 (Kalay et al.[10]), 6.3 (Kaya et al.[12]), 3.1 (Jhorawat et al.[16]) and 3.1 (Bosch et al.[13]). General information on each study, designs, results and methodological characteristics capable of generating biases are set out in Table 1. Analysis of each beta-blocker drug and its results in the included studies is set out in Table 2.

TABLE 1. ANALYSIS OF STUDIES INCLUDED IN THE SYSTEMATIC REVIEW, IN CHRONOLOGICAL ORDER OF PUBLICATION

Author, publication year	City, Country	Intervention (N)	Comparison (N)	Results and data
Kalay et al., 200610	Kayseri, Turkey	Carvedilol (25)	Control group with placebo (25)	Intervention was superior. Initial LVEF and after six months: Carvedilol Group = 70.5% vs. 69.7%, p = 0.3; Control Group = 68.9% vs. 52.3%; p = 0.001.
Georgakopoulos et al., 201011	Athens, Greece	Metoprolol (25)	Control group without placebo (40) and Enalapril group (43)	No difference. LVEF after 12 months: Metoprolol Group = 63.3%, Enalapril Group = 63.9%, Control Group = 66.6%; p = 0.06.
Kaya et al., 201312	Kayseri, Turkey	Nebivolol (27)	Control group with placebo (18)	Intervention was superior. LVEF after six months: Nebivolol Group = 63.8%, Control Group = 57.5%; p = 0.01. NT-pro-BNP at zero and six months: Nebivolol Group = 147-152, p = 0.77; Control Group = 144-204, p = 0.01.
Bosch et al., 201313	Barcelona, Spain	Carvedilol + Enalapril (45)	Control group without placebo (45)	Intervention was superior. Incidence of HF or reduction of LVEF> 10%: Intervention Group = 9.5% vs. Control Group = 19%, p = 0.22. Difference in LVEF variation between groups: echocardiogram analysis = -3.11 (p = 0.04); cardiac resonance analysis = -3.40 (p = 0.09). Death or HF: 6.7% vs. 22.2%; p = 0.036. Various chemotherapy drugs used - unspecified on results in the group that used anthracyclines (40% of Intervention Group).
Elitok et al., 201414	Istanbul, Turkey	Carvedilol (40)	Control group without placebo (40)	Intervention was superior. LVEF after six months: Carvedilol Group = 64.1%, Control Group = 63.3%; p = NS; systolic strain on the septal wall: Carvedilol Group = 20.1, Control Group = 16; p <0.005; systolic strain on the lateral wall: Carvedilol Group = 18.2, Control Group = 14; p <0.005.
Tashakori Beheshti et al., 201615	Mashhad, Iran	Carvedilol (30)	Control group without placebo (40)	Intervention was superior. Mean difference in pre and post QT LVEF did not differ between groups, but mean pre and post QT strain of all walls was higher in the Control Group.
Jhorawat et al., 201616	Chandigarh, India	Carvedilol (27)	Control group without placebo (27)	Intervention was superior. LVEF variation after six months: Carvedilol Group = + 0.89%, Control Group = -7.74%; p = 0.003. Variation of LV systolic diameter after six months: Carvedilol Group = + 0.41 mm, Control Group = + 3.99; p <0.05.
Gulati et al., 201617	Lørenskog, Norway	Metoprolol + Candesartan = 30; Metoprolol + placebo = 32 (62)	Groups: Candesartan + placebo (32); placebo + placebo (32)	No difference. Mean LVEF reduction: without Metoprolol = 1.8% percentage point; with Metoprolol = 1.6% percentage point; p = 0.772.

LVEF = left ventricle ejection fraction; HF = heart failure; NT-pro-BNP = N-terminal pro–B-type natriuretic peptide; QT = chemotherapy; LV = left ventricle

TABLE 2. SPECIFIC ANALYSIS OF EACH BETA-BLOCKER AGENT USED IN THE STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Beta-blocker drug	Studies included	Number of participants with the beta-blocker in the studies	Results in the studies
Carvedilol	Kalay et al.10, Bosch et al.13, Elitok et al.14, Tashakori Beheshti et al.15, Jhorawat et al.16	167	The five were positive, but two presented differences only in the longitudinal strain, and not in LVEF (Elitok et al.14, Tashakori Beheshti et al.15)
Metoprolol	Georgakopoulos et al.11, Gulati et al.17	87	Both were negative.
Nebivolol	Kaya et al.12	27	Positive.

LVEF = left ventricle ejection fraction

DISCUSSION

The high incidence of neoplasia is a worldwide trend due to several factors, including increased life expectancy, modern living habits and environmental pollution. Among the therapeutic arsenal of cancer treatment, anthracyclines are chemotherapeutics widely used in several neoplasms, with cardiotoxicity being one of its main adverse effects.[2]

In this systematic review, the main international scientific publications on the cardioprotective role of beta-blockers in preventing anthracycline cardiotoxicity were included and evaluated. Data obtained from the included clinical trials point to a potential cardioprotective function, but with limitations to a subclinical spectrum, in which a modest reduction of LVEF can be avoided after the use of chemotherapy. Still, some studies have limited themselves to finding benefits only in an even more restricted and precocious parameter, through the analysis of the strain through the echocardiogram. A reduction in left ventricular function is not always a predictor of heart failure,[18] which raises questions about the outcomes used in clinical trials so far.

Known cardioprotection mechanisms of beta-blockers

For the development of an effective preventive strategy, several studies have attempted to clarify the pathophysiological mechanism of anthracycline cardiotoxicity. Oxidative stress and increased signalling for apoptosis are more frequent hypotheses, followed by thrombosis or vasospasm of coronary artery, as well as platelet aggregation induced by cisplatin[19-21]. In addition to neurohumoral modulation, specific and individual actions of some beta-blocking agents could justify cardioprotection in the use of anthracyclines, but such data is scarce.

Carvedilol is a non-selective beta-blocker that also has action on alpha-1 receptors.[22] It also has antioxidant effects and inhibits NADH-diaphorase (NADH-d).[23] It has been shown that carvedilol is able to reduce the release of free radicals and apoptosis in cardiomyocytes after exposure to chemotherapeutic agents, preventing lipid peroxidation and increasing vitamin E concentrations.[7,22,24,25]

Nebivolol, a third-generation beta-blocker with high selectivity for beta-1 receptors, has cardioprotective properties via peripheral vasodilation mediated by nitric oxide,[26] as well as antioxidant properties.[27] In experimental studies with rats, antiapoptotic effects on infarction and reduction of anthracycline cardiotoxicity were demonstrated.[28,29]

Biases and limitations of studies included in the review

Seven of the eight studies included in this review were published less than 10 years ago, which demonstrates relatively recent interest in the subject, even though cardiotoxicity associated with the use of anthracyclines has been known for decades. Historically, after the elucidation of pathophysiological mechanisms and once the relationship between cardiac lesion and chemotherapy with anthracyclines was established, some studies were conducted, but the scientific evidence is still timid, especially when compared to other relevant subjects in cardiology.

Since all the studies included in this analysis were unicentric and with a small sample size, there are limitations in the external validity for all of them, although similar results have been obtained in the majority. The main types of biases identified were those of measurement, as there were no standardized methods for the evaluation of the variables analysed. Selection and confounding biases were minimized by the clinical trial design common to all and by the exclusion criteria of each study. The four open-label, non-placebo-controlled studies (Jhorawat et al.[16], Elitok et al.,[14], Georgakopoulos et al.,[11] and Bosch et al.[13]) had their internal validity compromised due to potential biases from the lack of blinding (allocation confidentiality), which may compromise the reliability and validity of data. The follow-up time used in the studies makes it impossible to assess the anthracyclines for chronic cardiotoxicity, a common limitation to all studies included.

The study by Bosch et al.[13] used the combination of carvedilol and enalapril as an intervention. Therefore, individual analysis of the beta-blocker in question becomes compromised. However, for the scientific value and methodological robustness, the study was included in the review, since it added value to the analysis of a beta-blocker as a potential cardioprotective agent in the use of anthracyclines. As for the study by Gulati et al.[17], it was a double blind, placebo-controlled, randomized, 2x2 clinical trial, which analysed the drugs candesartan and metoprolol separately and combined in this setting. Results included individual analyses of the drugs in the allocated groups (candesartan-metoprolol, candesartan-placebo, metoprolol-placebo and placebo-placebo), allow-

ing for the specific interpretation for the beta-blocker metoprolol in this systematic review.

The use of different criteria and measurements does not guarantee comparability between studies included. However, individual analyses of the studies can be very useful in view of the scarcity of robust scientific evidence on the subject. Regarding the echocardiographic parameter used, although the general reduction in LVEF was an important criterion for comparison, reductions to values lower than 50%, that is, expressive drops that constitute left ventricular failure, would have greater clinical relevance.

In addition, the persistence of left ventricular dysfunction was not analysed in the vast majority of studies included, which were followed-up for only six months. Long-term results could strengthen the scientific consistency about the use of beta-blockers in this setting, with the potential to demonstrate continued and long-lasting benefits. The studies performed so far have presented an excellent capacity to generate a rational hypothesis with biological plausibility, with preliminary results considered satisfactory. However, there is a lack of normative studies and sufficient robustness to mark the routine use of beta-blockers in protocols to prevent anthracycline-induced cardiotoxicity.

Considerable heterogeneity within the beta-blocker class may be a confounding factor in this analysis, given the different pharmacological actions of the drugs in question. It is postulated that the activity of inhibiting free radicals is important in the prevention of cardiotoxicity by chemotherapy, and that this is offered in a different way among the agents of the class, especially carvedilol. Despite the scientific data more consistent with its use in relation to cardioprotective action, the ideal beta-blocking agent for clinical research and use is still undetermined. Due to the differences in pharmacokinetic properties between the agents studied and the absence of class effect, we considered that the meta-analysis would not be adequate, even though the intention of the analysis was the beta-blockers class in general.

Other cardioprotective possibilities

No study used bisoprolol as an intervention. This beta-blocker, as it has a preference for action on beta-1 receptors and has high cardioselectivity,[30] may be an option for future studies with potential cardioprotective action against myocardial injury caused by chemotherapeutic agents. Nebivolol, which had only one study included, also presents a more modern action, with potential vasculoprotective action, and should be the subject of further investigations.

To date, only the drug dexrazoxane has formal recommendation in some situations for the prevention of cardiotoxicity associated with anthracyclines. This drug, an iron chelator that prevents formation of the iron-doxorubicin complex, has been studied in this context since the 1980s[31-33]. Satisfactory results have been observed in studies using dexrazoxane prior to chemotherapy with anthracyclines in different regimens.[34-37] However, according to the clinical practice guideline of the 2008 American Society of Clinical Oncology, dexrazoxane should not be routinely used in combination with doxorubicin or other anthracyclines. Its use should be recommended only if a cumulative dose of doxorubicin greater than 300mg/m² in adults, if predicted to be of therapeutic benefit with even higher doses of chemotherapy.[38] In Brazil, its use is limited in metastatic breast cancer when it occurs the use of high cumulative doses of anthracyclines.[4]

Other pharmacological classes have been studied as possible cardioprotectors against cardiotoxicity associated with anthracyclines. Inhibitors of angiotensin converting enzyme and angiotensin II receptor antagonists are drugs used and recommended in the therapeutic arsenal of heart failure and have, to date, weak scientific evidence of cardioprotection in chemotherapy. Some drugs were also analysed in studies selected for this review. While candesartan showed positive results in cardioprotective efficacy,[17] enalapril demonstrated neutrality when used alone.[11] Limitations of the evidence on these other classes keep beta-blockers one step ahead in relation to the volume of scientific information in this context.

The scientific gap in the topic extends to spironolactone, an aldosterone antagonist, also used in the treatment of heart failure.[39] One study demonstrated the short-term effectiveness of this drug in the prevention of anthracycline-induced cardiotoxicity,[40] however, despite the pharmacological rationale attractive, more studies are needed, especially in the long term. The combination of drugs with potential cardioprotective action, in turn, could offer a synergistic effect in the prevention of cardiotoxicity by chemotherapy, constituting a strategy to be considered in future studies. As with studies included in this review,[13,17] the use of medications commonly used in the treatment of heart failure, administered

in combination, represents a target of interest in clinical research,[41] considering their pharmacological properties, the currently accessible cost of most of drugs and the low risk of serious adverse events.

This review brings scientific benefits on a relevant topic, and has the merits of evaluating the quality of evidence with recommended methods, but is also subject to bias. The selective reporting of complete studies in a systematic review may constitute publication bias, which should be reported as a potential limitation of this study. In the context of systematic reviews, outcome selective reporting, or outcome reporting bias, should also be considered, although the implications of the mentioned biases in the conduct and reporting of the reviews are unclear. The meta-analysis, considering only one of the beta-blocking agents, may be beneficial and configures the focus of future research in the search for answers on cardioprotection in chemotherapy treatment.

CONCLUSIONS

Beta-blockers represent a pharmacological class of interest in the prevention of anthracycline-associated cardiotoxicity. Existing scientific evidence, still incipient, exposes the need for a broader and more precise investigation. Analysing in detail the studies included in this review, it is concluded that beta-blockers have a potential cardioprotective action, yet to be definitively proven in larger studies, with long-term follow-up and using relevant clinical outcomes. Based on available scientific data, carvedilol, an agent of the class with the most evidence of benefit and with a greater number of patients evaluated, stands out. The dosage regimen and the optimal time of administration should still be defined, as well as the magnitude of the benefit of its use or of other beta-blockers, to allow the construction of future cardioprotective protocols in susceptible populations that will be submitted to the use of anthracyclines.

Potential conflict of interest

The authors declare that there is no relevant conflict of interest.

Financing source

The present study had no external sources of financing.

Academic relation

This article is part of the End of Course Paper of Taissa Borges Bourguignon, Luíza Dias Torres and Lorenza Silveira Arruda for graduation in Medicine from the School of Sciences of the Santa Casa de Misericórdia de Vitória (Emescam).

APPENDIX 1. THE SEARCH STRATEGY USED IN MEDLINE/PUBMED WAS REPEATED ON THE OTHER DATABASES

1. adult*.tw
2. (cancer OR neoplas* OR malignan* OR tumor* OR solid tumor* OR blood tumor* OR hematopoietic tumor* OR lymphoid tumor* OR lymphoid malignan*).ti,ab
3. (doxorubicin* OR adriamycin* OR daunorrubicin* OR epirrubicin* chemotherap*).ti,ab
4. (beta-block* OR carvedilol OR propranolol OR metoprolol OR bisoprolol OR atenolol OR nebivolol).ti,ab
5. (prevention OR prophylaxis).ti,ab
6. (cardiac* OR cardiac fail* OR cardiac toxici* OR cardiotoxici* OR heart OR heart fail* OR cardiac dysfunction OR heart dysfunction OR cardiotoxicity OR cardiac toxicity OR cardiomyopathy).ti,ab
7. (systolic disfuntion OR diastolic disfunction OR myocardi* OR myocardial disfuntion OR cardioprotection).ti,ab
8. (clinical trial* OR intervention* OR interventional stud* OR cohort* OR cohort stud* OR historical cohort* OR case-control* OR case-control stud* OR observational stud*).tw
9. 1 AND 2 AND 3
10. 4 AND 5
11. 6 OR 7
12. 9 AND 10 AND 11
13. 8 AND 12

RESUMO

OBJETIVO: *Este estudo teve como objetivo analisar o papel dos betabloqueadores na prevenção da cardiotoxicidade induzida pelas antraciclinas em adultos.*

MÉTODOS: *Foi realizada uma revisão sistemática em bases de dados eletrônicos, incluindo os estudos relevantes que analisaram fármacos betabloqueadores como agentes cardioprotetores antes do início do uso de antraciclinas por pacientes oncológicos adultos.*

RESULTADOS: *Após aplicação dos critérios de elegibilidade e seleção, foram obtidos oito artigos considerados de boa qualidade, que se adequavam à temática proposta, sendo todos ensaios clínicos, quatro placebo-controlados, totalizando 655 pacientes incluídos. Destes, 281 (42,9%) fizeram uso de algum betabloqueador como intervenção, sendo o carvedilol o mais utilizado (167 pacientes – 25,5%). Seis estudos foram considerados positivos quanto à cardioproteção exercida pelos betabloqueadores, porém apenas quatro demonstraram diferença na fração de ejeção do ventrículo esquerdo após a quimioterapia nos grupos que usaram betabloqueadores em relação aos grupos controle. O carvedilol e o nebivolol, mas não o metoprolol, tiveram resultados positivos quanto à cardioproteção. Outros betabloqueadores não foram avaliados nos estudos incluídos.*

CONCLUSÕES: *Apesar de haver um potencial efeito cardioprotetor dos betabloqueadores, conforme demonstrado em ensaios clínicos pequenos e unicêntricos, sua utilização rotineira na prevenção da cardiotoxicidade associada às antraciclinas requer maiores comprovações científicas.*

PALAVRAS-CHAVE: *Cardiotoxicidade. Antraciclinas. Insuficiência cardíaca. Cardiopatias/prevenção e controle.*

REFERENCES

1. Gatta G, Capocaccia R, Coleman MP, Ries LA, Berrino F. Childhood cancer survival in Europe and the United States. Cancer. 2002;95(8):1767-72.
2. Wojtacki J, Lewicka-Nowak E, Lesniewski-Kmak K. Anthracycline-induced cardiotoxicity: clinical course, risk factors, pathogenesis, detection and prevention - review of the literature. Med Sci Monit. 2000;6(2):411-20.
3. Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. J Am Coll Cardiol. 2014;64(9):938-45.
4. Kalil Filho R, Hajjar LA, Bacal F, Hoff PMG, Diz MDPS, Galas FRBG, et al. I diretriz brasileira de cardio-oncologia da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2011;96(2 supl. 1):1-52.
5. Matos Neto RP, Petrilli AS, Silva CM, Campos Filho O, Oporto VM, Gomes LF, et al. Left ventricular systolic function assessed by echocardiography in children and adolescents with osteosarcoma treated with doxorubicin alone or in combination with dexrazoxane. Arq Bras Cardiol. 2006;87(6):763-71.
6. Harake D, Franco VI, Henkel JM, Miller TL, Lipshultz SE. Cardiotoxicity in childhood cancer survivors: strategies for prevention and management. Future Cardiol. 2012;8(4):647-70.
7. Lipshultz SE, Sambatakos P, Maguire M, Karnik R, Ross SW, Franco VI, et al. Cardiotoxicity and cardioprotection in childhood cancer. Acta Haematol. 2014;132(3-4):391-9.
8. Ponikowski P, Voors AA, Anker SD, Bueno H, Clelan JGF, Coats AJS, et al; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Disponível em: www.prisma-statement.org.
10. Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2006;48(11):2258-62.
11. Georgakopoulos P, Roussou P, Matsakas E, Karavidas A, Anagnostopoulos N, Marinakis T, et al. Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: a prospective, parallel-group, randomized, controlled study with 36-month follow-up. Am J Hematol. 2010;85(11):894-6.
12. Kaya MG, Ozkan M, Gunebakmaz O, Akkaya H, Kaya EG, Akpek M, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. Int J Cardiol. 2013;167(5):2306-10.
13. Bosch X, Rovira M, Sitges M, Domènech A, Ortiz-Pérez JT, Caralt TM, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol. 2013;61(23):2355-62.
14. Elitok A, Oz F, Cizgici AY, Kilic L, Ciftci R, Sen F, et al. Effect of carvedilol on silent anthracycline-induced cardiotoxicity assessed by strain imaging: a prospective randomized controlled study with six-month follow-up. Cardiol J. 2014;21(5):509-15.
15. Tashakori Beheshti A, Mostafavi Toroghi H, Hosseini G, Zarifian A, Homaei Shandiz F, Fazlinezhad A. Carvedilol administration can prevent doxorubicin-induced cardiotoxicity: a double-blind randomized trial. Cardiology. 2016;134(1):47-53.
16. Jhorawat R, Kumari S, Varma SC, Rohit MK, Narula M, Suri V, et al. Preventive role of carvedilol in adriamycin-induced cardiomyopathy. Indian J Med Res. 2016;144(5):725-9.
17. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J. 2016;37(21):1671-80.
18. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97(1):2869-79.
19. Octavia Y, Tocchetti CG, Gabrielson KL, Janssens S, Crijns HJ, Moens AL. Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. J Mol Cell Cardiol. 2012;52(6):1213-25.
20. Arola OJ, Saraste A, Pulkki K, Kallajoki M, Parvinen M, Voipio-Pulkki LM. Acute doxorubicin cardiotoxicity involves cardiomyocyte apoptosis. Cancer Res. 2000;60(7):1789-92.
21. Schimmel KJ, Richel DJ, van den Brink RB, Guchelaar HJ. Cardiotoxicity of cytotoxic drugs. Cancer Treat Rev. 2004;30(2):181-91.
22. Machado V, Cabral A, Monteiro P, Gonçalves L, Providência LA. Carvedilol as a protector against the cardiotoxicity induced by anthracyclines (doxorubicin). Rev Port Cardiol. 2008;27(10):1277-96.
23. Cheng J, Kamiya K, Kodama I. Carvedilol: molecular and cellular basis for its multifaceted therapeutic potential. Cardiovasc Drug Rev. 2001;19(2):152-71.
24. Spallarossa P, Garibaldi S, Altieri P, Fabbi P, Manca V, Nasti S, et al. Carvedilol prevents doxorubicin-induced free radical release and apoptosis in cardiomyocytes in vitro. J Mol Cell Cardiol. 2004;37(4):837-46.
25. El-Shitany AN, Tolba AO, El-Shanshory RM, El-Hawary EE. Protective effect of carvedilol on adriamycin-induced left ventricular dysfunction in children with acute lymphoblastic leukemia. J Card Fail. 2012;18(8):607-13.
26. Shibata MC, Flather MD, Böhm M, Borbola J, Cohen-Solal A, Dumitrascu D, et al; Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS). Rationale and design. Inter J Cardiol. 2002;86(1):77-85.
27. Münzel T, Gori T. Nebivolol: the somewhat-different beta-adrenergic receptor blocker. J Am Coll Cardiol. 2009;54(16):1491-9.
28. Groot AA, Mathy MJ, van Zwieten PA, Peters SL. Antioxidant activity of nebivolol in the rat aorta. J Cardiovasc Pharmacol. 2004;43(1):148-53.
29. Nigris F, Rienzo M, Schiano C, Fiorito C, Casamassimi A, Napoli C. Prominent cardioprotective effects of third generation beta blocker nebivolol against anthracycline-induced cardiotoxicity using the model of isolated perfused rat heart. Eur J Cancer. 2008;44(3):334-40.
30. Luna RL, Oigman W, Ramirez JA, Mion D, Batlouni M, Rocha JC, et al. Eficácia e tolerabilidade da associação bisoprolol/hidroclorotiazida na hipertensão arterial. Arq Bras Cardiol. 1998;71(4):601-8.
31. Blum RH. Clinical status and optimal use of the cardioprotectant, dexrazoxane. Oncology (Williston Park). 1997;11(11):1669-77.

32. Hellmann K. Cardioprotection by dexrazoxane (Cardioxane; ICRF 187): progress in supportive care. Support Care Cancer. 1996;4(4):305-7.

33. Fulbright JM, Huh W, Anderson P, Chandra J. Can anthracycline therapy for pediatric malignancies be less cardiotoxic? Curr Oncol Rep. 2010;12(6):411-9.

34. Iarussi D, Indolfi P, Casale F, Martino V, Di Tullio MT, Calabrò R. Anthracycline-induced cardiotoxicity in children with cancer: strategies for prevention and management. Paediatr Drugs. 2005;7(2):67-76.

35. Chatterjee K, Zhang J, Honbo N, Karliner JS. Doxorubicin cardiomyopathy. Cardiology. 2010;115(2):155-62.

36. Cvetkovic RS, Scott LJ. Dexrazoxane: a review of its use for cardioprotection during anthracycline chemotherapy. Drugs. 2005;65(7):1005-24.

37. Paiva MG, Petrilli AS, Moisés VA, Macedo CR, Tanaka C, Campos O. Cardioprotective effect of dexrazoxane during treatment with doxorubicin: a study using low-dose dobutamine stress echocardiography. Pediatr Blood Cancer. 2005;45(7):902-8.

38. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009;27(1):127-45.

39. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17.

40. Akpek M, Ozdogru I, Sahin O, Inanc M, Dogan A, Yazici C, et al. Protective effects of spironolactone against anthracycline-induced cardiomyopathy. Eur J Heart Fail. 2015;17(1):81-9.

41. Meattini I, Curigliano G, Terziani F, Becherini C, Airoldi M, Allegrini G, et al. SAFE trial: an ongoing randomized clinical study to assess the role of cardiotoxicity prevention in breast cancer patients treated with anthracyclines with or without trastuzumab. Med Oncol. 2017;34(5):75.

REVIEW ARTICLE

Association of Interleukin-10 -1082A>G (rs1800896) Polymorphism with Predisposition to Breast Cancer: a Meta-Analysis based on 17 Case-Control Studies

Mostafa Abedinzadeh[1]
Hossein Neamatzadeh[2]
Mohammadali Jafari[3]
Mohammad Forat-Yazdi[4]
Rezvan Nasiri[5]
Soudabeh Farahnak[6]
Elnaz Foroughi[7]
Masoud Zare-Shehneh[8]

1. Department of Internal Medicine, Kashan University of Medical Sciences, Kashan, Isfahan, Iran
2. Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
3. Department of Emergency Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Yazd, Iran
4. Department of Internal Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Yazd, Yazd, Iran
5. Department of Restorative and Esthetic, Arak University of Medical Sciences, Arak, Markazi, Iran
6. Department of Endodontic, Arak university of Medical Sciences, Arak, Markazi , Iran
7. Department of Pediatric Dentistry, Arak university of Medical Sciences, Arak, Markazi, Iran
8. Department of Medical Genetics, Shahid Sadoughi University of Medical Sciences, Yazd, Yazd, Iran

http://dx.doi.org/10.1590/1806-9282.64.08.756

SUMMARY

INTRODUCTION: *The association between the between IL-10 -1082A>G (rs1800896) polymorphism and breast cancer has been evaluated by several number case-control studies. However, these studies might be underpowered to reveal the true association.*

OBJECTIVE: *We have performed a comprehensive meta-analysis to investigate the association IL-10 -1082A>G polymorphism and breast cancer.*

MATERIALS AND METHODS: *A systematic literature search was conducted using PubMed, Google Scholar, and Web of Science up to September 20, 2017. Data was analysed with CMA software to identify the strength of the association by pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs).*

RESULTS: *A total of 17 case-control studies involving 3275 cases and 3416 controls obtained from database searches were examined. Overall, there was no significant association between IL-10 -1082A>G polymorphism and breast cancer risk under all genetic models. No significant publication bias was found for the five genetic models (G vs. A: OR = 1.184, 95% CI = 0.895-1.180, p= 0.230; GG vs. AA: OR = 1.430, 95% CI = 0.927-2.204, p= 0.106; GA vs. AA: OR = 0.966, 95% CI = 0.765-1.221, p= 0.774; GG+GA vs. AA: OR = 0.957, 95% CI = 0.697-1.314, p= 0.786; and GG vs. GA+AA: OR = 1.221, 95% CI = 0.981-1.518, p= 0.073). Moreover, there was no significant association between the IL-10 -1082A>G polymorphism and breast cancer risk by ethnicity.*

CONCLUSION: *Our findings indicated that IL-10 -1082A>G (rs1800896) polymorphism might not be a risk factor for the development of breast cancer.*

KEYWORDS: *Breast neoplasms. Interleukin-10. Polymorphism, genetic. Meta-analysis.*

DATE OF SUBMISSION: 08-Oct-2017
DATE OF ACCEPTANCE: 07-Jan-2018
Corresponding Author: Mohammad Forat-Yazdi
Department of Internal Medicine,
Shahid Sadoughi University of Medical Sciences, Yazd, Iran
Email: mohammad.foratyazdi@gmail.com

hn_1364@yahoo.com, neamatzadehh@gmail.com
s.keshavarzi.yazd@gmail.com, husen.karagunlu@gmail.com
mr.dehghanzadeh55@gmail.com, elnforoughi@gmail.com
mrsobhanardakani@gmail.com

INTRODUCTION

Breast cancer is one of the most commonly diagnosed invasive malignancies.[1-3] Breast cancer is the second most common cancer-related death in women worldwide and accounts for 15.4% of cancer-related deaths in women.[4,5] The pathogenesis of breast cancer is multifactorial. Hereditary breast cancer accounts for only 5-10% of all breast cancer cases and germline mutations with the two major breast cancer susceptibility genes BRCA1 and BRCA2, being responsible approximately for 2-3% of all cases.[6,7] Besides gene tests to identification of high-risk BRCA1 or BRCA2 mutations carriers, the ability to predict breast cancer development, is not well established yet.[7,8] The findings suggest that accumulation of several polymorphic variants is responsible for elevated risk of breast cancer.[9,10] However, the association of genetic variations with the clinical characteristics and prognosis in breast cancer has not been fully identified.[11]

The human interleukin 10 gene is a steroid hormone receptor gene located on chromosome 6 at 6q25.1. It contains eight exons spanning 295 kb.[12,13] The IL-10 promoter is highly polymorphic and three most common SNPs, including -1082, -819, and -592, within this region have been correlated with IL-10 production.[14] Several epidemiological studies have evaluated IL-10 -1082 polymorphism and its association with breast cancer.[15-21] However, the effects of polymorphisms in rs2077647, rs2228480 and rs3798577 were also controversial. It is clear that the number of studies, time of analysis and new studies included in a meta-analysis directly influences the credibility and stability of the findings. Therefore, we have performed this systematic review and meta-analysis to more accurately assess the association between IL-10 -1082A>G (rs1800896) polymorphism and breast cancer risk, using more recent published studies.

MATERIALS AND METHODS

Search Strategies

A computerized literature search of different databases, including PubMed, Web of Science, EMBASE, China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM) and Google Scholar was conducted up to September 20, 2017. The search strategy identified all possible studies using combinations of the following terms and keywords: ''Breast cancer'', ''interleukin 10'', ''IL-10 gene'', ''-1082A>G'', ''rs1800896'', ''polymorphism'', "variant" and "mutation". Furthermore, we have manually screened the bibliographies of relevant articles and reviews for additional studies that were not captured by the database search. Publications in both English and Chinese languages were included, and only published studies with full-text articles were included.

Inclusion and Exclusion Criteria

The studies included in this meta-analysis had to meet the following criteria: (1) any study published as a case-control or cohort study that evaluated the association between IL-10 -1082A>G (rs1800896) polymorphism and breast cancer risk; (2) the numbers of cases and controls for each genotype were reported or sufficient data was provided to calculate the odds ratio (OR). The following were exclusion criteria: (1) not designed as case-control or cohort studies, (2) reviews, abstracts or animal studies; (3) studies were not relevant to IL-10 -1082A>G (rs1800896) polymorphism and breast cancer; (4) not providing the genotype frequencies; and (5) duplicate of previous publication. If multiple studies from the same case series were available, the one including the most individuals was used in the analysis.

Data Extraction

The information was carefully extracted from all of the eligible studies independently by two investigators based on the inclusion criteria listed above and then examined by an expert in headaches. From each of the included articles the following data were collected: first author, year of publication, country of origin, ethnicity, total number of cases and controls, frequencies of genotypes, genotyping technique, minor allele frequencies (MAFs), P-value for Hardy–Weinberg equilibrium (HWE). In case of disagreement, consensus was obtained on every item by joint review of the study. The different ethnic descents were categorized as Asian, European, American or African.

Statistical Methods

The odds ratio (OR) and its 95% confidence interval (CI) was used to assess the strength of association between IL-10 -1082A>G (rs1800896) polymorphism and breast cancer risk under allele model (G vs. A), homozygote model (GG vs. AA), heterozygote model (GA vs. AA), dominant model (GG+GA vs. AA), and

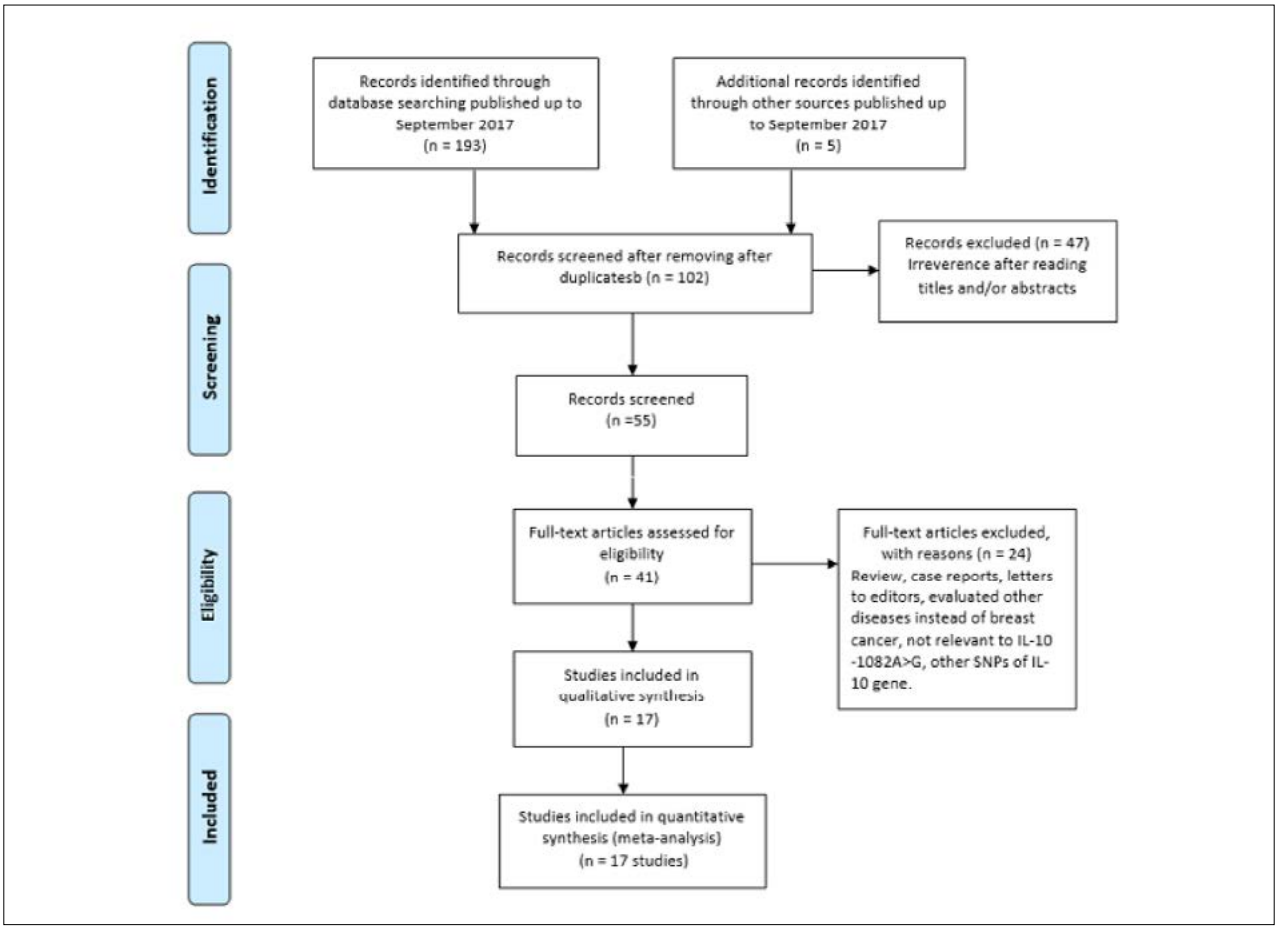
recessive model (GG vs. GA+AA). The significance of the pooled OR was determined by the Z-test. Heterogeneity assumption was checked by the Chi-square-based Q-test.[22] The effect of heterogeneity was quantified using the I^2 value as well as P value. A P-value less than 0.10 for the Q-test and I^2 value >50% indicates existence of heterogeneity among studies. The pooled OR was assessed in both fixed-effects model (the Mantel–Haenszel method)[23] and random-effects model (the DerSimonian and Laird methods),[24] so the pooled OR estimates of the included studies was calculated by the random-effects model. Otherwise, the fixed-effects model was used. Sensitivity analyses were performed to evaluate the stability of the results, namely, a single study in the meta-analysis was omitted in each turn to reflect the influence of the single data set on the pooled results. Deviation from the Hardy–Weinberg equilibrium (HWE) was checked among controls through exact test. Subgroup analyses by ethnicity and studies quality were performed subsequently. Begg's funnel plot was carried out to examine the potential publication bias between studies (P value less than 0.10 was selected to be statistically significant).[25] In addition, Egger's test on the natural logarithm scale of the OR was used to estimate the funnel plots asymmetry. [26] All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). All P values were two-sided, and P<0.05 was considered statistically significant.

RESULTS

Characteristics of Selected Studies

We have identified 211 published case-control studies before September 20, 2017 in the database search and by manual screening. Of these studies, the first screening excluded 109 publications that were excluded as duplicates or not relevant, leaving 102 studies for further selection. After removal of review articles, case reports, and those that did not meet our inclusion criteria, a total of 17 articles [4,12,13,15-21,27-33] with 3,275 cases and 3,416 controls were finally included in our meta-analysis. A flow diagram schematizing the inclusion and exclusion process of identified articles with the inclusion criteria is pre-

FIGURE 1. FLOW CHART OF LITERATURE SEARCH AND STUDY SELECTION.



sented in Figure 1. These studies were published between 2003 and 2017 and the average sample size was 192 cases per study. Of the 17 case-control studies focusing on the relationship between IL-10 -1082A>G (rs1800896) polymorphism and breast cancer, seven were conducted among Caucasians,[15-17,18-21] with 1336 cases and 1388 controls, eight among Asians[4,12,27-29,31,32] with 1,754 cases and 1,898 controls, and two among Africans,[30,33] with 185 cases and 130 controls. The studies were carried out in Italy, UK, USA, Canada, Turkey, Iran, China, India, Jordan and Egypt. The detailed characteristics of the included studies were shown in Table 1. The distribution of the genotypes in the control group of five case-control studies[13,27,30-32] was not in agreement with Hardy-Weinberg equilibrium (HWE). Twelve of 17 studies were in accordance with HWE were defined as high-quality studies. The genotypes distributions in the individual studies were presented in Table 1.

Quantitative synthesis

The main characteristics of these studies were listed in Table 2. The heterogeneity between studies was significant under all genetic models. Therefore, the random effect model was used for calculating the pooled OR. Overall, there was no significant associ-

TABLE 1. MAIN CHARACTERISTICS OF STUDIES INCLUDED IN THIS META-ANALYSIS.

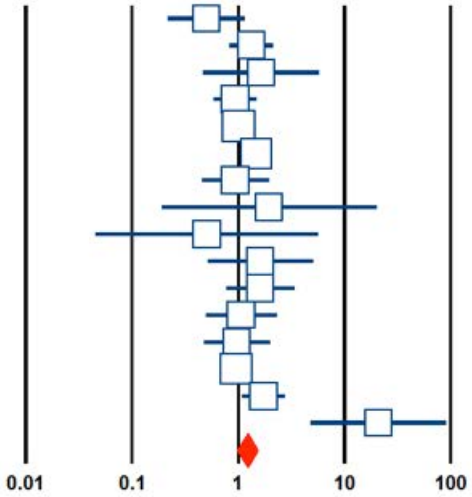
First Author/ Year	Country Ethnicity	Case	Control	Cases					Controls					MAFs	HWE
				Genotype			Allele		Genotype			Allele			
				AA	AG	GG	A	G	AA	AG	GG	A	G		
Giordani 2003 15	Italy (Caucasian)	125	100	60	54	11	174	76	33	51	16	117	83	0.415	0.614
Smith 2004 16	UK (Caucasian)	144	263	32	58	39	136	122	46	120	57	250	276	0.524	0.238
Guzowski 2005 17	USA (Caucasian)	50	25	10	28	12	48	52	9	12	4	30	20	0.400	1.000
Abdolrahim-Zadeh 2005 27	Iran (Asian)	275	320	119	116	40	177	373	146	125	49	417	223	0.348	0.012
Balasubramanian 2006 18	UK (Caucasian)	497	498	121	253	123	499	495	117	260	121	494	502	0.504	0.323
Onay 2006 19	Canada (Caucasian)	398	372	90	205	103	385	411	107	194	71	408	336	0.451	0.307
Scola 2006 20	Italy (Caucasian)	84	106	28	40	16	96	72	40	45	21	125	87	0.410	0.206
Gonullu 2007 21	Turkey (Caucasian)	38	24	13	22	3	48	28	16	7	1	39	9	0.187	0.834
Kong 2010 4	China (Asian)	315	322	285	29	1	599	31	285	35	2	605	39	0.060	0.422
Pooja 2012 12	India (Asian)	200	200	132	60	8	324	76	145	50	5	340	60	0.150	0.781
Liang 2013 28	China (Asian)	40	89	31	9	0	71	9	73	16	0	162	16	0.089	0.351
Vinod 2015 29	India (Asian)	125	160	76	31	18	183	67	67	78	15	212	108	0.337	0.254
Alsuhaibani 2016 30	Egypt (African)	80	80	16	47	17	79	81	14	50	16	78	82	0.512	0.024
Atoum 2016 31	Jordan (Asian)	202	210	157	29	16	343	61	151	42	17	344	76	0.181	0.001
Tian 2017 13	China (Asian)	312	312	51	132	129	234	390	27	154	131	208	416	0.666	0.050
Maruthi 2017 32	India (Asian)	285	285	80	146	59	262	308	89	159	37	234	336	0.408	0.009
Sabet 2017 33	Egypt (African)	105	50	15	41	49	71	139	27	21	2	75	25	0.250	0.396

MAFs: minor allele frequencies; HWE: Hardy–Weinberg equilibrium

FIGURE 2. FOREST PLOT OF IL-10 -1082A>G POLYMORPHISM AND BREAST CANCER RISK. A: OVERALL (RECESSIVE MODEL: GG VS. GA+AA); B: ASIANS (DOMINANT MODEL: GG+GA VS. AA), C: HWE STATUS (ALLELE MODEL: G VS. A).

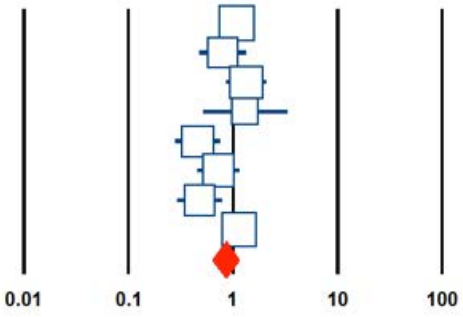
A

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Giordani 2003	0.507	0.224	1.148	-1.630	0.103	4.90
Smith 2004	1.342	0.839	2.148	1.227	0.220	9.08
Guzowski 2005	1.658	0.475	5.791	0.792	0.428	2.55
Abdolrahim-Zadeh 2005	0.941	0.599	1.480	-0.262	0.794	9.37
Balasubramanian 2006	1.025	0.768	1.368	0.165	0.869	12.32
Onay 2006	1.480	1.051	2.084	2.245	0.025	11.33
Scola 2006	0.952	0.462	1.965	-0.132	0.895	5.75
Gonullu 2007	1.971	0.193	20.131	0.573	0.567	0.83
Kong 2010	0.510	0.046	5.648	-0.549	0.583	0.78
Pooja 2012	1.625	0.522	5.056	0.838	0.402	2.99
Vinod 2015	1.626	0.784	3.372	1.307	0.191	5.70
AlSuhaibani 2016	1.079	0.502	2.322	0.195	0.845	5.35
Atoum 2016	0.977	0.479	1.990	-0.065	0.948	5.88
Tian 2017	0.974	0.708	1.339	-0.162	0.871	11.78
Maruthi 2017	1.750	1.117	2.741	2.443	0.015	9.44
Sabet 2017	21.000	4.850	90.926	4.072	0.000	1.94
	1.221	0.981	1.518	1.792	0.073	



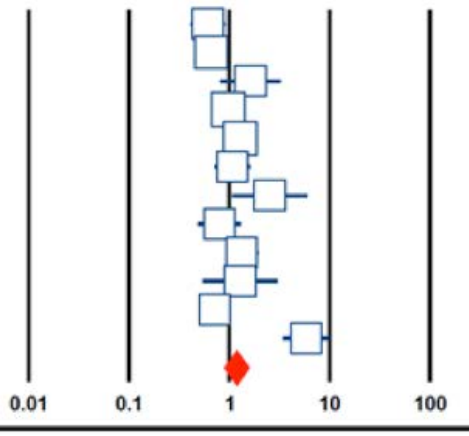
B

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Abdolrahim-Zadeh 2005	1.100	0.795	1.522	0.576	0.565	15.43
Kong 2010	0.811	0.487	1.349	-0.808	0.419	11.98
Pooja 2012	1.358	0.887	2.081	1.407	0.160	13.49
Liang 2013	1.325	0.529	3.318	0.600	0.549	6.48
Vinod 2015	0.464	0.288	0.748	-3.150	0.002	12.55
Atoum 2016	0.734	0.469	1.148	-1.357	0.175	13.10
Tian 2017	0.485	0.295	0.796	-2.862	0.004	12.21
Maruthi 2017	1.164	0.812	1.668	0.825	0.409	14.76
	0.857	0.643	1.143	-1.050	0.294	



C

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Giordani 2003	0.616	0.417	0.909	-2.440	0.015	9.01
Smith 2004	0.666	0.498	0.889	-2.753	0.006	9.79
Guzowski 2005	1.625	0.816	3.235	1.382	0.167	6.53
Balasubramanian 2006	0.976	0.819	1.164	-0.269	0.788	10.50
Onay 2006	1.296	1.061	1.584	2.538	0.011	10.37
Scola 2006	1.078	0.715	1.624	0.357	0.721	8.84
Gonullu 2007	2.528	1.068	5.984	2.109	0.035	5.31
Kong 2010	0.803	0.494	1.304	-0.888	0.375	8.20
Pooja 2012	1.329	0.917	1.926	1.503	0.133	9.16
Liang 2013	1.283	0.541	3.042	0.567	0.571	5.30
Vinod 2015	0.719	0.500	1.034	-1.782	0.075	9.22
Sabet 2017	5.873	3.439	10.032	6.481	0.000	7.77
	1.170	0.887	1.542	1.112	0.266	



ation between the IL-10 -1082A>G (rs1800896) polymorphism and breast cancer risk under the allele model (G vs. A: OR = 1.184, 95% CI = 0.895-1.180, p= 0.230), homozygote model (GG vs. AA: OR = 1.430, 95% CI = 0.927-2.204, p= 0.106), heterozygote model (GA vs. AA: OR = 0.966, 95% CI = 0.765-1.221, p= 0.774), dominant model (GG+GA vs. AA: OR = 0.957, 95% CI = 0.697-1.314, p= 0.786), and recessive model (GG vs. GA+AA: OR = 1.221, 95% CI = 0.981-1.518, p= 0.073, Figure 2A).

We have also carried out subgroup analyses that were stratified by ethnicity. Overall, no obvious evidence of associations between the IL-10 -1082A>G (rs1800896) polymorphism and susceptibility to the breast cancer were found in Caucasian, Asian and African populations under all genetic models (Figure 2B). Moreover, subgroup analysis of studies with high quality (HWE status) did not show significant association between IL-10 -1082A>G (rs1800896) polymorphism and increased risk of breast cancer (Figure 2C). The results of these analyses are shown in Table 2 and Figure 2.

Sensitivity Analysis

Sensitivity analysis was performed to confirm the stability and liability of the meta-analysis by sequentially omitting individual eligible studies. When any single study was excluded, the corresponding ORs were not materially changed (data was not shown), indicating the stability of our results. Additionally, we excluded the studies that genotype distribution in the controls deviating from HWE, and the corresponding pooled ORs were not significantly changed.

Publication Bias

Table 2 and Figure 3 present information related to the publication bias. We have performed Funnel plot and Egger's linear regression to assess the publication bias of the included studies. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Figure 3). In addition, the results of Begg's test also showed that there was no strong statistical evidence of publication bias.

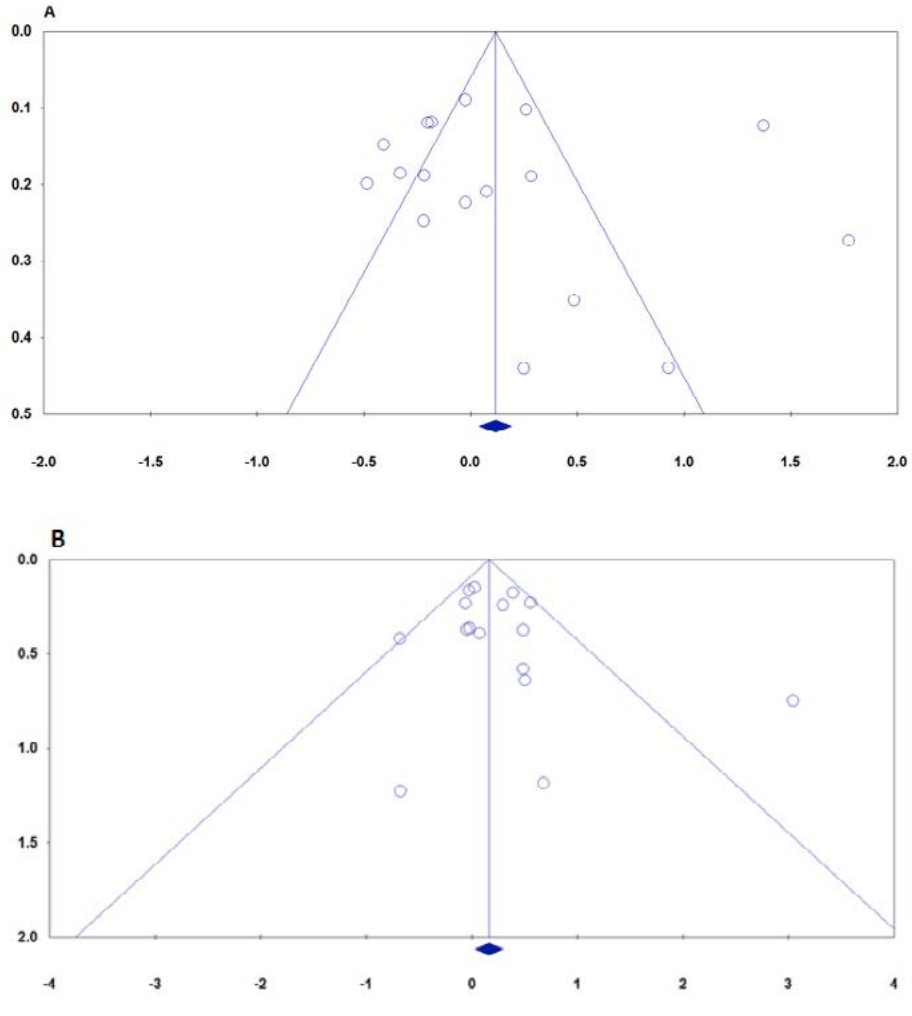


FIGURE 3. BEGG'S FUNNEL PLOTS (PUBLICATION BIAS) FOR THE ASSOCIATION BETWEEN IL-10 -1082A>G POLYMORPHISM AND RISK OF BREAST CANCER. A: ALLELE MODEL (G VS. A); B: RECESSIVE MODEL (GG VS. GA+AA).

TABLE 2. RESULTS OF META-ANALYSIS FOR RS1800896 (-1082A>G) POLYMORPHISM AND RISK OF BREAST CANCER.

Sub-group	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication Bias	
			I2%	PH	OR	95% CI	Ztest	POR	PBeggs	PEggers
Overall	G vs. A	Random	91.84	≤0.001	1.184	0.895-1.180	1.180	0.230	0.149	0.722
	GG vs. AA	Random	80.82	≤0.001	1.430	0.927-2.204	1.617	0.106	0.843	0.656
	GA vs. AA	Random	69.43	≤0.001	0.966	0.765-1.221	-0.287	0.774	0.964	0.936
	GG+GA vs. AA	Random	84.38	≤0.001	0.957	0.697-1.314	-0.271	0.786	0.685	0.690
	GG vs. GA+AA	Fixed	49.63	0.013	1.221	0.981-1.518	1.792	0.073	0.921	0.990
By Ethnicity										
Caucasian										
	G vs. A	Random	77.38	≤0.001	1.018	0.781-1.327	0.135	0.893	0.367	0.796
	GG vs. AA	Random	83.43	≤0.001	1.574	0.779-3.183	1.264	0.206	1.000	0.715
	GA vs. AA	Random	59.18	0.023	1.067	0.769-1.481	0.391	0.696	0.548	0.413
	GG+GA vs. AA	Random	88.89	≤0.001	0.876	0.458-1.675	-0.400	0.689	0.367	0.935
	GG vs. GA+AA	Fixed	22.75	0.256	1.159	0.963-1.394	1.561	0.118	0.763	0.854
Asian										
	G vs. A	Random	94.51	≤0.001	1.100	0.670-1.805	0.377	0.706	0.173	0.683
	GG vs. AA	Fixed	50.38	0.060	1.005	0.784-1.286	0.036	0.972	1.000	0.985
	GA vs. AA	Random	72.47	0.001	0.803	0.578-1.116	-1.308	0.191	0.107	0.408
	GG+GA vs. AA	Random	68.18	0.003	0.857	0.643-1.143	-1.050	0.294	0.536	0.489
	GG vs. GA+AA	Fixed	14.56	0.319	1.146	0.937-1.403	1.326	0.185	0.763	0.774
African										
	G vs. A	Random	96.13	≤0.001	2.377	0.409-13.808	0.965	0.355	NA	NA
	GG vs. AA	Random	94.09	≤0.001	6.104	0.139-267.71	0.938	0.348	NA	NA
	GA vs. AA	Random	83.36	0.014	1.700	0.410-7.055	0.731	0.465	NA	NA
	GG+GA vs. AA	Random	92.78	≤0.001	2.448	0.308-19.481	0.846	0.397	NA	NA
	GG vs. GA+AA	Random	91.91	≤0.001	4.446	0.243-81.259	1.006	0.314	NA	NA
High Quality Studies										
	G vs. A	Random	85.14	≤0.001	1.170	0.887-1.542	1.112	0.266	0.303	0.397
	GG vs. AA	Random	82.01	≤0.001	1.842	0.991-3.423	1.932	0.053	0.436	0.952
	GA vs. AA	Random	73.26	≤0.001	1.076	0.785-1.474	0.455	0.649	0.537	0.335
	GG+GA vs. AA	Random	88.06	≤0.001	1.036	0.649-1.654	0.150	0.881	0.303	0.648
	GG vs. GA+AA	Random	58.11	0.008	1.330	0.948-1.866	1.648	0.099	0.876	0.433

NA; not applicable.

Minor Allele Frequency

The present data revealed variation in the minor allele frequency of the IL-10 -1082A>G polymorphism worldwide (Table 1). The minor allele frequency range was from 18.7% (Turkey) to 52.4% (UK) among Caucasians, 6% (China) to 66.6% (China) among Asians, 25% to 51.2% among Africans (Egypt).

Discussion

Previous meta-analysis by Dai et al.[34], demonstrated that IL-10 -1082A>G polymorphism did not significantly associate with breast cancer risk. They have included only nine case-control studies with 1851 cases and 1910 controls on IL-10 -1082A>G polymorphism association. To further explore and examine the association of IL-10 -1082A>G polymorphism with breast cancer, we conducted this meta-analysis only with most recently published studies on different populations. Compared with the previous meta-analyses,[14] in this meta-analysis we have focused only on association between -10 -1082A>G polymorphism and breast cancer using 17 case-controls studies with 3275 cases and 3416 controls. However, Dai et al.[34] study essentially remain an open field, as meta-analysis of their results' reliability and the number of studies were considerably smaller than that needed to reach robust conclusions. Moreover, they have not included the Abdolrahim-Zadeh et al.[27] study that was published in 2005 in Iran. Also, in the current meta-analysis, we have carried out subgroup analysis by ethnicity among African population. Overall, our results were consistent with Dai et al.[34] results and did not show a significant relationship between IL-10 -1082A>G

polymorphism and breast cancer. In the subgroup analysis by ethnicity, there was also no association between IL-10 -1082A>G polymorphism and breast cancer risk in Caucasians, Asians and Africans.

Between-study heterogeneity is a common problem in meta-analysis for genetic association studies.[35,36] In the current meta-analysis, there was a significant heterogeneity in association of IL-10 -1082A>G (rs1800896) polymorphism under all genetic models. A number of characteristics that vary among studies could be the sources of heterogeneity such as age, gender, ethnicity, sample size, including criteria, source of controls, and genotyping method.[35,37] Therefore, we used meta-regression by ethnicity, which aim to reduce heterogeneity; however, we did not find any meaningful reduction in stratified analysis by ethnic and high quality studies, both of which were considered to be the relevant factors of Heterogeneity.

The main strengths of the current meta-analysis were obtaining more precise estimates, absence of publication bias, pooled data from studies from different ethnicities and sensitivity analysis indicated that our results were statistically robust. Despite these advantages, our meta-analysis also has some limitations which should be acknowledged when interpreting the results. First, the sample size was relatively small, and all data were from case-control studies. Second, we have included only studies that were published in English and Chinese languages and available full-text papers in the current meta-analysis; therefor, some eligible studies that have not been unpublished or were reported in other languages were missed, which may bias the power of our results. Third, the current meta-analysis results were based on single-factor estimates without adjustment for other risk factors such as age, gender, folate status, and specific environmental or lifestyle factors, should be conducted if possible. Finally, gene-gene, gene-environment or even the different polymorphisms of the IL-10 gene interactions were not estimated in this meta-analysis due lacking of the sufficient data.

In conclusion, our meta-analysis suggests that IL-10 -1082A>G (rs1800896) polymorphism not associated with an increased risk of breast cancer. Nevertheless, more studies are warranted to confirm the results and to establish the underlying molecular mechanisms that are involved.

RESUMO

INTRODUÇÃO: *A associação entre o polimorfismo IL-10 -1082A> L (rs1800896) e o câncer da mama foi avaliada por vários estudos de casos-controle. No entanto, esses estudos podem ser insuficientes para revelar a verdadeira associação.*

OBJETIVO: *Efetuamos uma meta-análise abrangente para investigar a associação entre o polimorfismo IL-10 -1082A> G e câncer de mama.*

MATERIAIS E MÉTODOS: *Uma busca sistemática da literatura foi conduzida usando PubMed, Google Scholar e Web of Science até 20 de setembro de 2017. Os dados foram analisados com o software CMA para identificar a força da associação por proporções compartilhadas (RUP) com correspondentes intervalos de confiança de 95% (ICs).*

RESULTADOS: *Um total de 17 estudos de casos-controle envolvendo 3.275 casos e 3.416 controles obtidos a partir de pesquisas de banco de dados foram examinados. Em geral, não existe uma associação significativa entre o polimorfismo IL-10 -1082A> G e o risco de câncer de mama, sob todos os modelos genéticos. Não foi encontrado nenhum viés de publicação significativo para os cinco modelos genéticos (G vs. A: OR = 1,184, IC 95% = 0,895-1,180, p=0,230; GG vs. AA: OR = 1,430, IC 95% = 0,927-2,204, p=0,106; GA vs. AA: OR = 0,966, IC 95% = 0,765-1,221, p=0,774; GG + GA vs. AA: OR = 0,957, IC 95% = 0,697-1,314, p=0,786 e GG vs. GA + AA: OR = 1,221, IC 95% = 0,981-1,518, p=0,073). Além disso, não houve associação significativa entre o polimorfismo IL-10 -1082A> L e o risco de câncer de mama por etnia.*

CONCLUSÃO: *Nossos resultados indicam que o polimorfismo IL-10 -1082A> G (rs1800896) não pode ser um fator de risco para o desenvolvimento de câncer de mama.*

PALAVRAS-CHAVE: *Neoplasias da mama. Interleucina-10. Polimorfismo genético. Metanálise.*

REFERENCES

1. Gatta G, Capocaccia R, Coleman MP, Ries LA, Berrino F. Childhood cancer survival in Europe and the United States. Cancer. 2002;95(8):1767-72.
2. Wojtacki J, Lewicka-Nowak E, Lesniewski-Kmak K. Anthracycline-induced cardiotoxicity: clinical course, risk factors, pathogenesis, detection and prevention - review of the literature. Med Sci Monit. 2000;6(2):411-20.
3. Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. J Am Coll Cardiol. 2014;64(9):938-45.
4. Kalil Filho R, Hajjar LA, Bacal F, Hoff PMG, Diz MDPS, Galas FRBG, et al. I diretriz brasileira de cardio-oncologia da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2011;96(2 supl. 1):1-52.
5. Matos Neto RP, Petrilli AS, Silva CM, Campos Filho O, Oporto VM, Gomes LF, et al. Left ventricular systolic function assessed by echocardiography in children and adolescents with osteosarcoma treated with doxorubicin alone or in combination with dexrazoxane. Arq Bras Cardiol. 2006;87(6):763-71.

6. Harake D, Franco VI, Henkel JM, Miller TL, Lipshultz SE. Cardiotoxicity in childhood cancer survivors: strategies for prevention and management. Future Cardiol. 2012;8(4):647-70.

7. Lipshultz SE, Sambatakos P, Maguire M, Karnik R, Ross SW, Franco VI, et al. Cardiotoxicity and cardioprotection in childhood cancer. Acta Haematol. 2014;132(3-4):391-9.

8. Ponikowski P, Voors AA, Anker SD, Bueno H, Clelan JGF, Coats AJS, et al; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.

9. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Disponível em: www.prisma-statement.org.

10. Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2006;48(11):2258-62.

11. Georgakopoulos P, Roussou P, Matsakas E, Karavidas A, Anagnostopoulos N, Marinakis T, et al. Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: a prospective, parallel-group, randomized, controlled study with 36-month follow-up. Am J Hematol. 2010;85(11):894-6.

12. Kaya MG, Ozkan M, Gunebakmaz O, Akkaya H, Kaya EG, Akpek M, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. Int J Cardiol. 2013;167(5):2306-10.

13. Bosch X, Rovira M, Sitges M, Domènech A, Ortiz-Pérez JT, Caralt TM, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol. 2013;61(23):2355-62.

14. Elitok A, Oz F, Cizgici AY, Kilic L, Ciftci R, Sen F, et al. Effect of carvedilol on silent anthracycline-induced cardiotoxicity assessed by strain imaging: a prospective randomized controlled study with six-month follow-up. Cardiol J. 2014;21(5):509-15.

15. Tashakori Beheshti A, Mostafavi Toroghi H, Hosseini G, Zarifian A, Homaei Shandiz F, Fazlinezhad A. Carvedilol administration can prevent doxorubicin-induced cardiotoxicity: a double-blind randomized trial. Cardiology. 2016;134(1):47-53.

16. Jhorawat R, Kumari S, Varma SC, Rohit MK, Narula M, Suri V, et al. Preventive role of carvedilol in adriamycin-induced cardiomyopathy. Indian J Med Res. 2016;144(5):725-9.

17. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J. 2016;37(21):1671-80.

18. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97(1):2869-79.

19. Octavia Y, Tocchetti CG, Gabrielson KL, Janssens S, Crijns HJ, Moens AL. Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. J Mol Cell Cardiol. 2012;52(6):1213-25.

20. Arola OJ, Saraste A, Pulkki K, Kallajoki M, Parvinen M, Voipio-Pulkki LM. Acute doxorubicin cardiotoxicity involves cardiomyocyte apoptosis. Cancer Res. 2000;60(7):1789-92.

21. Schimmel KJ, Richel DJ, van den Brink RB, Guchelaar HJ. Cardiotoxicity of cytotoxic drugs. Cancer Treat Rev. 2004;30(2):181-91.

22. Machado V, Cabral A, Monteiro P, Gonçalves L, Providência LA. Carvedilol as a protector against the cardiotoxicity induced by anthracyclines (doxorubicin). Rev Port Cardiol. 2008;27(10):1277-96.

23. Cheng J, Kamiya K, Kodama I. Carvedilol: molecular and cellular basis for its multifaceted therapeutic potential. Cardiovasc Drug Rev. 2001;19(2):152-71.

24. Spallarossa P, Garibaldi S, Altieri P, Fabbi P, Manca V, Nasti S, et al. Carvedilol prevents doxorubicin-induced free radical release and apoptosis in cardiomyocytes in vitro. J Mol Cell Cardiol. 2004;37(4):837-46.

25. El-Shitany AN, Tolba AO, El-Shanshory RM, El-Hawary EE. Protective effect of carvedilol on adriamycin-induced left ventricular dysfunction in children with acute lymphoblastic leukemia. J Card Fail. 2012;18(8):607-13.

26. Shibata MC, Flather MD, Böhm M, Borbola J, Cohen-Solal A, Dumitrascu D, et al; Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS). Rationale and design. Inter J Cardiol. 2002;86(1):77-85.

27. Münzel T, Gori T. Nebivolol: the somewhat-different beta-adrenergic receptor blocker. J Am Coll Cardiol. 2009;54(16):1491-9.

28. Groot AA, Mathy MJ, van Zwieten PA, Peters SL. Antioxidant activity of nebivolol in the rat aorta. J Cardiovasc Pharmacol. 2004;43(1):148-53.

29. Nigris F, Rienzo M, Schiano C, Fiorito C, Casamassimi A, Napoli C. Prominent cardioprotective effects of third generation beta blocker nebivolol against anthracycline-induced cardiotoxicity using the model of isolated perfused rat heart. Eur J Cancer. 2008;44(3):334-40.

30. Luna RL, Oigman W, Ramirez JA, Mion D, Batlouni M, Rocha JC, et al. Eficácia e tolerabilidade da associação bisoprolol/hidroclorotiazida na hipertensão arterial. Arq Bras Cardiol. 1998;71(4):601-8.

31. Blum RH. Clinical status and optimal use of the cardioprotectant, dexrazoxane. Oncology (Williston Park). 1997;11(11):1669-77.

32. Hellmann K. Cardioprotection by dexrazoxane (Cardioxane; ICRF 187): progress in supportive care. Support Care Cancer. 1996;4(4):305-7.

33. Fulbright JM, Huh W, Anderson P, Chandra J. Can anthracycline therapy for pediatric malignancies be less cardiotoxic? Curr Oncol Rep. 2010;12(6):411-9.

34. Iarussi D, Indolfi P, Casale F, Martino V, Di Tullio MT, Calabrò R. Anthracycline-induced cardiotoxicity in children with cancer: strategies for prevention and management. Paediatr Drugs. 2005;7(2):67-76.

35. Chatterjee K, Zhang J, Honbo N, Karliner JS. Doxorubicin cardiomyopathy. Cardiology. 2010;115(2):155-62.

36. Cvetkovic RS, Scott LJ. Dexrazoxane: a review of its use for cardioprotection during anthracycline chemotherapy. Drugs. 2005;65(7):1005-24.

37. Paiva MG, Petrilli AS, Moisés VA, Macedo CR, Tanaka C, Campos O. Cardioprotective effect of dexrazoxane during treatment with doxorubicin: a study using low-dose dobutamine stress echocardiography. Pediatr Blood Cancer. 2005;45(7):902-8.

38. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009;27(1):127-45.

39. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17.

40. Akpek M, Ozdogru I, Sahin O, Inanc M, Dogan A, Yazici C, et al. Protective effects of spironolactone against anthracycline-induced cardiomyopathy. Eur J Heart Fail. 2015;17(1):81-9.

41. Meattini I, Curigliano G, Terziani F, Becherini C, Airoldi M, Allegrini G, et al. SAFE trial: an ongoing randomized clinical study to assess the role of cardiotoxicity prevention in breast cancer patients treated with anthracyclines with or without trastuzumab. Med Oncol. 2017;34(5):75.