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Summary

INSTRUCTIONS FOR AUTHORS

SALUS – Journal of Health Sciences / Revista de Ciências da Saúde
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The general publication rules are summarized in the "Uniform Requirements" for Manuscripts Submitted to Biomedical Journals: "Writing and Editing for Biomedical Publication" (www.icmje.org/recommendations). Special suggestions are given to systematic bibliographic reviews and meta-analyzes, retrospective and observational studies on epidemiology, clinical trials, diagnostic accuracy and prospective studies, case reports and case studies. We ask the authors to check the information below before submitting the manuscript to SALUS.

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The Salus – *Journal of Health Sciences* is the scientific magazine by EMESCAM – Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (School of Sciences of Santa Casa de Misericórdia in Vitória) and it is published every four months.

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- 3rd Step: authors' registration
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- 7th Step: generating the copyright transfer statement, conflict interest and a copy of the Legal Opinion by the Institution's Ethic Committee of Research.
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Investigations in human beings must be submitted to the Ethics Committee of the Institution, fulfilling the Declaration of Helsinki from 1975, reviewed in 2008. (World Medical Association, available at:www.wma.net/en/30publications/10policies/b3/17c.pdf), and the Resolution CNS 466/12 – Brazilian National Health Council (Conselho Nacional de Saúde), available at http://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf

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1. To have created and planned the activities that led to the work, or interpreted the results found, or both;
2. To have written the work or revised the successive versions and taken part in the revision process;
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People who do not match the above requirements and who had merely technical or general support participation may be mentioned in the Acknowledgement section. The kind of contribution from each author to the study performance and to the manuscript preparation must be explained in the following areas, at the moment of submission:

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The use of acronyms must be low. When long expressions need to be repeated, it is recommended that its capital initial letters substitute them after the first mention, which must be followed by the initials between parentheses.

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Only the generic name of the used medication must be mentioned in the work; the use of commercial names is inadvisable.

SALUS adopts the Universal Official Anatomical Terminology, approved by the International Federation of Associations of Anatomists (IFAF)

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Sections of the Manuscript

Title and Authors: The work title, in Portuguese and English, must be concise and

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Abstract (in Portuguese and English): The abstract must be structured in four sections: Objective, Methods, Results and Conclusion. The Abstract in English must follow the same structure of the Abstract in Portuguese. Acronyms must be avoided. The maximum number of words must follow the recommendations of the table (Limits for each article type). The abstract must not be structured in Case Report articles (informative or free). The clinical-surgical correlations and multimedia sections dispense abstract.

Descriptors: Three to five descriptors (keywords) must also be included. The descriptors may be consulted in the electronic address http://decs.bvs.br/, which contains words in Portuguese and English or www.nlm.nih.gov/mesh, for only English words, or in the respective links available at the submission system of the magazine.

Manuscript Body: The Original Articles and Experimental Works must be divided in the following sections: Introduction, Method, Results, Discussion, Conclusion and Acknowledgements (optional). The Case Reports must be structured with the sections: Introduction, Case Report and Discussion; and the Clinical-surgical Correlations must be divided in Clinical Data, Electrocardiogram, Radiogram, Echocardiogram, Diagnosis and Operation. The Multimedia section must present the following sections: Patient Featuring and Description of the Employed Technique. The Review Articles and Special Articles may be structured in sections according to the author's order.

The Letters to the Editor must, at first, comment, discuss or criticize articles published in SALUS, but they may also refer to other themes of general interest. It is recommended a 1.000 words maximum and it includes five references, maximum, with or without title. Whenever possible, an answer from the authors of articles in discussion will be published along with the letter.

References

The references of printed and electronic documents must be standardized according to the Vancouver style, elaborated by the *International Committee of Medical Journal Editors* (ICMJE, available at: http://www.icmje.org).

The references must be identified with Arabic numerals in the text, superscript, obeying the citation order in the text. The accuracy of the references is an author's responsibility. If more than two references are cited in sequence, only the first and the last must be typed, separated by a dash (Example: [6-9]). In cases of alternate citation, all the references must be typed separated by comma (Example: [6,7,9]).

All authors must be cited in publications with up to 6 authors; in publications with more than 6 authors, the first 6 are cited followed by the Latin expression "et al.".

Titles of journals must be abbreviated according to the List of Journals Indexed for MEDLINE (available at:http://www.nlm.gov/tsd/serials/lji.html).

References Models

Magazine Article

Issa M, Avezum A, Dantas DC, Almeida AFS, Souza LCB, Sousa AGMR. Fatores de risco pré, intra e pós-operatórios para mortalidade hospitalar em pacientes submetidos à cirurgia de aorta. Rev Bras Cir Cardiovasc. 2013; 28(1):10-21.

Organization as Author

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension. 2002;40(5):679-86.

Without indication of authorship

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

Article published electronically before the print version ("ahead of print")

Atluri P, Goldstone AB, Fairman AS, Macarthur JW, Shudo Y, Cohen JE, et al. Predicting right ventricular failure in the modern, continuous flow left ventricular assist device era. Ann Thorac Surg. 2013 Jun 21. [Epub ahead of print]

Article of Internet Journal

Machado MN, Nakazone MA, Murad-Junior JA, Maia LN. Surgical treatment for infective endocarditis and hospital mortality in a Brazilian single-center. Rev Bras Cir Cardiovasc [online]. 2013[cited 2013 Jun 25];28(1):29-35. Available at:http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-76382013000100006&lng=en&nrm=iso

Book Chapter

Chai PJ. Intraoperative myocardial protection. In: Mavroudis C, Backer C, eds. Pediatric cardiac surgery. 4th ed. Chichester: Wiley-Blackwell; 2013. p.214-24.

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Cohn LH. Cardiac surgery in the adult. 4th ed. New York: McGraw-Hill;2012. p.1472.

Thesis

Dalva M. Estudo do remodelamento ventricular e dos anéis valvares na cardiomiopatia dilatada: avaliação anátomo-patológica [Tese de doutorado]. São Paulo: Universidade de São Paulo, 2011. 101p.

Legislation

Conselho Nacional de Saúde. Resolução n. 466, de 12 de dezembro de 2012. Dispõe sobre diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos. Bioética. 1996;4(2 Supl):15-25.

Conselho Nacional de Controle de Experimentação Animal. Resoluções n. 12 e 13, de 20 de setembro de 2013. Dispõem sobre a diretrizes brasileiras para o cuidado e a utilização de animais para fins científicos e didáticos (DBCA) e prática de eutanásia.

Other examples of references may be consulted at the website: http://www.nlm.nih.gov/bsd/uniform_requirements.html

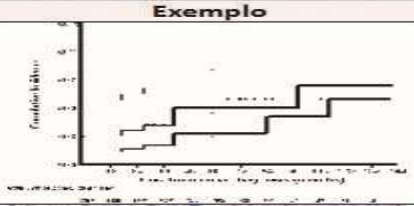
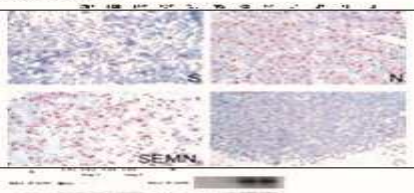
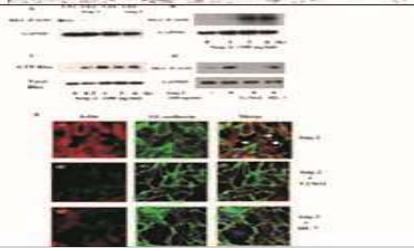
Tables and Pictures

The Tables and Pictures must be numbered according to order appearance in the text, contain a title and be in separate files. The tables must not contain redundant data, previously mentioned in the text. They must be open in the sides and with a totally white background.

The acronyms used in the tables must be mentioned in alphabetical order, in the footnote, with their respective full forms. Similarly, the acronym used in pictures must be explained in the legends.

The pictures will only be published in colors if the author agrees to afford the costs of impression of colorful pages.

Only images in formats TIFF or JPEG will be accepted, with minimum resolution according to the kind of image, for both black and white and colorful images, according to the Table below:

Tipo	Exemplo	Formato	Resolução
LineArt (imagens com linhas lineares, normalmente gráficos com texto)		TIF ou JPG	900 a 1200dpi
Halftone (imagens, normalmente fotografias)		TIF ou JPG	300dpi
Combo (mistura de gráfico e imagem)		TIF ou JPG	500 a 900dpi

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The following criteria sorted by type of publication must be observed, aiming to rationalize the space in the magazine and allow more articles per edition. The electronic word count must include the initial page, abstract, text, references and picture legends. The titles have 100 characters limit (counting the spaces) for Original Articles, Review and Updating Articles and Experimental Work; the other categories have 80 characters (counting the spaces) title limit.

	Original Article	Editorial	Review / Updating Article	Case Report	Case Report and Literature Review	Brief Communication and Preliminary Note	Letter to the Editor	Experimental Work	Clinical-Surgical Correlation	Multimedia
Maximum number of authors	10	4	5	4	6	4	2	10	4	4
Abstract – Maximum number of words	250	-	200	100	100	100	-	250	-	-
Maximum number of words	6,000	1,000	8,000	1,500	3,000	2,000	400	6,000	800	800
Maximum number of references	40	10	75	6	20	6	6	40	10	10
Number of tables and pictures	8	2	8	2	6	2	1	8	2	1
Abbreviated Title	—	—	—	—	—	40 Characters	—	—	—	—

Table Model:

Table 1 – Model table

AREAS	UNESP	UNICAMP	USP	TOTAL
Interdisciplinary	**2**	**2**	**2**	**6**
Biological and Health	**2**	**2**	**2**	**6**
Exact and Technological	**2**	**2**	**2**	**6**
Human and Arts	**2**	**2**	**2**	**6**
TOTAL	**8**	**8**	**8**	**24**

Picture Model:

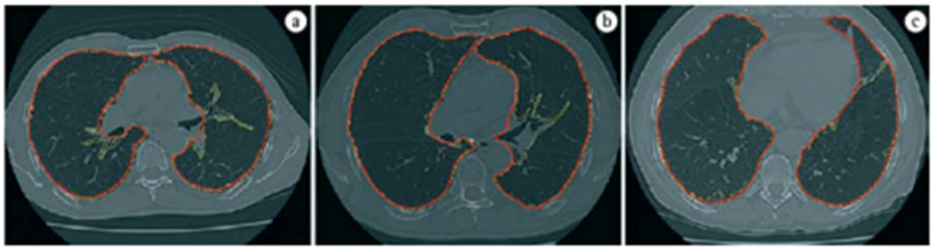

Figura 3 – Exemplos de segmentações classificadas como parcialmente concordantes para o sistema Osiris (contorno amarelo) e o SIStema para a Detecção e a quantificação de Enfisema Pulmonar (SISDEP; contorno vermelho). Sobreposição dos contornos de segmentação em imagens de TCAR em nível de hilo (em a e b) e em nível de base (em c). Em a, a concordância é parcial por imprecisões geradas na segmentação dos dois sistemas; em b, por imprecisão realizada pela segmentação do SISDEP; e em c, por imprecisão ocasionada pela segmentação do sistema Osiris.

Check it before sending the work

- Submission letter indicating the manuscript category.
- Statement by authors and co-authors saying that they agree with the content of the manuscript.
- Approval Letter by the Ethics Committee of Research.
- Manuscript written in software Word 97 or above (formatted to A4); font size 12, space 1.5, font Times New Roman; paged; mathematical symbols and Greek characters using font Symbol.
- Manuscript in the limits adopted by SALUS for its category.

EDITORIAL

WHO PAYS THE PUBLISHING-COSTS OF FREE ACCESS ARTICLES?

For more than one century, the scientific investigators have published their discoveries in national and international journals created by scientific societies, which are maintained by their members. Interesting, this has occurred even when the scientific journals were edited only in the print version; in some cases, the journals were delivered to members living in other countries. Those journals used to accept manuscripts from both members and non-members and, importantly, without paying the costs of the production of the accepted articles. Since then until now, to access an article, the reader had/has to be a member of the society or to get a copy at the subscribed institutional library. However, it does not necessarily mean that if you are a member of a society you have free access to all publications of that society (some publish more than five journals).

Lately, the above scenario has changed dramatically and some investigators are surprised by daily emails announcing the launching of a new society-independent scientific journal and inviting them to submit a manuscript for publication in that journal, which usually is a journal publishing free access articles for the readers, but which costs a lot for the authors of the manuscripts. The reasons for the continuous launching and existence of hundreds of free/open access scientific journals appears to be as consequence of different factors. It could be because the world has experienced a fantastic increase in the number of new investigators and consequently an extraordinary increase in the number of manuscripts being submitted for publication. In contrast, great part of the journals belonging to scientific societies did not increase in the same proportion, reaching situations in which in the past a specific journal used to accept 70% of the manuscripts submitted and now the same journal uses to accept only up to 20%. Moreover, many investigators, who in the past had faced difficulties to have written their manuscripts in a proper scientific English language, now they can use specialized companies, such as the American Journal Experts, to translate and/or to edit their manuscripts before the submission. It is also important to emphasize that nowadays the production process of a volume of journal, such as the Salus Journal of Health Sciences, has been facilitated by the use of Adobe Acrobat Professional program, which contains excellent tools for editing articles.

What is the problem with the increasing number of open access journals? In my opinion, when one considers the conduct quality of peer review, so far it seems acceptable. The major problem is who pays or should pay the bill of the production-costs of a print or online version of an article? For instance, the costs of an accepted article ranges from U$ 1,000.00 to 2,000.00, which, in developed countries, is paid by the grant of the investigator or by his/her institution. However, in Brazil, it took time to the governmental agencies supporting science and technology and the universities to understand that they should pay that bill. However, most of those companies that publish scientific journals in the system “the investigator pays for publishing the manuscript and the reader has open access to the article” do not use to care about the dramatic political and economic crisis affecting Brazil. They should considered that this country has contributed with fantastic discoveries aiming a better understanding of diseases and how to prevent/treat them. Consequently, without budget for paying the costs of publication of papers, when an investigator receive the letter of acceptance of the manuscript, he/her get excited and very happy, but the following phrase tells the investigator that he/she got a bill that has to be immediately paid and, then, comes the frustration of having to pay it with his/him own pocket.

So what is the picture that we get here? The good news is that the investigators have now the opportunity to publish a high-quality manuscript in the free access online Salus Journal of Health Sciences. It means that everyone can copy, transmit and adapt the work, when proper credit is given. Moreover, the investigator will not be charged by the article-production costs. The Salus Journal of Health Sciences has an ISSN, each article has a specific DOI and, if you submit at least one of your best manuscripts, in a couple of years, this journal has a high probability of be included among those that have an impact Factor (IF) in the Journal Citation Reports/Thomson Reuters.

Elisardo Corral Vasquez, PhD

REVISTA SALUS
JOURNAL OF HEALTH SCIENCES

ORIGINAL ARTICLE

Excessive daytime sleepiness in subjects with sleep breathing disorders

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[4] Master of Biomedical Engineering from the Vale do Paraíba University, Physiotherapist – Professor and Coordinator of the Physical Therapy undergraduation course at the Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória – EMESCAM.

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Keywords

Disorders of Excessive Daytime Sleepiness; Sleep Apnea Syndromes; Sleep Disorders

Abstract

Objectives: This study aimed at determining the prevalence of Excessive Daytime Sleepiness (EDS) in patients with sleep breathing disorders, as well as at investigating the sensitivity and specificity of the Epworth Scale to detect the Obstructive Sleep Apnea/Hypopnea Syndrome (OSAH); correlate the apnea-hypopnea index (AHI) and with the degree of EDS; age with the severity of OSAHS; the degree of excessive daytime sleepiness. **Method:** a cross-sectional study was carried out with a retrospective data collection, through medical analysis. The subjects were divided into two groups and three subgroups according to the AHI. The descriptive analysis was performed using mean, standard deviation, 2x2 tables, and statistics using the Pearson's correlation. $p < 0.05$ was considered. **Results:** out of the

65 individuals studied, 68% were males with a mean age of 55.18 years, 34.31 AHI events/hour, and a score of 9.63 for the EDS. The EDS was prevalent in 52% of patients, particularly in the control group, depicting a low sensitivity in detecting the disease. By correlating the AHI with age, it was found a weak, negative and statistically significant correlation. **Conclusion:** the EDS proved to be prevalent in more than half of the population, though the Epworth Scale showed little sensitivity to OSAH and cannot, therefore, be solely used as a criterion for detecting the disease. It is worth highlighting the necessity of further studies on the matter to shed light on excessive daytime sleepiness, considering the latter is associated with the occurrence of accidents, morbidity, and has become a public health issue.

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Introduction

Sleeping is considered a vital necessity for the human life. By playing a role of utmost importance for the preservation of the homeostatic conditions and for the physical and psychic functioning, its quality and amount are essential for the performance of brain and organic functions. Therefore, factors that interfere in sleeping pose a significant consequence on the subject's life.[1]

According to Dal-Fabbro et al[2], the Apnea Syndrome/Obstructive Sleep Apnea (OSAH) is one of the most prevalent sleep disorders in the population, being initially described in 1973 by Christian Guilleminault.

The OSAH is a clinical condition characterized by repetitive obstructions of the upper respiratory tracts (URT) due to a total (apnea) or partial (hypopnea) inspiratory collapse, leading to a decrease of oxygen serum levels and to an increase in the levels of carbon dioxide, resulting in micro wake ups, causing an impact on sleep quality and thus interfering in daily life activities.[3,4]

Abreu et al[5] have also affirmed that the OSAH is associated with the development of systemic arterial hypertension and an array of other cardiovascular conditions, such as congestive heart failure, arrhythmia, heart disease and cerebral vascular accident.

The OSAH diagnosis is determined by the apnea and hypopnea index (AHI) over 5 events per hour of sleep, obtained through polysomnography, a "gold standard" test for the diagnostic of sleep disorders. Such index allows the classification of the OSAH into mild, moderate and severe.[4,6]

The literature indicates that the OSAH risk factors are: male gender, being over 50 years of age, obesity, increase of the neck volume, craniofacial alterations, genetic factors, drinking and smoking habits, consumption of drugs such as sedatives and hypnotics.[7]

The OSAH classic manifestation is as excessive daytime sleepiness (EDS). Clinically defined as a difficulty to maintain a desired level of alertness or as an excessive amount of sleep, the EDS is reported by patients as complaints about tiredness and lack of energy.[3,5]

The EDS hinders the practice of daily activities, causes memory and concentration decrease, learning

disabilities, tendency to nervousness and/or depression, headache, hyperactivity (in children), social embarrassment, social issues and sexual dysfunction. It can also be manifested as a difficulty to keep one's attention and vigil while performing monotonous tasks such as watch TV or read a book.[4,8]

The Epworth Sleepiness Scale (ESS) is largely used to subjectively assess the EDS. The ESS was developed by Johns in 1991 in the form of a self-assessment questionnaire, which evaluates the probability of falling asleep in the eight situations comprising daily activities such as reading, watching TV, sitting in any public place, talking to someone and or after a meal, among other situations. The global score ranges from 0 to 24, and when over 10, the presence of the EDS is suggested.[4,9]

Both the EDS and the OSAH are commonly associated to automobile, domestic and labor accidents, as well as the worsening and or the beginning of cardiac diseases that lead to a high level of death rates. Given that, the importance of carrying out this study is in the necessity of enhancing the knowledge of health professionals and society towards the issues concerning the EDS and OSAH, which rapidly become a public health issue and still remain relatively unknown.

Therefore, the objective of this study was to verify the prevalence of the EDS in patients with sleep breathing disorders, as well as investigate the sensibility and specificity of the ESS in detecting the presence of the OSAH. The aim was also to correlate the AHI with the EDS degree, and age with the OSAH severeness and with the degree of excessive daytime sleepiness.

Method

A cross-sectional study was carried out with a retrospective data collection performed at the Sleep Disorders Treatment Center (RespirAR), in partnership with the Sleep Medicine Center (MEDSONO).

Data was collected at RespirAR through an analysis of medical reports by using a data collection form, filled out by the researchers, which contained items concerning the patient's profile (gender, age), polysomnography study data (AHI) and the Epworth Scale (EDS).

Patients considered for this study were adults of both genders that have been admitted at RespirAR between January 2009 and June 2013, had taken the Nocturnal Polysomnography Test and the Epworth Scale questionnaire. Patients ruled out from this study were the ones when the administration of the Epworth Scale test was longer than six months from undergoing the Polysomnography Test.

Subjects were divided into two groups according to the AHI, following the criteria established by the *International Classification of Sleep Disorders*[6]: G1, patients not diagnosed with OSAH (AHI < 5 events/h), characterizing the control group; and G2, patients with a confirmed diagnosis of mild OSAH (AHI > 5 events/h). G2 was then divided into three subgroups: G2.1, patients with mild OSAH (AHI between 5 and 15 events/h); G2.2, patients with moderate OSAH (AHI between 15 and 30 events/h); and G2.3, patients with severe OSAH (AHI > 30 events/h).

For the descriptive analysis of the data, averages, standard deviation and 2x2 tables to relate the qualitative data through Microsoft Excel 2013 have been used. The statistical analysis was obtained from the coefficient from the Pearson Correlation, which determines the linear relationship between two random variables to verify the existence of a positive or negative correlation. The software used was the *Statistical Package for the Social Sciences* (SPSS *Statistics*), version 20.0. A $p=\leq 0.05$ significance has been considered.

The ESS sensibility was calculated by dividing the number of true positive patients (TP), which corresponds to the patients that have the EDS and not the OSAH, and by also adding up TP and false positive patients (FP). That is, patients who have the EDS and not the OSAH is expressed by the following formula: SENS = TP/TP+FP. By contrast, the EDS specificity was calculated by dividing the number of true negatives (TN), that is, the patients that do not have the EDS and have not been also diagnosed with the OSAH, by the sum of the number of TN and false negatives (FN), which corresponds to the group of patients who have not been diagnosed with the EDS, but have OSAH, expressed by the following formula: SPE = TN/TN+FN.

The present study followed the rules and guidelines of the Resolution 466/12, being its conduction approved by the EMESCAM Ethics and Research Committee, under no. 044/2010.

Results

104 medical reports have been analyzed, and 39 ruled out from this study, in accordance with the exclusion criteria, with a remaining sample of 65 reports.

Based on the AHI, the sample was divided into G1 or control group, composed of 11 patients diagnosed with OSAH (17%) and G2, a group with a confirmed OSAH diagnostic, composed of 54 patients (83%). The latter were then divided into three subgroups: G2.1 with 3 patients (6%), with mild OSAH; G2.2 with 13 patients (24%) with moderate OSAH; and G2.3 with 38 patients (70%), with severe OSAH. Table 1 shows the characteristics of the total sample studied and of groups G1 and G2, separately.

Table 1: sample characterization

		Total Sample	G1	G2
AHI		34,31 ± 25,11	2,07 ± 1,56	40,88 ± 18,78
Age*		55,18 ± 15,76	46,68 ± 13,41	56,73 ± 15,18
ESS		9,63 ± 4,79	11,09 ± 3,73	9,33 ± 4,96
Gender	M	68%	36%	74%
	F	32%	64%	26%

*Sample: n=57; G1: n= 9; G2: n= 48; ESS = Epworth Sleepiness Scale; AHI = Apnea/Hypopnea Index

Source: The author

In the association between OSAH and EDS, a prevalence of 52% (34) of patients with EDS has been found in the total sample, when separately analyzed. Out of the 54 patients diagnosed with OSAH (G2), 27 (50%) had EDS. As for G1, the control group, the EDS was present in 7 (64%) of the patients (n=11), according to what is shown in Table 2.

Table 2: Association between OSAH and EDS

OSAH and EDS	**Yes**	**No**	Total
Yes (G2)	27	27	54
No (G1)	7	4	11
Total	34	31	65

OSAH = obstructive sleep apnea/hypopnea syndrome
EDS = Excessive daytime sleepiness

Source: The author

Upon drawing a relationship between the presence of SDE and OSAH severeness, the following result was obtained: for the G2.1 group, mild OSAH (n=3), 2(66.6%) patients have been diagnosed with SDE, for the G2.2, moderate OSAH (n=13), 6 (46.1%) patients diagnosed with SDE and for the G2.3 group, severe OSAH (n=38), 19 (50%) found with SDE, as summarized in tables 3, 4 and 5.

Table 3: Association between mild OSAH and EDS

Mild OSAH and SDE	Yes	No	Total
Yes (G2.1)	2	1	3
No	32	30	62
Total	34	31	**65**

OSAH = Obstructive Sleep Apnea/Hypopnea syndrome; EDS = Excessive Daytime Sleepiness

Source: The author

Table 4: Association between moderate OSAH and EDS

Moderate OSAH and EDS	Yes	No	Total
Yes (G2.2)	6	7	13
No	28	24	52
Total	34	31	**65**

OSAH = obstructive sleep apnea/hypopnea syndrome
EDS = Excessive Daytime Sleepiness

Source: The author

Table 5: Association between severe OSAH and EDS

Severe OSAH and EDS	Yes	No	Total
Yes (G2.3)	19	19	38
No	15	12	27
Total	34	31	**65**

OSAH = Obstructive Sleep Apnea/Hypopnea syndrome**;** EDS = Excessive Daytime Sleepiness

Source: The author

The sensibility and specificity of the Epworth Sleepiness Scale (ESS) in detecting mild, moderate and severe OSAH is represented in table 6.

Table 6: ESS sensibility and specificity and OSAH severeness

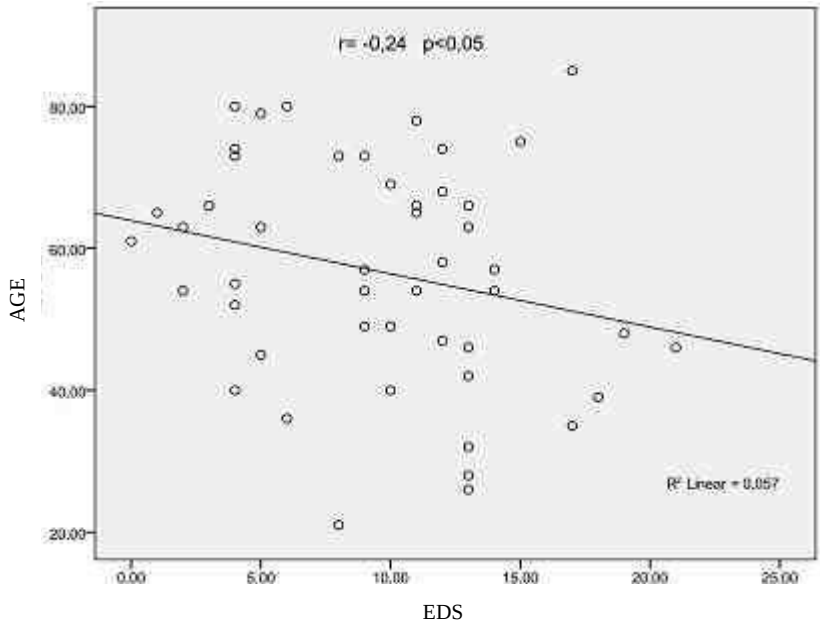
OSAH severeness	n	ESS	
		Sensibility	Specificity
Mild OSAH	n=3	5.8%	96%
Moderate OSAH	n=13	17.6%	77.4%
Severe OSAH	n=38	55.8%	38.7%

OSAH = Obstructive Sleep Apnea/Hypopnea syndrome; ESS = Epworth Sleepiness Scale

Source: The author

When performing the Pearson correlation between the AHI and with the EDS degree out of the total sample, statistically significant data was not found (p = > 0.05). A similar case occurred in the correlation between the AHI and the age of analyzed patients in the present study. However, when correlating age and EDS, a weak and negative correlation was found (r = - 0.24) and statistically significant (p = > 0.05), as shown in graph 1.

Graph 1: Correlation between AGE and EDS



Discussion

Tangerina et al[10], in a similar study, have studied the polysomnographic findings of 45 patients diagnosed with and without OSAH, reaching an AHI general average of 30.8 ± 31.9 events per hour of sleep, a value close to the average shown in the present study, which is of 34.31 ± 25.11. Once again similar to this study, the authors divided their total sample into patients with and without OSAH, that is, patients with an AHI > 5 events/h < 5 events/h, respectively. As for the OSAH group, a total of 35 (78%) patients, the average AHI found was of 38.7 ± 32. As for the group not diagnosed with OSAH, 10 (22%) patients, 2.96 ± 1.6, while in this group the percentage found between patients diagnosed and not diagnosed with OSAH was of 83% against 17%. The AHI average for the OSAH group was of 40,88 ± 18,78 and for the group not diagnosed with OSAH, 2.07 ± 1.56, once again showing the similarities in the findings between both studies.

In patient stratification, according to the OSAH severeness, the G2 group was divided into two subgroups, in which it was found a 6% (3) mild OSAH prevalence, 24% (13) of moderate and 70% (38) of the severe one. Knorst, Souza and Martinez[11] when analyzing 300 patients seen at a sleep clinic with a confirmed OSAH diagnosis, have found similar results upon dividing their sample by using the same criteria applied in this study. The prevalence found was of: 12% (36) of patients with mild OSAH, 17.3% (52) for moderate and 69.3% (208) for severe.

Still analyzing the patient profile variable, it could be noted that concerning age, the average obtained in this study was of 55.18

± 15.76, varying between 21 and 85 years old, which corroborates with the studied literature that underlines the ages between 50 and 60 years old as important risk factors for the development of OSAH[7]. However, more recent studies have shown a growing age average even narrower, as per the study carried out by Rodrigues et al[12] in which 112 patients seen in an OSAH ambulatory were studied and the average age found was of 47.95 ± 11.25 with a range between 17 to 77 years old.

When age averages were compared between groups G1 and G2, it was found a difference of a little more than 10 years old between them (46.68 ± 13.41 *vs.* 56.73 ± 15.18 years old), a datum that conflicts with the studies of Carvalho[7], who affirms that growing old is directly proportionate to the increase in the OSAH incidence.

The age effect on the prevalence of OSAH deserves enlightenment. However, studies tend to be cohesive when affirming that there is a positive correlation among age, obesity and circumference of the neck. In other words, the weight and circumference of the neck, that make up the list of risk factors for OSAH, proportionally increase as one gets older, which also makes it a risk factor for the disease.

As for gender, male patients make up 68% (44) of this study's sample, being such average even higher when assessing the group diagnosed with OSAH, G2, out of which 74% of the sample were male subjects. Alternatively, when assessing the control group, G1, only 36% of the patients were male. Daltro et al[14] have found a percentage fairly close to the latter. Among the 1,595 patients at the Sleep Laboratory of the Portuguese Hospital in Salvador, state of Bahia, Brazil, 71.7% were male. In another study, Dal-Fabbro et al[2] have analyzed 50 patients with a polysomnographic-based confirmed OSAH test and, among those subjects, 66% were of the male gender; once again showcasing the similarities between the results obtained in this study and the ones from the literature.

However, Malhotra and White[15], in a bibliographic review of the literature, have highlighted that although more recent studies have confirmed that OSAH affects more subjects of the male gender, attention must be paid to the fact that women may be being underdiagnosed. Collop, Adkins and Phillips[16] and Musmam[17] still add by saying that the sleep apnea is more clinically evident in male subjects, with a more frequent snoring event and witnessed apnea. In women, apnea tends to present less specific symptoms such as sleepiness and fatigue, these being easily misunderstood with daily stress, or simply neglected, which makes such patients less often referred to polysomnography.

Regarding EDS, a 52% prevalence has been found when comparing groups. Such rate was even higher in the control groups. The averages obtained through the Epworth Sleepiness Scale also diverged when both groups were compared, having the control group, once again, obtained higher rates to the ones found in the OSAH group. This fact has demonstrated the low sensibility of the scale in screening the patients bearing such disease.

Gondim et al[3] have conducted a retrospective study with 125 patients with and without OSAH and have found, among similar findings to this study's, a prevalence of 54.4% of patients with EDS in the general population. However, when comparing the populations with moderate and severe, mild and no OSAH occurrence, the findings have demonstrated a significant higher prevalence in the first group. Also corroborating with Gondim et al[3], Boari et al[18] have conducted a study with 66 patients that were submitted to the polysomnography test and that also responded to the ESS. It was not found a correlation between the parameters in patients with mild and moderate OSAH. However, statistically significant values have been observed in patients with the severe form of the disease; 65% of the

patients obtained abnormal values of sleepiness.

Upon correlating the AHI with the Epworth Scale scoring, a statistically significant correlation was not found. Musman et al[17], when analyzing 323 patients submitted to polysomnography due to a previous suspicion of sleepiness disorder, have also not found a significant correlation between the sleepiness measured by the Epworth Scale and OSAH. The author relates the results to the scale subjectivity and performance.

In what concerns the EDS, conflicting results have often been in evidence in the literature, once sleepiness becomes a daily growing and frequent symptom throughout all individuals due to an everyday escalating demand from these subjects.

In the study conducted by Bittencourt et al[19], in which 2,110 individuals from 150 different Brazilian cities were interviewed by the Datafolha institute and questioned, among various subjects, about sleeping complaints. It was found that 63% of the interviewed population has presented at least one complaint regarding sleep. Given that, it is possible to draw that a low-quality sleeping habit, associated to arduous working hours during the day, may lead such individuals to present the SDE without necessarily being OSAH bearers.

Another piece of data that confronts with the latter is when sleepiness is to be compared to the age of the individuals from the sample, a weak, negative and statistically significant correlation was obtained. That is, the younger the individual, the greater the population sleepiness rate. That leads one to ponder over the fact that the young population has presented more signs of sleepiness, even when not presenting signs of a sleep disorder.

According to Chervin[9], although being a globally and widely used instrument to measure sleepiness, questions hover over the arguments of what the Epworth Sleepiness Scale actually measures. Chervin claims that all authors using such scale are certainly measuring the same matter. However, in the absence of a full understanding of the physiological process that unchains sleepiness, the best way to measure it is still vague, posing a question to the sensibility of such scale, mainly in determining a predisposition to the OSAH of any other specific disease.

Conclusion

The prevalence of excessive daytime sleepiness (SDE) in this study was of 52% in the total population. The individuals were mostly males, and the mean age was of 55.18 ± 15.76 years old, with a AHI average of 34.31 ± 25.11 events per hour of sleep and for the ESS, 9.63 ± 4.79.

Upon comparing the AHI degree with the EDS, data that cannot be incisively affirmed for not being statistically significant. The same fact is true in the correlation between the AHI and the age of patients. When comparing age with EDS, a weak and negative correlation has been found, though statistically significant.

The EDS was found in half of the patients diagnosed with OSAH, presenting low values of sensibility and specificity, besides being recurrent in mostly of the patients not diagnosed with SAHOS, leading one to believe that the Epworth Scale cannot be the sole instrument to detect such disease. In this way, that makes necessary the administration of other tests that can better predict such disorders, making clear the reference to the polysomnography test.

It is also worth highlighting the necessity of new studies on excessive daytime sleepiness to better inform the individuals bearing such illness, which is commonly related to accidents and the development of cardiovascular morbidity, which have become a key public health issue.

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ORIGINAL ARTICLE

Analysis of complications of pregnant women with heart disease attended at a hospital of Vitória-ES

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Keywords

Cardiopathy; Pregnancy; Pregnancy Complications

Abstract

Introduction: heart disease remains the leading non-obstetric cause of maternal mortality in pregnancy and childbirth, and predispose the infant to complications. **Objective:** to analyze neonatal and maternal complications in pregnant women with heart disease. **Method:** case series study with retrospective data collection through medical records. Thirteen pregnant women with heart disease, served from 2005 to 2014, constituted the sample. Proceeded to the analysis of complications in pregnancy: prenatal time, gestation time, delivery, complications during pregnancy, medications used in pregnancy, breastfeeding in the recent postpartum and death. As for the newborn: weight, length, Apgar score, intrauterine growth restriction, length of stay in the neonatal intensive care unit, oligohydramnios, preterm birth and death. **Results:** among the 13 pregnant women, 15 pregnancies occurred. There were no maternal or neonatal deaths. All pregnancies were

full term, cesarean delivery and prenatal care was initiated in the 1st quarter. Out of the 15 monitored pregnancies, 5 had complications. Regarding neonates: All had adequate weight for gestational age and three newborns needed hospitalization in the neonatal intensive care unit. **Conclusion:** the incidence of maternal complications occurred in 33% of the pregnancies, 60% were women with valvular disease. The complications which occurred could have been found in normal pregnancies, having no direct relationship to heart disease. It can be inferred that prenatal associated with the multidisciplinary team and the stability of the disease were fundamental in the absence of complications related to heart disease.

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Introduction

When modifying the maternal physiology, the gestation promotes metabolic, anatomic and hemodynamic changes in the woman's body. These phenomena may worsen previous morbid situations or produce symptoms that, despite being physiological, are harmful.[1]

Due to expected changes in pregnancy, women with cardiac lesions of obstructive character can experience, for the first time, symptoms on that period. This is due to the raise of preload generated by the increase of blood volume. The reduction in afterload, added to systemic vasodilation, can further worsen the symptoms in these patients.[2]

The hypercoagulable state of the second half of pregnancy and the postpartum period increases the risk of patients with mitral lesion, atrial fibrillation and prosthetic heart valves to acquire thromboembolic events. Therefore, it is justified, that the stenotic valvular lesions present an unfavourable clinical outcome when compared to failure, due to those physiological changes.[3]

Heart disease stands as the main non-obstetric cause of maternal mortality in the cycle of the postpartum period.[4]

As demonstrated by Avila et al.,[4] in a study with 1000 pregnant women with heart disease, was found heart disease of rheumatic origin in 55.7% of cases and congenital diseases in 19.1%. During the study, 76.5% of pregnant women with heart disease had no cardiovascular complications and, among the complications, the most relevant was heart failure, which represented 12.3% of cases among the remaining 23.5%.[4]

The most common complications are premature birth, low birth weight at gestational age and perinatal death.[5] Siu et al.,[6] in a study with 562 pregnant women with heart disease, found neonatal complications in 122 pregnancies (20%). Akther et al.,[7] in a study with 60 pregnant women with valvular heart disease, found mitral stenosis as the most common valvular heart disease, accounting for 50% of valvular abnormalities

The evaluation of the relationship between maternal cardiac function and pregnancy outcomes plays an important role in reducing the risks for pregnant women with heart disease.[5]

Accordingly, it is necessary the development of more research in this field.

Method

It was conducted a study of series of cases with retrospective data collection through medical records in the files of Hospital Santa Casa de Misericórdia de Vitória-ES (HSCMV).

The sample consisted in pregnant women with heart disease at the Obstetrics and/or Cardiology Ward of HSCMV, during January 1 2005 to January 1 2014.

Criteria of inclusion: pregnant women with heart disease: valvular heart disease, congenital diseases, coronary artery disease, cardiomyopathy, post-operative cardiac surgery and cardiac arrhythmias; Exclusion criteria: women with morphological abnormalities of the reproductive system and kidney disease.

It was analyzed the incidence of pregnancy complications in relation to the mother and the newborn: regarding to the newborn, weight, length, Apgar score, intrauterine growth restriction, length of stay in the neonatal intensive care unit, oligohydramnios, prematurity and death were analyzed; with respect to the mother, prenatal time, gestation time, method of delivery, pregnancy complications, medications used in pregnancy, breast-feeding in the postpartum period and death were analyzed.

The study was approved by the Ethical Committee of research by the Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória – EMESCAM. All data was compiled using the Microsoft Excel® program.

Results

Regarding maternal outcomes, there were no deaths. Only an abortion was recorded, being in a pregnancy previous to specialized cardiac monitoring. The prenatal care for all pregnant women started in the first trimester of pregnancy.

Of the 15 watched gestations, ten (67%) had no complications. The registered complications are shown on table 1.

TABLE 1– Registered gestational complications

Congenital Diseases
Deep Vein Thrombosis
Pre-eclampsia
Valvulopathy
Oligohydramnios, placental abruption, gestational diabetes
Gestational diabetes
Abdominal wall hematoma

Source: the author

Regarding drugs used during pregnancy, women who did not have complications in pregnancy, childbirth and in the newborns made use of nitrofurantoin, enoxaparin and methyldopa. In pregnancies with complications, the medications used were propranolol, furosemide, enoxaparin, captopril, levothyroxine, metoprolol succinate, penicillin G benzathine and escitalopram.

The watched cardiopathies are described in table 2.

TABLE 2– Analyzed maternal cardiopathies (n=15)

Maternal cardiopathies analyzed		
Valvulopathies	**Gestations**	
Mitral stenosis and double aortic lesion	1	6.67%
Aortic insufficiency and mitral insufficiency (MI)	1	6.67%
Mitral and aortic mechanical prosthetics	1	6.67%
Mitral insufficiency	1	6.67%
Mitral valve prolapse (MVP)	4	26.66%
Congenital diseases		
Uncorrected patent ductus arteriosus	1	6.67%
Corrected patent ductus arteriosus	2	13.31%
Corrected ventricular septal defect.	1	6.67%
Congenital pulmonary stenosis	1	6.67%
Marfan syndrome (MVP and MI)	1	6.67%
Marfan syndrome (aortic mechanical prosthetics, MVP and MI)	1	6.67%

Source: the author

All women in the study had their deliveries via caesarean section and breastfed in the recent postpartum period.

Regarding neonatal outcome, nutritional assessment showed that they all had the proper weight for the gestational age.

The average length, at birth, of infants was 48,4cm and standard deviation of 1,3.

All patients in the study had their pregnancy terminated with 38 or 39 weeks, i.e., there were no preterm births.

There were no cases of intrauterine growth restriction.

Regarding Apgar, in the first minute it ranged from 6 to 10 (MA 8,26; DP 1,03) and in the fifth minute ranged from 8 to 10 (MA 9,40; DP 0,63).

Three newborns (20%) required admission to the neonatal intensive care unit: the first, child of a pregnant woman with mitral insufficiency, needed three days of phototherapy; the second, child of a pregnant woman with mitral insufficiency and aortic insufficiency, needed two days of phototherapy; and the third, child of a pregnant woman with mitral stenosis and double aortic lesion, needed three days of hospitalization due to meconium aspiration syndrome

Discussion

A deep vein thrombosis (DVT) case occurred during the first trimester of gestation in a patient with pulmonary stenosis. There is no relation of cause-effect between the existence of pulmonary stenosis and the increase of incidence of DVT in the literature.

Epidemiological studies have reported incidence of up to 12 cases of DVT per every 10000 gestations, and estimated a DVT frequency five times higher in pregnant women, compared to non-pregnant women of same age.[8]

It is possible to explain the predisposition to DVT in the first trimester of pregnancy, because in this period there is an increase in

venous pressure due to an overflow in the hypogastric and common iliac arteries, due to the relaxation of vascular smooth muscle and opening of mediated progesterone arteriovenous anastomosis.[9]

According to meta-analysis of 12 studies on the impact of the trimester in the occurrence of thrombosis, 22% of cases occur in the first trimester, reinforcing the hypothesis of no relationship between heart disease and the occurred event.[10]

In this study, there were two cases of gestational diabetes mellitus (GDM), identified in a 37-year-old woman with mitral stenosis and double aortic lesion and in a 40-year-old woman with mitral valve prolapse. GDM is defined as any degree of glucose intolerance, resulting in hyperglycaemia of varying severity, with onset or diagnosis during pregnancy.[11]

The patient who developed GDM in this study was included in the risk group for developing this disease, by being older than 25 years at the time of conception.[11]

The incidence of GDM in Brazil ranges from 2.4% to 7.2%, depending on the criteria used for diagnosis.[12] There is a lack of studies seeking to establish whether the diseases are a cause of GDM, but currently maternal heart disease is not considered as a risk factor.[11] GDM found in women bearer of double aortic lesion and mitral stenosis may be an occasional finding.

In this study, it was documented a case of a 40-year-old patient, already mentioned in the discussion, bearer of mitral valve prolapse, which had placental abruption, oligohydramnios and GDM. Pregnancy in women older than 35 years is associated with increased risk of maternal, fetal and obstetric complications.[13]

The causes of oligohydramnios are the premature rupture of the amniotic membranes, placental insufficiency, presence of fetal abnormalities, hypertensive disorders, smoking and post-maturity.[14,15]

The placental abruption may be the result of several pathophysiological processes, often from unknown origin.[16] One of the main causes of this event is the hypertensive disease. The oligohydramnios and maternal age are pointed out in the literature as possible risk factors.[17, 18]

During this study, one pregnant woman with uncorrected patent ductus arteriosus had pre-eclampsia, pathology that affects 8% of every pregnancy and is the major cause of perinatal and maternal deaths in developing countries.[19]

After analysing literature data, it was not found relation between pre-eclampsia and congenital heart disease, it can be inferred that the occurrence of this episode of hypertension during pregnancy was not motivated by underlying heart disease.

A patient with mitral and aortic mechanical prosthesis, in anticoagulation, had abdominal wall hematoma after an elective caesarean section. The incidence of abdominal hematoma in the population is generally small. The most important risk factors associated with this complication are anticoagulation (most important factor), chronic kidney disease, surgery and trauma.[20]

It is probable that the hematoma that this patient had is related to the use of anticoagulation, being related to cardiopathy secondarily.

During the gestations with neonatal complications, 3 in total, some drugs were used. These pregnancies used: 1 - propranolol with furosemide; 2 - propranolol alone; and 3 - use of levothyroxine with metoprolol succinate and penicillin G benzathine

Levothyroxine can be used safely during pregnancy without adverse effects on the fetus.[21] Penicillin G benzathine has no adverse effects reported in fetuses, but there are no controlled studies on its use during pregnancy; therefore, it is recommended to use when the benefits outweigh the risks.[22] Propranolol, metoprolol and furosemide

should be used only when the benefits outweigh the risks and there is no other drug of choice.[23-25]

The possible side effects of propranolol are bradycardia and fetal and neonatal hypoglycaemia, intrauterine growth restriction, polycythemia, thrombocytopenia and hypokalemia.[23] Furosemide may be responsible for birth defects in newborns.[24] Metoprolol has no reported adverse fetal effects, but there are no controlled studies on its use during pregnancy.[25] Possible adverse effects of these medications have not been observed in neonates. These drugs can be ruled out as causes of neonatal complications.

Two infants required hospitalization in the NICU of two to three days to conduct phototherapy. Phototherapy is performed on infants to treat jaundice.[26]

There may be hyperbilirubinemia according to ABO and Rh incompatibility between mother and fetus. ABO incompatibility occurs almost only when the mother's blood group O.[27]

ABO incompatibility occurs in 20% to 25% of pregnancies, and hemolytic disease of the newborn develops in 10% of gestations.[28] Other causes of neonatal hyperbilirubinemia is the beginning of breastfeeding, use of diazepam by the mother during pregnancy and gestational diabetes.[27]

The newborns studied in our research that required hospitalization for phototherapy had blood type A+ with O+ mother and blood type A+ with B+ mother. Blood incompatibility of the ABO system observed in the first case is the likely cause of the need for hospitalization of the infant for three days for phototherapy. In the second case, the newborn had to be hospitalized for two days for performing phototherapy, but the cause of jaundice was unclear.

A newborn had to be admitted to the neonatal intensive care unit due to meconium aspiration syndrome, which occurs between 1% and 3% of pregnancies. Fatal outcome occurs between 5% and 40% of the cases, due to short term and long term complications.[29] The exact mechanism of meconium release in this case cannot be clarified.

According to data already reported in the literature by Avila et al.,[4], 67% of pregnancies that followed the specialized cardiac monitoring protocol were free of complications.

Conclusion

Each cardiopathy, despite its peculiarities, can be enhanced due to physiological alterations resulted from pregnancy.

It was verified the incidence of maternal complications in 33% of pregnancies, 60% of which occurred in women with valvulopathy.

Importantly, the complications that occurred could have been found in normal pregnancies, having no direct relationship to heart disease.

It is possible to be inferred that prenatal associated with a multidisciplinary team and stability of cardiovascular disease were fundamental in the absence of complications related to heart disease.

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EXPERIMENTAL STUDY

Carboxytherapy effect on the cicatrization of contaminated skin wounds of rats

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Keywords

Wounds and Lesions; Carbon Dioxide; Cicatrization.

Abstract

Objective: To investigate the effect of carboxytherapy in contaminated skin wound on the back of rats. **Method**: 15 Wistar rats weighting between 264g and 394 g (MD 313± IQD 18.50) were operated. In these animals a skin wound was produced their back with about 1.5 cm diameter and 0.5 cm depth. 24 hours after the animals were divided into two groups: control (n = 6) underwent puncture of the skin wound in its outer edge, subcutaneously, at 12 pm, 6 pm, 3pm and 9 pm; experiment (n = 9) submitted to the puncture wound in the same location as the control group and injected 2 ml of carbon dioxide in each location. This procedure was performed on the 1st, 2nd, 3rd and 4th and 5th postoperative days. Volumetry was held at 1, 4, 8 and 11 days. The animals were killed on the 11th day, then it was removed a skin fragment for histopathological examination. **Results:** The animals have evolved satisfactorily. There was reduction in the wounds of both groups. This was evidenced by the photographs of lesions and confirmed by volumetry in the same group ($p<0.05$). This phenomenon occurred in both groups. There were no differences between the macroscopic, microscopic and volumetric features (p>

0.05) of the wounds between the control group and the experimental group. **Conclusion**: carboxytherapy did not interfere with the cicatrization of contaminated open skin wound produced on the backs of rats.

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Introduction

Wound treatment is described from the oldest times of human history. The first document that attests to the appearing of a wound in ancestors of men, Australopithecus *africanus*, has approximately 5 million years.[1] This record shows a cranial lesion probably caused by a blunt object. The first caveman might have covered a wound with moss to avoid leaking a certain viscous material (hemostasis). The intentional surgical wound and trepanation were performed about 10.000 years ago and finger amputation in about at least 7.000 years. In the year of 3100 BC, in Mesopotamia it was discussed the issue of wounds. Egyptian papyrus of 2800 BC. to 1600 BC. attests to treatment of chronic lesions.[2] The Egyptian would have been the first to use bandages on wound treatment. This people used animal fat and honey in the lesion, then covered it with a bandage of linen. The fat would create a physical barrier to contamination, honey had antibacterial function and linen would absorb secretion. Wound closing seems to have started in the 6th century, in ancient India, as was described in Susruta Samshita.[3] The surgical instruments description suggests that intentional wounds were common and that lesions were used to facilitate healing.[2] In this document was recommended debridement of loose and pulpy skin in burns.[3] Hippocrates (470-360 BC) was in favor of primary intention cicatrization and the use of moist bandages. He was the author of "*vis medicatriz naturae*" aphorism, which means "the healing power of nature". This included healing the wound. In the roman empire, Cornelius Celsus described the acute signs of inflammation: flushing, tumor, warmth and pain. He said that acute wound would heal rapidly or spontaneously and that chronic wound would heal due to infection, mechanical irritation or inadequate circulation. Galen lived in the Greco-Roman period and preconized wine and suture to treat the wound. Posteriorly, for this purpose, it was used medication and local applications.[4] In middle age, powders, ointments and cataplasms were used for the treatment of traumatic lesions. In Renaissance lived Ambroise Paré (1510-1590), father of Surgery, who condemned the cauterization and popularized hemostasis by ligation. He said "I tended to the wound, God healed it", showing his humility. William Stewart Halsted (1852-1922), professor of surgery at Hospital John Hopkins, introduced surgery fundamental principles such as: not to pinch excessive tissue; use gloves during surgery; not use silk threads in infected wounds and perform rigorous hemostasis. In addition to these, it is assigned to Halsted other recommendations on wound treatment: gentleness, cleanliness, confrontation of the wound edges, good vascular supply, avoid tension, avoid dead space,[5] which ultimately, favors tissue cicatrization. Contemporary medicine, despite all advances, is still challenged to treat many types of wounds.

In the treatment of open wounds, different types of medications have been used. In the experimental level it has been used the melipona honey,[6] Aloe Vera,[7] Laser,[8]

metronidazole,[9] fibroblast growth factor,[10] Passiflora edulis,[11] allantoin,[12] a combination of medium chain triglycerides, linoleic acid, soybean lecithin and vitamins A and E,[13] Aroeira extract, aqueous extract of babassu,[16] crude extract of jatropha gossypiifolia and propolis.[18-20]

Carboxytherapy has been used in treatment of many infirmities: stretch marks, cellulite, wrinkles, sagging, leg ulcers, peripheral artery disease with results still uncertain. Reports on carboxytherapy in contamined open skin wounds of rats were not found.

Considering that carboxytherapy has vasodilating effect, it was hypothesized that it might improve the healing of open skin wound. Therefore, it was performed this study aimed to evaluate the effect of carboxytheraphy in the cicatrization by secondary intention of contaminated skin wounds in the back of rats.

Method

After approval by the Animal Experimentation Ethics Committee of EMESCAM, 15 Wistar rats were studied, they were male, adults, with weight varying between 264g and 394g (M. 313 ± IQR 18.50). Each animal was punctured with one round shape wound in the dorsal region, in a way that the bottom margin of the wound would stay at the top of an imaginary line drawn between the ends of the scapulae, with 1.5 cm diameter, cutting the skin and subcutaneous tissue to the aponeurosis. The animals were randomly divided into 02 groups: group 1 (n = 9): carboxytherapy; Group 2: control (n = 06): puncture in the wound.

In the carboxytherapy group, it was performed a subcutaneous puncture in 4 different places with an insulin needle and 2ml of carbon dioxide was injected (12h, 6h, 3h and 9h) from the 1st to the 5th postoperative days (5 sessions). In the control group, the puncture was performed in the same places, with the same needle in the same days of carboxytherapy.

The rat's dorsal wound was caused in the following sequence:

- Anesthesia with 5% ketamine hydrochloride was administered at a dose of 75 mg/kg/weight (Vetanarcol - Laboratory König - Inc - Argentina) and xylazine hydrochloride 2% at a dose of 8 mg/kg (Kensol - König Laboratory – Inc - Avellaneda- Argentina);

- Shaving of the dorsal region of 4cm^2, with a shaving razor, performed after an imaginary line, cross section, from one ear to another, towards the dorsal-caudal;

- Local antisepsis with chlorhexidine at 10%, topical;

- Removal of skin fragment and subcutaneous cellular tissue, of round shape, with 1,5cm diameter and 0,5cm deep in the dorsal region;

- Wound hemostasis by local compression with gauze.

Photographs of the wound were taken for documentation.

The volume of the wound was evaluated at the 1st postoperative day by volumetry technique which was suggested by the research advisor (picture 1).[21] This technique consists in the following steps: a - saline solution was dripped on the wound with micropipettes of 10 microliters and 100 microliters. Volumetry was re-evaluated on 4th day, 8th day and 11th day; b - The lesion was filled with saline solution; c – Verification on the micropipettes of volume necessary to fill the wound in microliters.

Figure 1 – Aspects of the technique of volumetry through micropipette (a) used to drip saline solution into the wound to calculate wound volume. A magnifying glass and lights (b) helped measure total filling of lesion and consequently its volume.

Source: the author.

Wound treatment (carboxytherapy) was performed with the machine Carbtek Advanced Dual Channel Plus (Manufacturer - DAF Produtos Hospitalares Ltda. Avenue Ibiúna, 86 - Vila Arucanduva 03507-010 São Paulo – SP - Brasil)

The animals were randomized (carboxytherapy group and punction group) as following:

- It was written the number 1 or 2 in a square chip with 2cm edge. 9 chips were numbered with number 1 (group 1) and 6 with the number 2 (group 2). Each chip was place in an opaque envelop, sealed. Then, one individual who wasn't part of the study, scrambled and withdrew one chip which corresponded to the animal group (group 1 carboxytherapy and group 2 control). The researchers did not know which group the animal belonged.

After the treatment, the animals were returned to their cages and remained there with free diet and water. Analgesia of the animals was made by placing 200 mg of paracetamol in the water drinker and nubaim at 0.1ml/kg body weight subcutaneously.

In the day of surgery, carboxytherapy group, in the 1st, 4th, 8th and 11th days the wounds were photographed volumetry performed. In the 11th day it was removed a fragment of 3cm length by 3cm wide which included the wound in its central region, cutting the skin and subcutaneous of normal and wound areas. The animals were killed with Hypnol (3% sodium Pentobarbital – Syntec do Brasil Ltda) in dose of 120mg/kg.

The removed skin fragments were conserved in formalin 10% and then included in paraffin, submitted to transversal cuts of 4 μ with a microtome, and stained with hematoxylin-eosin (HE) to evaluate the histological changes.

Microscopy was performed by a binocular microscope pathologist, and the pathologist did not know to which group the animal belonged.

Statistic treatment

To calculate the median and standard deviation of the wound volume, descriptive statistics were used.

To compare the weight of the rats from the beginning to the end of the experiment, the Wilcoxon test was used.

To compare the volume of the wound between the different periods after surgery, in the same group, the Friedman test was used.

To compare the volume of the wound on the same day between the carboxytherapy and the control groups we used the Mann Whitney U test.

The tests were bicaudal, and p≤0.05 values were considered statistically significant.

Results

The wounds were produced without difficulties. Carboxytherapy was initiated 24 hours after wound production so it would be characterized as contaminated.

Animal weight had no significant difference between the beginning and the end of experiment in the carboxytherapy group of animals (median 313, interquartile range 24, median 330, interquartile range 46, p=0.594). However, in the animals of control group there was a significant weight increase (median 293, interquartile range 34.5, median 321.5, interquartile range 16.75, p=0.046).

It was observed similar closure of wounds in both groups, in visual macroscopic evaluation (Picture 2). There was a significant reduction in the wounds volume from the beginning to the end of the experiment both in carboxytherapy and control group (puncture) (p<0.05). The wound volume in control group in relation to carboxytherapy group had no significant differences in postoperative periods (table 1).

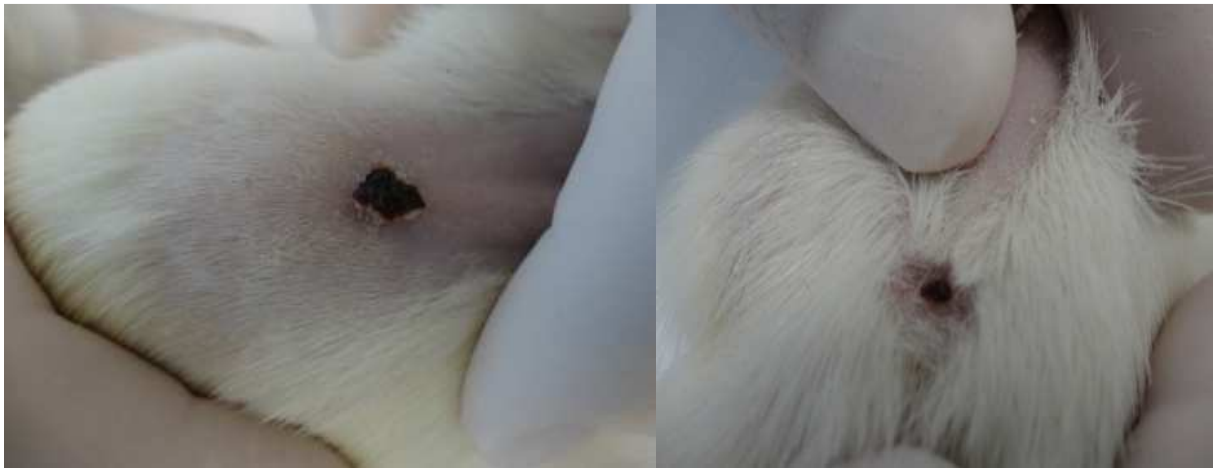

Figure 2: to observe the macroscopic aspect of the wound which was similar in the carboxytherapy group (Picture to the left) and control group (Picture to the right).

Source: the author.

Table 1 – Volumetry (in microliters) in the different postoperative periods between carboxytherapy and control groups.

	Postoperative Days											
Groups	1st PO			Groups			1st PO			Groups		
	M.D	D.I.Q	p	M.D	D.I.Q	p	M.D	D.I.Q	p	M.D	D.I.Q	p
Carboxy	163,33 ± 40,59			77,77 ± 22,79			16,00 ± 5,33			3,33 ± 0,86		
Control	146,00 ± 18,41		0.60	71,66 ± 14,71		0.68	12,00 ± 3,63		0.06	2,33 ± 1,03		0.08

M – Median. IQR – Interquartile Range. PO – Postoperative
Mann Whitney test. p ≤0.05 – significant.

Source: the author.

Histological analysis showed in both groups, without difference, non-specific chronic inflammation, ulcerated with granulation tissue, edema and giant cell reaction of the foreign body type associated

with surgical material. Surface presence of fibrin-leukocyte crust.

In the control group, histological sections stained with hematoxylin and eosin showed skin fragments exhibiting non-specific ulcerated chronic inflammation with tissue granulation and edema. There was no cicatrization difference between carboxytherapy and control group.

Discussion

Local treatment of open skin wounds is as ancient as the history of surgery.[1-5] It involves cleaning, debridement, application of substances with possible cicatrizing effect and coverage or not of the lesion with gauze and tape. Despite the large number of locally applied substances[7-20] that would have cicatrizing effect, there is still research for other methods because not always one method is effective for all wounds.

The weight of animals submitted to carboxytherapy had no significant variation from the beginning to the end of the experiment – 11th day ($p>0.05$). This is probably due to the stress followed by pain to which these animals were submitted. Besides, carboxytherapy causes reduction of subcutaneous fat volume. However, in the control group, not submitted to carboxytherapy, under lesser stressing situation, there was a significant weight gain from the beginning to the 11th postoperative day.

A challenge in the study of cicatrization is its evaluation. Although the ordinary methods of evaluation of cicatrization of an open skin wound are applied, none of them gives an accurate, quantitative sense, of the degree of closure of the lesion. Therefore, our proposal in this study was to use the volumetry of wounds[21] giving a dimension of cicatrization in length, width and depth. The volumetry method of choice is to drip saline solution with the micropipette. Subsequent reviews of this method allow us to infer whether the wound is decreasing its volume (is cicatrizing) in a very objective way. It should be noted that volumetry is a recent method idealized by Paulo and Fiorot to evaluate cicatrization of an open wound. This is a safe method, because it evaluates the cicatrization that occurs from the periphery to the center of the wound, and from the bottom to the surface.

The idea of using carbon dioxide in the open skin wound was based on its vasodilator effect. Nevertheless, in this study, the subcutaneously injected carbon dioxide was not able to accelerate the cicatrization of open skin wounds of rats. There was no significant difference in the average volume of the wounds on the 1st, 4th, 8th and 11th days between carboxytherapy and the control group ($p> 0.05$). It is possible that the dose used was not optimal, as well as the carbon gas application time, or indeed carbon dioxide, despite its vasodilator effect did not alter scarring. This can be seen by analyzing the photos, which seems show no difference between the cicatrization of a wound from one group to another. The histopathological examination showed no scarring differences between one group and another, and neither did volumetry.

Conclusion

Carbon dioxide applied in the subcutaneous cellular tissue of a contaminated open wound of rats was not capable of accelerating cicatrization.

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EXPERIMENTAL STUDY

Prevalence of coliforms and *staphylococcus aureus* in hands of food handlers of an open-air market in the municipality of Vitória-ES

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Keywords

Coliforms; *Escherichia coli*; *Staphylococcus aureus*; methicillin resistant *Staphylococcus aureus*; Food Handling.

Abstract

Introduction: Foodborne diseases (FDs) represent a major public health issue and negatively reflect on the health of populations and on the economic development of countries, leading to labor incapacity and costs with treatments and hospitalization. **Objective:** Assess the importance of professional food handlers in open-air markets in the spread of microbial pathogens. **Method:** The samples consisted of biological material collected from both hands of 17 vegetable handlers working in an open-air market in the municipality of Vitoria. The material was analyzed for isolation and identification of total and heat-resistant coliforms, *Escherichia*

coli and *Staphylococcus aureus* followed by the antimicrobial susceptibility testing. **Results:** It was possible to verify the presence of total and heat-resistant coliforms and strains of *Staphylococcus aureus*. No *Escherichia coli* strain was isolated. **Conclusion:** The results indicate that food handlers in open-air markets play an important role as potential disseminator of pathogenic bacteria. The study indicates the need to widen the practices of sanitary and hygiene control of these workers, as well as encourage them to maintain proper and regular hand washing, make available clean running water in their workplace and teach them to assign tasks so as to separate money from food.

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Introduction

Foodborne diseases (FDs) represent a major public health issue and negatively reflect on the health of populations and on the economic development of countries, leading to labor incapacity and costs with treatments and hospitalization. In Brazil, between 1999 and 2004, 3,410,048 hospitalizations due to FDs were recorded, with an average of 568,341 cases and 8,427 thousand deaths per year.[1,2]

According to the Atlanta Center for Disease Control and Prevention (CDC), most of the FDs are linked to the inadequate handling of food. Therefore, food handlers play an important role in the transmission of foodborne diseases, partly due to poor personal hygiene and domestic habits, besides a deficiency in hygiene and environmental control.[3,4]

The collective food services have grown globally, and in Brazil this market serves about 2 million workers. Thus, a lack of hygiene control of the food sold by these handlers represents a major obstacle in the introduction of control measures to control FDs.[5]

The transmission of infectious diseases through hands was described 120 years ago by Semmelweis, but it was Price who actually studied the type of skin bacteria, classifying them into "resident and transitory".[6]

The bacteria of the genus *Staphylococcus* are Gram-positive motionless cocci, part of the family Micrococcaceae and, due to dividing themselves in different layers, they are formed in grape-like clusters when analyzed in a microscope. They are facultative anaerobic bacteria, catalase producers under anaerobic conditions. They are also important pathogens for humans since they are responsible for a wide range of systemic diseases, including skin infections, soft tissues, bones, urinary tract besides food poisoning, the latter the scope of this study.

The species *Staphylococcus aureus*, besides being the most virulent, is often associated to staphylococcus diseases, whether they be food-based or not, which makes this group the target of several studies.[7,8] Its colonies are of a golden yellow coloration as a result of carotenoid pigmentation that are formed during the growing phase, hence the name of the species.[8]

Men and animals are the main recipients of *S. aureus*. In humans, the nasal cavity is the main habitat of these bacteria and, from there, they may reach the skin as well as wounds, air, water, soil, milk and any surface or object that has had contact with a

human.[7] Approximately 15% of healthy adults are persistent carriers of *S. aureus* in the nasopharynx.[8] Thus, the nasal carriers that work handling food become important sources of food contamination, and potential causative agents of food poisoning.

Food poisoning through *S. aureus* is one of the most common FDs, being an intoxication rather than an infection, since the symptoms are caused by the ingestion of food containing the bacterial toxin, and not by the direct action of the microorganism.[7,8] Such toxins, known as enterotoxins, are heat-resistant, which makes them an asset to the food industry, considering that most foods undergo a thermal treatment during its processing, which would not inactivate the toxin if present, making the food more prone to causing some kind of poisoning. The enterotoxins can cause vomiting, diarrhea, inflammation with the development of enteritis, making up a wide spectrum of symptoms.[7]

Staphylococcus become a meaningful part of the resident microbiota in many individuals and, due to the pathogenicity of some strains and capacity to produce enterotoxins, it is important to eliminate them by washing the hands. However, individuals with a relatively low educational level are not often aware of the importance of such hygiene habits.[6]

The coliforms have been initially described as potential microorganisms indicators of fecal contamination in fresh water.[9] The use of *Escherichia coli*, one of its representatives, as an indicator of fecal contamination in water was proposed in 1892, provided that this microorganism exclusively lives in the intestine tract of humans and hot-blooded animals.[7]

Over the years, such concept has become broader, and nowadays the research on coliforms, besides used for water quality evaluation, has also been used for the evaluation of poor hygiene and sanitary conditions while handling, producing and preparing foods. Such microorganisms are classified as total coliforms and heat-resistant coliforms.[10,11]

The group of total coliforms is composed of bacteria of the family Enterobacteriaceae and include all the bacteria that are Gram-negative, rod-like, non-sporogenic, aerobic or facultative anaerobic, able to ferment lactose with the production of gas when incubated at *35*-37°C (95-98.6°F) for 24-48 hours. It includes about 20 species of bacteria belonging to the genuses *Escherichia, Klebsiella, Enterobacter and Citrobacter*. Out of the latter, only *Escherichia coli* has as a primary habitat the intestinal tract of humans and animals. The others, besides being found in feces, are also present in other environments, such as in plants and soil. Consequently, the presence of total coliforms in food does not necessarily indicate a recent fecal contamination or the occurrence of enteropathogens.[7,12,13]

The heat-resistant coliforms, previously referred to as fecal coliforms, correspond to the total coliforms that are able to continuously ferment lactose with the production of gas, when incubated at 44.5%-45.5ºC (112.1-113.9 ºF) for 24 hours. Under these conditions, around 90% of the *E. coli* cultures are positive, while among the other genuses, only some strains of *Enterobacter and Klebsiella* maintain such characteristic. In this way, the research on heat-resistant coliforms or *E. coli* in food provides solid information on product hygiene and efficiently indicates an occasional presence of entheropathogens.[7,13]

Among the bacteria of admittedly fecal habitat, *E. coli* is the most known and easily differentiated among the non-fecal members. Several ones from its lineage are proven to be pathogenic to humans, able to cause serious infections and even death. These pathogenic strains are classified according to their effects in the recipient. The categories that cause intestinal infection are collectively called *E. coli* diarrheagenic, and may be classified as:

enteropathogenic *E. coli* (EPEC), enterotoxigenic (ETEC), enteroinvasive (EIEC), enterohemorrhagic (EHEC) e enteroaggregative (EAEC).[12] Data reported by the Center for Disease Control on food poisoning and infection surges in the US food service indicate food handlers accounting for 26% of the responsibility for such surges.[14] Considering that in Brazil there are few lines of research assessing the occurrence of microorganisms in food handlers, despite being a relevant and current issue, the present study was then designed to investigate total and heat-resistant coliforms (*Escherichia coli) a*nd *Staphylococcus aureus* in the hands of stallholders handling in natura food and working at open-air markets.

Method

The samples of the present study are composed of biological material collected from 17 vegetable handlers working in an open-air market in the municipality of Vitória, state of Espírito Santo, Brazil. The professionals who agreed on being submitted to the research had to sign the Term of Informed Consent at the moment of the interview that preceded the material collection.

Nail bed sample

Each research participant had the material from both hands, including nail bed, collected with sterilized Swab, packaged and transported in a Stuart™ medium as per described in the Manual of Clinical Microbiology for the Control of Infection Related to Assistance and Healthcare, identified with a number for the subject, and taken to the Microbiology Laboratory at the Escola Superior de Ciências da Santa Casa de Misericórdia in Vitória (EMESCAM) for analysis.[15]

The Stuart™ medium presents a nutritive composition able to guarantee the survival of microorganisms, although it considerably hinders their multiplication due to a lack of nitrogen source in the medium.[15]

Sample analysis

The material was analyzed so as to isolate and identify Total Coliforms, Heat-resistant Coliforms, *Escherichia coli* and *Staphylococcus aureus* by using specific selection medium followed by the performance of confirmatory tests for identification and susceptibility to antimicrobials. The storage and analysis were carried out *at the* Microbiology Laboratory at the Escola Superior de Ciências da Santa Casa de Misericórdia in Vitória (EMESCAM), according to the current norms of Biosafety.

Staphylococcus aureus isolation and identification

Specific medium seeding

For the isolation of *S. aureus*, the samples were seeded in a Hypertonic Mannitol Agar (HMA) medium and incubated in a bacteriological incubator at 35ºC±1ºC (95ºF) for 48 hours. After this period, there was a growth of microorganisms resistant to the presence of high saline concentrations (7.5%), such as bacteria of the genus *Staphylococcus.* As there was growth of *Staphylococcus aureus*, it has been observed the color alteration of the culture medium, from pinkish to yellow, due to the turning of the pH indicator (phenolsulfonphthalein/PSP), resulting from the fermentation of mannitol. In case of no mannitol fermentation (S. non-aureus), the medium color remained unaffected (mannitol negative).[16,17]

The suggestive colonies of *Staphylococcus aureus* have been seeded in a new plate containing a HMA medium for the pure and subsequent performance of confirmatory tests of identification.

Identification confirmatory tests

GRAM coloration

Initially, the GRAM coloration of the suggestive colonies of *Staphylococcus aureus* present in the material *was carried out* according to the following process: fixate the material sample on the slide. Cover the slide with the Crystal Violet dye for 1 minute. Wash the slide in running water. Cover the slide with Lugol for 1 minute. Wash the slide in running water. Remove dye excess with alcohol/acetone for about 20 seconds. Wash the slide in running water. Cover the slide with safranin for 30 seconds. Wash the slide in running water. Dry the slide. With an optical microscope, in the presence of *S. aureus,* cocci have been identified as grape-like clusters of a purplish color, due to Gram coloration.[17]

Catalase Test

This experiment has allowed the differentiation of the catalase-producer microorganisms (*Staphylococcus* spp.) from the non-producers (*Streptococcus* spp.).[17]

The suggestive colonies of *Staphylococcus* spp. were placed on a glass slide and, afterwards, a drop of 3% hydrogen peroxide was added. When positive, the immediate presence of bubbles was observed due to the conversion of the hydrogen peroxide into water and gaseous oxygen, which confirms the presence of *Staphylococcus* spp. The non-emergence of bubbles rules out the possibility of staphylococcal colonies.[16,17]

DNase test

This test verifies the production of the deoxyribonuclease enzyme, which degrades acid nucleic (DNA). The test is useful to differentiate *Serratia*, from the *genus* Enterobacter, *Staphylococcus aureus* from the coagulase-negative *Staphylococcus and Moraxella catarrhalis* from the Neisseria *species.*[17]

The suspicious colonies were seeded with a platinum loop in circular movements on a DNase Agar plate. The plates were placed in an inverted position and incubated at 35±2°C (95±35.6°F) for 48 hours. After incubation, the cultivation was covered with a 1N hydrochloric acid solution (HCl). The acid was allowed to penetrate the entire surface of the medium for 2 minutes and a reaction was observed. Upon showing a clear zone encompassing the growth areas on the DNase Agar, after the addition of 1N HCl, a positive reaction was confirmed. By contrast, the negative reaction was indicated by any clouding or precipitation around the colonies.[17]

Disc diffusion test for antimicrobial susceptibility assessment

In order to determine the susceptibility pattern to oxacillin, isolates of *S. aureus* were used, taken from the pure sample from the plates with a positive result for them. The antimicrobial susceptibility test (AST), based on the agar diffusion principle with paper filter discs through the Bauer-Kirby method[17]

The method consists in obtaining the bacterial inoculum containing 10^8 CFU/mL, corresponding to the 0.5 MacFarland Scale standard. Therefore, each tested lineage was inoculated in tubes containing 5mL of a 0.85% saline solution, with the use of a previously heated bacterial loop, in a sufficient amount to reach the 0.5 standard clouding of the mentioned scale. With the aid of a sterile swab, the culture was seeded in Petri plates containing Mueller-Hinton agar until obtaining a uniform smear. After smear drying, discs with selected antibiotics were applied to the surface of the culture medium, with the aid of a sterile pickup, in accordance with the recommendation of the Clinical Laboratory Standards Institute. After that, the plates were incubated at 37ºC±1ºC (98.6ºF) for 24 hours.[18]

Oxacillin susceptibility assessment through disc diffusion test

For the assessment of presence of the *methicillin/oxacillin resistant S. aureus* (MRSA/ORSA), with the use of cefoxitin, the disc fusion test was performed, based on the Kirby-Bauer method, according to the methodology described above. However,

instead of using the oxacillin discs, the cefoxitin discs were used (30 µg). For the interpretation of the inhibition halos, the data described in Table 1 were used.[17]

Table 1 – *Staphylococcus aureus* screening: ORSA/MRSA with cefoxitin disc

Microorganism	Inhibition halo (mm)	
S. aureus	≤ 21*	≥ 22*
SCN	≤ 24*	≥ 25**

SCN: Staphylococcus coagulase-negative; *report as resistant oxacillin; **report as sensitive oxacillin. The cefoxitin result is not reported in the result.

Source: Oplustil (2010)

Isolation and identification of total coliforms and heat-resistant coliforms

Presumptive test for coliforms

The swab used for collection was introduced and agitated in a tube containing 10mL of Lauryl Sulfate Tryptose (LST) with an inverted Durham tube. The LST contains lactose and the observation of growth with gas production stemming from lactose, after 24-48 hours at 35ºC±1ºC (95ºF), is considered suspicious of the presence of coliforms.[19]

The LST tubes were incubated at 35±0.5ºC (95±32.9ºF) for 24/±2h and growth with gas production was observed. Tubes that showed growth and production of gas were considered positive. In case negative, it was reincubated until completing 48±2h, and the reading was repeated.[19]

Presence confirmation of Total Coliforms

For total coliform confirmation, a loopful of each suspect tube was transferred to a 2% Brilliant Green Bile Broth (BG) and incubated at 35±0.5ºC (95±32.9ºF) for 24/±2h. Growth with gas production was observed. Tubes that showed growth and production of gas were considered positive. In case negative, it was reincubated until completing 48±2h, and the reading was repeated. If once again negative, the sample was considered negative for total coliforms.[19]

Presence confirmation of Heat-resistant Coliforms

For the confirmation of heat-resistant coliforms, a loopful of each suspect tube was transferred to a *E. coli* (EC) Broth tube and incubated at 45.5±0,5ºC (113.9±32.9ºF) for 24/±2h. The tubes remained submerged in water up to a height higher than the surface of the culture. The procedure did not exceed 30 minutes between inoculation and transference to the inoculation bath.[19]

After this period, growth with gas production was observed. Tubes that showed growth and production of gas were considered positive. In case positive, the sample was considered positive for heat-resistant coliforms, being necessary to perform a confirmatory test for *E. coli*. In case negative, the sample was considered negative for heat-resistant coliforms.[19]

E. coli presence confirmation – Culture in selective/specific medium

The positive EC tubes for heat-resistant coliforms were suspicious of the presence of *E. coli*. In this case, they were submitted to a confirmatory test.

A handful of each tube was streaked (streaking technique) in Levine-Eosin Methylene Blue Agar (L-EMB), in a differential selective group to distinguish *E. coli* from the other heat-resistant coliforms. The plates were incubated at 35±1ºC (95±33.8ºF) for 24±2h and, after this period, the growth of typical colonies of *E. coli*, nucleoid colonies with a black center were observed, with or without a metallic glow.[19]

The suggestive *E. coli* colonies were seeded on a new plate containing a L-EMB medium for pure isolation and subsequent performance of confirmatory identification tests.

E. coli presence confirmation – biochemical proofs

In case of growth of typical colonies, two well isolated colonies from each plate were transferred to Standard Agar Tubes (PCA) for counting, then inclined and incubated at 35±1ºC (95±33.8ºF) for 24±2h. Given that, pure colonies were obtained and submitted to the GRAM coloration and Citrate Test.

Citrate Test

A loopful with a light culture inoculum was inoculated in a Koser citrate broth, incubated at 35ºC±1ºC (95ºF) for 96 hours while growth was observed (positive test) or not (negative test). The *E. coli* strains are citrate-negative.[19]

Statistical Analysis

Type of study: descriptive out of a series of cases, with the carrying out of descriptive statistics.

Inclusion and exclusion criteria

Subjects that participated of the Project: (1) older than 18 years old; (2) handlers of *in natura* food at an open-air market in the municipality of Vitória, Espírito Santo; and (3) those that agreed on joining the study by signing the Term of Informed Consent.

Considerations

The existing risks for the professionals in the procedures of biological material collection were: (1) nail bed bleeding, which can be spontaneously solved, except in specific occasions; and (2) occasional possibility of contamination for professionals. However, all the material used in the procedures was sterilized according to the norms of the Ministry of Health.

After analysis, the results were handed in individually and under absolute confidentiality to each subject in a previously arranged and informed date.

The biological material has been disposed of in accordance with the protocol of the Health Service Residue Management Program (PGRSS), following the Board of Trustee's Resolution (RDC) no. 306/2004 by the Brazilian Health Surveillance Agency (ANVISA), implemented in the laboratories of the Microbiology and Parasitology disciplines at EMESCAM. The set of information and work data will be stored for five years in the archives of the Microbiology and Parasitology disciplines of EMESCAM.

Ethical and Biosafety commitment

This project has been approved by the Ethics and Research Committee (ERC) of the Escola Superior de Ciências da Santa Casa de Misericórdia in Vitória (EMESCAM), complying with the requirements of Resolution no. 446 as of December 2012 by the Brazilian National Health Council. All food handlers from the open-air market, subjects of research, were made aware of the project's goals, that is, to outline the prevalence of coliforms and *Staphylococcus aureus* present in their nail beds. They were also informed that the results are classified, their privacy guaranteed and that they would be granted access to the research results if they wished so.

The biological material was only collected by the research subject after signing of the Term of Informed Consent. The biological samples obtained have been stored. As previously described in the material and methods section, the samples will not be used for unplanned means as per the Term of Informed Consent without a new authorization from the volunteering handler and from the ERC.

Results

Assessment of the presence of *Staphylococcus aureus* and its susceptibility to oxacillin

Samples from both hands were collected from 17 stallholders, adding up to 34 samples. Among these samples, 20 *Staphylococcus aureus* lineages (58.8%) were isolated. 8 samples from the left hand and 12 from the right hand were isolated. In 7 (41.2%) stallholders, *S. aureus* was isolated in both hands. The lineages assessed *in vitro* as opposed to oxacillin showed susceptibility in 18 (90%) samples and resistance in 2 (20%) samples (Table 2).

Table 2 – Isolate numbers of *S. aureus* in the hands of open-air market food handlers. Assessment of sample susceptibility to oxacillin

Microorganism	Right hand	Left hand	Both hands	Susceptibility to oxacillin
S. aureus	8	12	7	18

Source: The author

Assessment of the presence of contamination indicators. Presence of coliforms.

Among the studied stallholders, it was possible to verify the presence of total coliforms in 7 (20.5%) samples, and heat-resistant in 3 (8.8%) samples in their hands (Table 3). However, the presence of *E. coli*, an important indicator of fecal contamination, was not verified in the hands of food handlers.

Table 3 – Number of contamination indicators isolates in the hands of food handlers in open-air market

Indicator	Right hand	Left hand	Both hands
Total coliforms	4	3	2
Heat-resistant coliforms	1	2	1
Escherichia coli	0	0	0

Source: The author

Discussion

The presence of *S. aureus* and coliforms is considered an important indicator of improper conduct in the handling of foods.[9] Their presence in the hands of food handlers makes evident a worrisome situation in the environment studied, since the presence of these microorganisms, associated to the food handlers' poor hygiene and sanitary conditions, may cause food poisoning.[20] Such fact confirms the hypothesis of the present research and showcases the importance of food handlers in the transmission of FDs.

Food handlers, whether they operate in the industry or food businesses, are important driving sources of *Staphylococcus aureus* due to the fact they are mostly asymptomatic carriers. Whether it be in preparation, transportation, distribution or commercialization of foods, the presence of this microorganism is an indicative of poor hygiene and sanitary conditions and interpreted as an indicative of contamination from the food handlers' skin, mouth and/or respiratory system.[9,20]

For growing in temperature ranging from 7-47.8ºC (44.6-118.04ºF) and for producing toxins between 10-46ºC (50-114.8ºF), these enterotoxins are thermostable at 100ºC (212ºF) for up to 30 minutes, besides being resistant to hydrolysis from the gastric enzymes and the jejunum, turning out to be perfect for causing foodborne diseases. Thus, once the food had been contaminated by the staphylococcus producer of enterotoxins, and the toxins had been produced in a sufficient amount, not even a food mild reheating and exposition to gastric acid will suffice to avoid poisoning.[8]

The precise mechanism of the toxic activity is still not fully understood, but it is believed to be necessary around 10^5–10^6 CFU of *S. aureus* per gram of food so the toxin can be produced in such a level to be able to cause poisoning. Normally the bacteria are found in a small amount, which makes an infection difficult, since the multiplication is necessary.[7,8]

In this study it was possible to prove the presence of *Staphylococcus aureus* in the hands of 13 out of the 17 assessed stallholders, being this presence observed in one or in both hands, adding up to 20 positive samples. Surprisingly, two of these samples have shown resistance to methicillin, which makes these results increasingly important.

The first time an antimicrobial drug was clinically used was against a sample of *S. aureus*, following the discovery of the penicillin. The drug met the needs accordingly until the 1960s, when resistant isolates started to be resistant to this antimicrobial. In order to tackle this problem, the methicillin was created, a synthetic beta-lactam that was resistant to the action of the beta-lactamases produced by the *S. aureus*. However, due to its capacity to rapidly develop resistance, it was not long for reports to show on samples also resistant to this antimicrobial, which have been referred to as *methicillin resistant Staphylococcus aureus (MRSA),* characterized by the resistance to all beta-lactam antimicrobial.[21,22]

Until 1980, MRSA reports consisted of isolated cases, but after 1982 epidemic strains were described as multiresistant, able to colonize and cause infection surges, becoming a widely known cause for morbidity and mortality around the world.[23] Initially, these infections were limited to hospitals, but in the last years infections associated or acquired in a community have increasingly occurred in healthy subjects with no identifiable risk factor. That is alarming since patients infected by MRSA are five times likely to die than patients infected by methicillin sensitive *S. aureus* (MSSA), which makes the MRSA one of today's key health issues.[21,22]

Some studies have reported the detection of genes that codify staphylococcus enterotoxins among lineages of MRSA. This way, it can be concluded that this group can also be involved in food poisoning surges, provided the ingestion of the toxin ingestion takes place. However, it is important to consider that the resistance to the methicillin is not a relevant factor for the production of enterotoxins. The presence of MRSA in food may not represent a greater risk of food poisoning.[23]

Considering that the *S. aureus* is widely present in nature, its elimination from the environment becomes virtually impossible. The handling of by humans, one of the recipients of this bacterium, already increases a risk of contamination, being necessary to take measures to avoid its transmission.[7,24] Therefore, stallholders are tentative sources of contamination and dissemination of *S. aureus*, especially of resistant strains, and its presence in their hands represents poor hygiene conditions at the workplace. Hence, it will only be possible to reduce the rates of infections and contaminations through prevention and control of the transmission of multiresistant organisms. Washing the hands, a simple attitude, can help tackle this public health issue.[22,24]

Regarding the presence of coliforms, their presence in 9 out of 17 stallholders has been observed, which means that more than 50% of them had the bacterium in their hands. It represents a substantial number of research subjects that had contact with enterobacteria, leaving room for a possible contamination to the handled food.

Coliforms constitute a group of bacteria present in feces and in the environment. They are generally subdivided into two groups: the total ones, which are from the environment and used as indicators of food hygiene quality, and the heat-resistant ones, which originate from recent fecal contamination and are used as sanitary quality indicators of foods.[25]

The presence confirmation of total coliforms occurred in 5 different stallholders, while the presence of the heat-resistant ones was confirmed in 2 stallholders. The rate of fecal coliforms indicates the amount of organisms from human feces, that is, fecal contamination. This definition, at first, mainly focused on microorganisms from the intestinal tract. The group of total coliforms includes at least three genuses, *Escherichia*, *Enterobacter* and *Klebsiella*, out of which *Enterobacter* and *Klebsiella* include non-fecal strains. Due to this reason, the presence of fecal coliforms in food is less representative, as an indication of fecal contamination as opposed to the direct numbering of E. coli, though much more meaningful than the presence of total coliforms given the high incidence of E. coli in the fecal group.[26]

The *presence* confirmation of *Escherichia coli* is of great importance since it represents a major indicator of fecal presence. However, despite the presence of heat-resistant and total coliforms have been confirmed in this study, positive samples in a selective medium of *Escherichia coli* have not been found. In doing so, regarding this important indicator, the results have been considered satisfactory, thus allowing these subjects to safely commercialize their products. The food handlers, subjects of this research, have been considered tentative transmitters of gastrointestinal infectious diseases, given that *Staphylococcus aureus* or total and heat-resistant coliforms had been isolated in some of the food handlers. Such data show the necessity to improve the good practices of hygiene and sanitary control for these workers.

Most of the people dealing with food lacks hygiene and sanitary knowledge to handle it, not being aware that they might be asymptomatic carriers of pathogenic microorganisms. As a consequence, this fact makes room for poor hygiene practices employed by unskilled subjects, posing a greater risk of food contamination.[20]

The health condition of the food handlers, as well as their hygiene habits, directly affect the final quality of product. They must be trained and prepared to perform their job. It is of utmost importance to highlight that hygiene in handling and the proper preparation techniques of food contribute to decrease the risks of the FDs.[20]

Conclusion

All things considered, it is concluded that the best habits must be encouraged, such as regular hand washing, toilet availability with clean and running water at the market site, and also teach them to assign tasks among co-workers so as to separate money from food.

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REVIEW ARTICLE / UPDATE

Thyroid function disorders induced by amiodarone

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Abstract

Amiodarone is an antiarrhythmic rich in iodine and a medication prescribed in clinical practice for the treatment of cardiac arrhythmias. Its use is related to dysfunction in various organs such as the thyroid gland. It is known that most patients remain euthyroid, but some dysfunctions, for instance hypothyroidism and thyrotoxicosis type I and II, may occur in 15 to 20%, being hypothyroidism more frequent. The treatment for this issue is levothyroxine. The treatment depends on the type of thyrotoxicosis diagnosed in the patient. It is therefore necessary to screen for the diagnosis and treatment of thyroid dysfunction early and effectively, since the permanence of these dysfunctions may lead to a worsening of the heart function of the patient.

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Introduction

Amiodarone was introduced in clinical practice in the 60's, initially as an antianginal agent, and later studies of its electrophysiological effects established its use as an antiarrhythmic agente,[1] being widely used specially in refractory arrhythmias to conventional treatment.[2]

This drug has a chemical structure similar to thyroid hormones: triiodothyronine (T_3), thyroxine (T_4), Reverse T3 and its active metabolite, desethylamiodarone (DEA). Each amiodarone molecule has two iodine atoms, which corresponds to 37% of its molecular weight. [3,4]

Regarding thyroid gland dysfunction, hypothyroidism and type I and II thyrotoxicosis, it is estimated that 15% to 20% of patients under the medication develop these effects. This percentage raises to 50% over four years of treatment.1 These secondary effects may linger for months after discontinuation of the drug, a fact that is due to its long half-life and storage capacity in adipose tissue.

Thus, when starting the use of the drug, it is of great importance to perform a complete medical history and watch over laboratorial parameters. This makes it possible to assess and identify patients predisposing the development of thyroid dysfunction.

It is known that in average, 10% of the molecule is deiodinated on a daily basis and the drug maintenance dose ranges between 200mg to 600mg per day. Thus, the amount of iodine available in the body ranges between 7mg to 21mg daily. This amount is higher than the daily intake of iodine recommended by WHO, which is 0,15mg to 0,3mg per day.[5]

Amiodarone action mechanisms in thyroid physiology

Amiodarone interference in the thyroid hypothalamic-pituitary axis is due to intrinsic effects of the drug and its iodine content.

Iodine, substrate for the synthesis of thyroid hormones, is transported to inside thyroid follicular cell where it will be organified. This process is self-regulated to avoid iodine overcharge. In a situation of iodine excess, the synthesis of thyroid hormones is inhibited and this process is known as Wloff-Chaikoff effect, which is transitory and followed by an escape mechanism.

In cases of thyroid autoimmune disease, there are, many times, defects in this self-regulation with failure of the escape mechanism.[4,6,7] The explanation for the development of this condition would be an inhibition of the synthesis of thyroid hormones resulting from iodine overload due to metabolization of amiodarone, leading to hypothyroidism. Iodine excess can also lead to a potentiation of thyroid autoimmunity and increased synthesis of thyroid hormones (Jod-Basedow effect) in patients with Graves' disease or nodular goiter, leading to hyperthyroidsm.[4]

Regarding the intrinsic action of amiodarone, there is deiodinase inhibition at central and peripheral level, block of peripheral uptake of thyroid hormones, direct cytotoxicity to thyroid and decreased binding of T_3 to its receptor.

At peripheral tissues, mainly liver, thyroid and kidney, amiodarone inhibits the action of type I deiodinase enzyme, responsible by peripheral conversion of T_4 into T_3, as well as reverse T3 (rT_3) into diiodothyronine (T_2). This is probably due to a mechanism of competitive antagonism due to the similarity with the T_4 structure.[2]

There is also an inhibition of activity of enzyme deiodinase type II (DIO2) which operates at pituitary level converting T_4 into T_3. After discontinuation of the drug, this inhibitory effect can persist for several months. In addition to enzyme inhibition, amiodarone also blocks the entry of thyroid

hormones in peripheral tissues.[5] Both described mechanisms lead to increased serum concentrations of T_4 and rT_3, besides the decrease of T_3. However, most patients remain clinically euthyroid.[2]

Regarding the TSH values, the changes observed with use of amiodarone are time and dose dependent. The increase in plasma TSH initially occurs in response both to the fall in the concentration of T_3 in central level (by inhibition of the deiodinase type 2) and to the connection of DEA to intracellular receptors T_3, antagonizing it.[8]

Thyroid cytotoxicity may occur by direct action of amiodarone, resulting in destructive thyroiditis, as well as by the excess of iodine present in the drug, inducing phenomena of apoptosis and oxidative stress.[9]

Regarding to thyroid autoimmunity, studies show that it is unlikely that treatment with amiodarone triggers the appearance of autoantibodies. However, it may precipitate or worsen pre-existing autoimmunity in susceptible individuals, since most patients who develop amiodarone-induced hypothyroidism has positive values of antithyroid autoantibodies before treatment.[5,10]

The appearance of thyroid dysfunction induced by amiodarone may be related to predisposing factors such as dietary iodine ingestion, presence of personal and/or family history of thyroid disease and presence of antithyroid antibodies prior to use of the drug.

The thyrotoxicosis is more frequent in regions with insufficient iodine intake, whereas hypothyroidism is found in areas with sufficient iodine supply. The overall incidence of thyroid dysfunction in patients using amiodarone ranges from 14% to 18%, and the incidence for hyperthyroidism ranging from 5% to 10% and hypothyroidism 10% to 20%.[4] In the United States, the cases of hypothyroidism are more prevalent, compared to thyrotoxicosis, whereas in Europe this correlation is the inverse.[2]

Amiodarone-induced hypothyroidism

Amiodarone-induced hypothyroidism occurs earlier if compared to hyperthyroidism and its development is independent of the daily doses of the drug. It is observed an association with advanced age, female gender and autoimmune thyroid disease.[8] Therefore, the dosage of antithyroid antibodies, especially antiperoxidase antibodies (anti-TPO) should be given, as are markers of autoimmune thyroid disease.

Previous occurrence of Hashimoto's thyroiditis is an established risk factor for the occurrence of hypothyroidism,[2] which occurs generally between 6 to 12 months of amiodarone use.

Additionally, the extra intake of iodine, added to the previous presence of autoantibodies, can lead to the destructive thyroiditis phenomena. The clinical manifestations of amiodarone-induced hypothyroidism are weight gain, weakness, hair loss, dry skin, cold intolerance and lethargy, this one being the most common. These signs and symptoms are, in majority, difficult to diagnose, once it can be attributed to the heart disease in these patients. Goiter and myxedema are uncommon.[9]

The hypothyroidism diagnosis is usually simple. Laboratory characteristics include high levels of TSH, usually above 20mU/L, associated to reduced free T_4 (FT_4) values.[8] However, it can be observed a subclinical form of the disease, with moderately elevated TSH (levels between 4,3mU/L and 20mU/L) and normal FT_4.[9]

In patients with subclinical hypothyroidism, the levothyroxine (L-T_4) treatment should be taken if there are antithyroid antibodies present. Symptomatic patients with no

antibodies should be re-evaluated in three months. Evaluation should be made in frequent intervals (six weeks and later in every three months) in case of absence of antibodies and symptoms.[11]

The TSH serum level constitutes the first-line test for hypothyroidism diagnosis. However, it is necessary to consider the TSH increase that occurs in the first three months of amiodarone therapy. The free T_3 (FT_3) levels have no use for diagnosis.[9]

Hypothyroidism treatment by amiodarone is based on levothyroxine use. Initially in low doses (25mcg to 50mcg) with posterior gradual increase.

Interruption of drug intake brings little benefit. However, on patients who need to keep the drug use, there is need of a higher levothyroxine dose if compared to other hypothyroidism conditions. Higher doses should be considered in some situations such as obesity, children and young adult, severe hypothyroidism, jejunoileal bypass post-surgery and cirrhosis.[4] On the other hand, in patients in which can discontinue the drug use, it is known that hypothyroidism is transitory and may revert spontaneously, being indicated mainly in symptomatic patients.[4] In these cases it should be re-evaluated the need to continue therapy or to adjust doses between six to twelve months after commencement of reposition.[9]

TSH is the most important parameter to monitor this therapy,[2] being recommended the dosage every four to six weeks.[4] It is appropriate to maintain the TSH levels at the upper limit of normality, especially in patients with severe cardiopathy.[3] You can reach the euthyroid state in two to four months after discontinuation of amiodarone.[5] After normalization of thyroid hormones, laboratory monitoring could be done in every six to twelve months.[4]

Amiodarone-induced thyrotoxicosis

Thyrotoxicosis, potentially grave and unpredictable situation, is more common in areas deficient in iodine, male gender (3:1), young people and patients with previous thyroid pathology, although it may affect normal thyroid tissue.[5] Its appearance is not dependent on amiodarone doses, just as it is observed in hypothyroidism.

Two subtypes of amiodarone-induced thyrotoxicosis are described, which differ regarding etiology, prognosis and treatment.

The type I thyrotoxicosis occurs in patients with underlying thyroid disease, such as self-nodular goiter and Graves' disease, and is a consequence of Jod Basedow phenomena (iodine induced hyperthyroidism), typical of geographic regions with deficiency on dietary iodine.[12]

The Type II thyrotoxicosis occurs in normal thyroid tissue, caused by a direct thyroid destruction by amiodarone or its metabolites (subacute destructive thyroiditis). This fact results in release of preformed thyroid hormones into the circulation. Because of this destructive process after the state of thyrotoxicosis, a transient hypothyroidism can be observed.[9]

It should be remembered that both forms may be associated, being difficult to distinguish them. The clinical presentation is similar in both types of hyperthyroidism and can manifest with weight loss, excessive sweating, hyperkinesia, muscle weakness, heat intolerance, diarrhea and hair loss. The ophthalmopathy is usually absent unless hyperthyroidism develop in a patient with previous Graves' disease.[9] The differential diagnosis, therefore, involves clinical, laboratory and imaging parameters.

The evaluation should include a detailed medical history and physical examination to determine if the patient has a pre-existing thyroid disease such as nodular goiter, or Graves' disease, which suggests hyperthyroidism type I.[4]

The detection of antibodies antiTPO and Thyroid Stimulating Hormone Receptor Antibodies (TRAb) which are generally absent, helps to differentiate patients with a previous thyroid condition, suggesting hyperthyroidism type I.[5]

Conventional ultrasound can help detect structural changes, such as a nodular goiter or an enlarged gland, but does not allow to distinguish the types of hyperthyroidism.[2] However, the colored Doppler flow ultrasound is an inexpensive method of quick and easy implementation, non-invasive and effective in distinguishing the two types of hyperthyroidism.[2] The hypervascularity evidence is suggestive of type I hyperthyroidism, while its absence was associated with type II hyperthyroidism.[3]

The utilization of thyroid scintigraphy with radioactive iodine (RAIU) can help differentiate the two types of hyperthyroidism. The uptake is typically normal or high in type I; In the type II, it is observed a reduced uptake, since there is little absorption of iodine due to destruction and damage in thyroid tissue.

The dosage of interleukin 6 (IL-6) is a good marker of destruction of the thyroid follicular epithelium, although it is not specific. The levels are normal or slightly elevated in type I and significantly elevated in type II.[3]

It is worthy to note that none of the proposed diagnostic methods is able to distinguish the two kinds of hyperthyroidism by itself, requiring the combination of different techniques.[9] The main clinical and laboratory characteristics to differentiate types of hyperthyroidism are summarized in Table 1.

Table 1 – Diferential diagnosis of the amiodarone-induced thyrotoxicosis forms (3)

Characteristics	Type I	Type II
Previous thyroid disorder	Yes	No
Nodular or diffuse goiter	Frequently present	Usually absent
Antithyroid antibodies	Frequently present	Absent
Radioactive iodine uptake	Low, normal or high	Low / suppressed
Serum IL-6	High, discreetly	Very high
Doppler ultrasound	Hyperflow signs	Low flow signs
Thyroid ultrasound	Goiter (diffuse or nodular)	Normal

Source Fonte: Pavan R., Jesus AMX, Maciel LMZ. A amiodarona e a tireoide. Arq Bras Endocrinol e Metab. 2004; 48(1): 176-182.

Note: adapted by the authors.

The treatment of amiodarone-induced hyperthyroidism is a challenge, being non unanimous among health professionals. The most controversial treatment option consists in the suspension, or not, of amiodarone. In cases where the interruption is possible, the replacement by another drug is an acceptable condition. However, the suspension is not accompanied by immediate effect due to the long half-life of the drug.[8]

In general, in less harmful forms of hyperthyroidism, 20% of cases have spontaneous remission.[5] However, in most cases, treatment is needed once the thyroid hormones are deleterious on the heart disease of the patients.

In type I hyperthyroidism, the main objective is to inhibit the synthesis of thyroid hormones. Thionamides are the drugs of choice because they block the hormonal synthesis,[4] besides to peripherally inhibit the deiodinase enzyme, effect observed only in propylthiouracil (PTU).[8] It is commonly used in higher doses (methimazole 40-60mg/day or

propylthiouracil 600mg to 800mg/day),[5] because excess of iodine in the thyroid gland, from the intake of amiodarone, confers resistance to the action of thyonamide. The dosage is gradually decreased to lower maintenance values.[12]

Methimazole is the drug used as first-line, due to the possibility of ingestion once per day (half-life longer than propylthiouracil), faster normalization of hormone levels and lower incidence of side effects (cutaneous and gastrointestinal manifestations, arthralgia, agranulocytosis, hepatotoxicity and vasculitis). Due the chance of occurring bone marrow suppression, patients should be counseled about the warning signs, such as fever, sore throat and ulcers in oral cavity. The side effects associated with methimazole are dose dependent, as propylthiouracil is not dose dependent.[4]

It can be used together with this therapy the potassium perchlorate (1g/day), which is capable of inhibiting the uptake of iodine, improving the effectiveness of thionamides. Doses higher than 1g/day are associated with the occurrence of agranulocytosis and aplastic anemia.[5] The toxicity limits their use and patients using thyonamide and potassium perchlorate should do a blood test every 15 days. The interruption of potassium perchlorate administration should occur when the euthyroid state is reached, typically after six weeks.4

Lithium carbonate (900mg-1350mg / day, 4 to 6 weeks), by owning action in synthesis reduction and hormone secretion, can be an alternative in more severe cases or refractory to initial treatment,[5] which can be associated with thyonamide.

In hyperthyroidism type II treatment, thyonamide and potassium perchlorate are not indicated, because it is about a destructive thyroiditis. Therefore, it is preferable the use of corticosteroids due to their anti-inflammatory and membrane stabilizer effects, and inhibition of peripheral conversion of T_4 into T_3.[2] Different types of corticosteroids may be used, such as prednisone (15mg-80mg daily), and dexamethasone (3mg, 6mg daily)[5] for two to three months.[4,13]

The treatment with radioactive iodine (^{13I}I) is usually not possible due to low or suppressed uptake of this isotope; however, it can be used in the definitive treatment in the few patients with evidence of a high uptake (high RAIU).[14]

When hyperthyroidism is resistant to treatment and it is urgent to restore euthyroid state, there are other alternatives: plasmapheresis and thyroidectomy.[4] The total thyroidectomy is an option indicated in the definitive treatment of both forms of thyrotoxicosis[8] in the following situations: patients resistant to initial therapy; adverse reactions to treatment; Patients with severe symptoms; impossibility of amiodarone suspension and in cases of deterioration of cardiac function.[9] It must be done a control of thyrotoxicosis before surgery through the use of iopanoic acid. This fact is associated with reduction of surgical risk of cardiac patients,[16] but this drug is no longer available for us.[5]

It is important to emphasize that hyperthyroidism types I and II may be associated. A form known as thyrotoxicosis type III or mixed. The treatment proposed in this case is the combination of methimazole, potassium perchlorate, and corticosteroids. This is the most beneficial type of treatment.[5]

The question of whether or not to discontinue amiodarone, in the case of hyperthyroidism, must be based on cardiac criteria. This drug is extremely effective as an antiarrhythmic and in some patients the suspension may lead to some risks. Other than that, amiodarone blocks the beta-adrenergic receptor and antagonizes the thyroid hormone receptors, performing a heart protective effect, which when removed, may worsen heart condition. However, it is recommended to stop amiodarone use whenever possible, whether in the case type I or type II.[2,3,16-18]

Thyroid function monitoring while using amiodarone

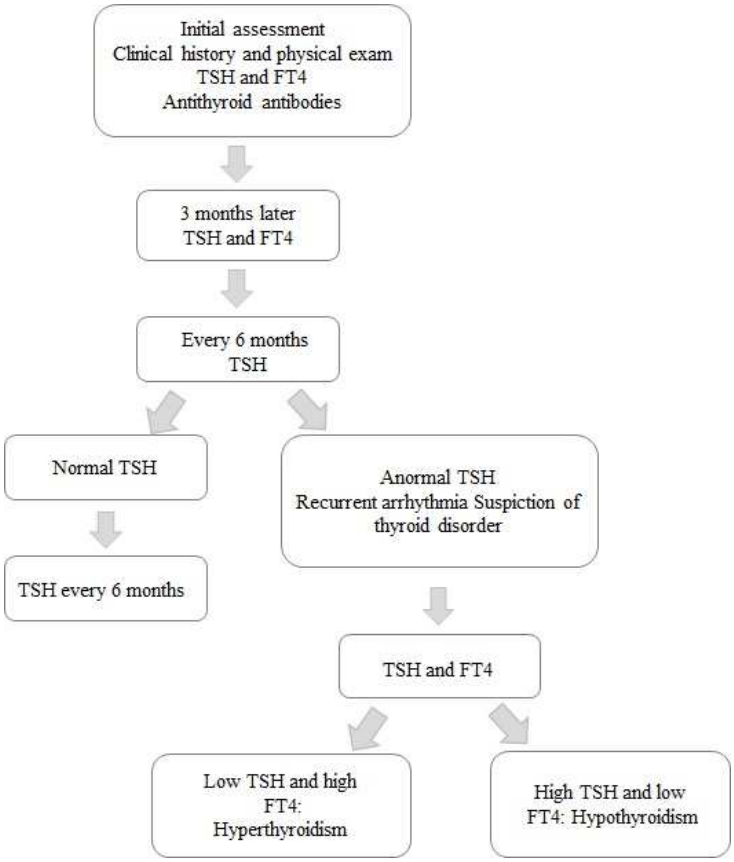
Clinical and laboratory evaluation of thyroid function should be performed before, during and after amiodarone use. It is necessary to care about this mainly because of the frequent thyroid alterations observed in this group of patients, besides the possibility of worsening previous cardiac function.

The first evaluation is composed by a detailed medical history, physical examination which includes thyroid gland palpation. This trial seeks to keep track of patients with higher risk to develop thyroid pathologies. The presence of diffuse nodular goiter points to a higher predisposition to hyperthyroidism, as well as the presence of antiTPO antibodies is associated to the occurrence of hypothyroidism.[10]

Another initial care is the dose of TSH, FT_4 and antiTPO antibodies. It is worthy to point that thyroid function should be evaluated every six months or in presence of clinical alterations that develop along treatment.[8] Besides, screening should continue even after drug withdrawal, due to its long half-life.[9] Patients with higher predisposition to gland alterations should have an individualized and thorough evaluation interval.[9]

TSH dose is considered the best test to monitor thyroid function, although euthyroid patients on amiodarone use may have reduced TSH levels.[10] The management and monitoring of thyroid function are summarized in Picture 1.

Picture 1 – Thyroid function monitoring regarding amiodarone use (9)



Source: LOPES, Z. M. T. C. Patologia da tireoide associada ao consumo de amiodarona. 2013. 40 f. Dissertação (Mestrado em Medicina) – Faculdade de Medicina, Universidade da Beira do Interior, Covilhã, 2013.

The detailed flowchart above shows the steps to be followed in the clinical monitoring of thyroid function of a patient using amiodarone, and how to diagnose and changes in thyroid function when suspecting a thyroid disorder.

Conclusion

Amiodarone induces changes in thyroid function tests which are, mostly, explained by the excess of iodide and inhibition of deiodinase activity. Clinically relevant thyroid dysfunction is not uncommon during therapy with amiodarone, but requires careful diagnosis and treatment.

The frequency with which amiodarone causes thyroid dysfunction, as well as other complications, should be observed to emphasize the need for monitoring. It should include the TSH dose both before the introduction of amiodarone as well as long-term serial actions.

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REVIEW PAPER / UPDATE

Elaboration of pressure ulcer prevention protocol

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Pressure Ulcer; Patient Care; Guideline Adherence

Abstract

Introduction: Pressure ulcers are a major health problem causing complications to the patient and increased hospital costs due to its high cost of treatment. However, it is an entirely preventable disease avoiding its severe consequences. **Objective:** A pressure ulcer prevention protocol was developed, in order to systematize

assistance to patients in risk of their development, and also to establish preventive measures with the resources available at Hospital Santa Casa de Misericordia de Vitoria (HSCMV), through multidisciplinary approach to family / caregivers. **Method:** This is a study with a non-experimental research design, descriptive, literature review type. **Conclusion:** It has been concluded that it is advantageous to implement this protocol, reducing thus the variability of clinical management, ensuring a more qualified patient care.

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Introduction

Popularly known as scabs, the pressure ulcer (PU) is a skin lesion and/or a lesion on the underlying tissue caused by isolated pressure or pressure combined with friction and / or shearing (pressure exerted when the patient is moved on a bed or a chair) between the skin and an external surface. It usually occurs in bone protuberance regions in contact with a support surface. This prolonged compression generates a local blood flow reduction, reducing nutritional offer and tissue oxygenation, favoring tissue ischemia and necrosis ocurrence[1].

It is a common condition but largely avoidable, that has an important economic impact on the health system. The costs related to PU care are the third largest expenditures after cancer and cardiovascular diseases.[2,3] This is due to hospitalization time lengthening especially, and also the patient condition deterioration, increasing the risks for infections like osteomyelitis and sepsis. [1,2]

The interest to develop this work has been raised, when high rates of PU were verified along medicine internship practices in several wards at Hospital Santa Casa de Misericórdia de Vitória. Information and the most relevant data related to pressure ulcer prevention were put together in a protocol format to be used since patient admission to patient leave, reducing clinical management variability and ensuring the patient a more qualified care. A handout folder has been designed with important guidance for vulnerable patients caregivers, allowing them to identify early lesions and start its prevention.

Epidemiology

UP incidence rates vary largely in the literature, due to the care level characteristics, differing in severe care, long stay care and home care. In the USA, PU incidence ranges from 0.4% to 38% in severe care; from 2.2% to 23.9% in the long stay care, and from 0 to 17% in home care.[2]

There are a few studies about PU incidence in Brazil. However, they have demonstrated that the estimated clinical medicine PU incidence is 42.6%; in surgery units, 39.55; and in intensive care units ranges from 10.62% to 62.5%. This large incidence suggests insufficient deliveries from the health care professionals to the hospitalized patients.[4]

Risk factors and susceptible areas

Individual susceptibility depends upon a series of factors conjugated with tissue perfusion alterations. Intrinsic risk factors (inherent to the individual) for PU include old age, bedding restrictions, tobaccoism, cognitive and sensorial disabilities, malnutrition and other comorbidities affecting tissue integrity and cicatrization (as urinary incontinence, edema, hypoalbuminemia, malnutrition and conditions affecting blood microcirculation). Extrinsic risk factors related to the lesion mechanism and related to the lesion mechanism and independent of the individuals) include forces like friction and shearing, humidity and positioning. Patients for long periods in bed are the main group of lesion development. These risk factors must be always assessed by the health professionals during patient admissions.1,3

There are no body surfaces immune to the ischemic effects of haste, but PU frequently occurs over a bone prominence. The PU most affected regions are the heel bone (21.7%), the ischium (19.7%), the sacrum (19.5%), the buttocks (13.4%) and the ankles (3.4%), as shown on Figure 1.

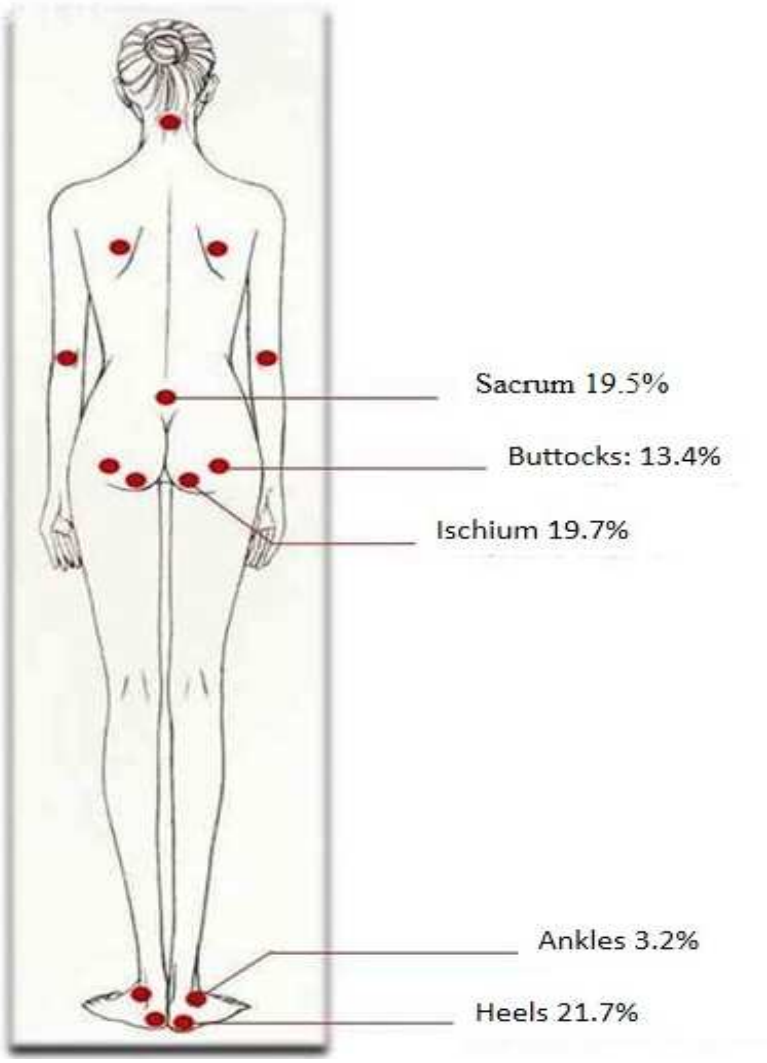


Figure 1: Most affected PU regions

Source: Figure modified by the authors. Obtained at: https://br.pinterest.com/pin/313844667756781823/

Furthermore, ulcers in the extremities is a factor associated to cicatrization time. Thus, the heel bone PU, being the most common one and a longer cicatrization time concern, must be targeted with specific preventive measures.[3,5]

Classification

Pressure ulcers are wounds classified by severity and depth. The staging system most commonly used is the National Pressure Ulcer Advisory Panel (NPUAP). This classification is described in Figure 2.

Figure 2: PU classification

Source: Figure modified by the authors. Obtained at: http://www.npuap.org/resources/educational-and-clinical-resources/pressure-ulcer-categorystaging-illustrations/

Risk and management stratification

PU risk scale adoption aids decision taking, helping the health provider to figure out the care plan and program the preventive medical conducts. Braden scale (Figure 3) is the most largely adopted, gathering the following factors: sensorial perception, humidity, activity, mobility, nutrition, friction and shearing. Its usage during risk factors assessment allows the patient clinical condition verification.[1]

Figure 3: Braden Scale

Patient name:_____ Gender:___ Age: ____

Inspector name:_____ Date: ___/___/_____

Aspects	Assessment		Score
Sensorial Perception	Totally limited Sensorial Very limited Slightly limited No limitation	1 2 3 4	
Moisture	Totally wet Very wet Occasionally wet Rarely wet	1 2 3 4	
Activity	Bedridden Chair restrained Walks occasionally Walks frequently	1 2 3 4	
Mobility	Totally motionless Strongly limited Slightly limited No limitations	1 2 3 4	
Nutrition	Very poor Probably inadequate Adequate Excellent	1 2 3 4	
Friction & Shearing	Problem Potential problem No problem	1 2 3	
TOTAL			

Source: figure modified by the authors. Obtained at the journal: Which factors predict incident pressure ulcers in hospitalized patients? A prospective cohort study. Br J Dermatol. 2014 Jun;170(6):1285-90.

The nursing professional is one of the main caregivers of bedridden patients with pressure ulcers, however, prevention of UP is a multidisciplinary process that begins in the recognition of patients at risk and prompt institution of specific preventive measures for these patients, once the common sense among authors say that preventing UP is less costly and more important than the proposed treatment.[6]

Objectives

General objectives

Elaborate a prevention protocol for pressure ulcer, to be established in the wards of the Santa Casa de Misericordia de Vitoria Hospital.

Specific objectives

Systemize risk patient assistance and establish preventive measures accordingly with the availability of resources at Santa Casa de Misericordia de Vitoria Hospital (HSCMV), with a multidisciplinary approach to the patient's family members and caregivers.

Justification

The international literature shows that the introduction of PU prevention protocols and educational programs reduce the incidence of this disease. In a hospital, after educational intervention, the incidence was reduced from 23% to 5%, and in an orthopedics unit, from 55% to 29%.[3,6]

Pressure ulcer prevention is relevant not only for the patient, reducing morbidity and hospital time, but for the hospital too, reducing costs. Looking at the collected data and also looking at the few practical protocols in use, it does characterize this instrument development action as a valid and necessary step.[4]

Method

Study design

This is a study with a non-experimental outline, a descriptive and qualitative literature review type. PubMed site databases MEDLINE, SciELO and LILACS-BIRREME national and international literature were reviewed, and a selection of papers published in the last 15 years addressing pressure ulcer has been done. For each above-mentioned database, the following key words have been used: 1) pressure ulcer, 2) protocol, 3) pressure ulcer prevention, as the primary descriptors. The secondary descriptors have been: 1) pressure ulcer protocol, 2) pressure ulcer treatment. Bibliography research has included original prospective and retrospective research papers, review papers, editorials and directives written in the Portuguese, Spanish and English idioms, listed by their relevance. A 15 Year Bibliography Review, PubMed classified pursuant to their relevance has been researched, and 19 papers were selected subjectively, taking into account their epidemiological importance, prevention measures and clinical management.

Assessment tool elaboration

The tool has been developed upon the prevention sections from the recommendations and guides of NPUAP (National Pressure Ulcer Advisory Panel) 2014, EPUAP (European Pressure Ulcer Advisory Panel) and PPPIA (Pan Pacific Pressure Injury Alliance), where preventive recommendations are also described and supported by evidence based medicine. In the same way, the 2013 Ministry of Health Protocol has been complementarily used, with its relevant information and recommendations. Braden Scale has also been used to stratify PU risks.

Pressure ulcer prevention educational hand-out making

The PU Educational Handout was developed upon the prevention sections from the recommendations and guides of NPUAP (National Pressure Ulcer Advisory Panel), EPUAP (European Pressure Ulcer Advisory Panel) and PPPIA (Pan Pacific Pressure Injury Alliance), where preventive recommendations are also described and supported by evidence based medicine. In the same way, the 2013 Ministry of Health Protocol has been complementarily used, with its relevant information and recommendations.

Pressure ulcer protocol

An early and personal intervention program developed for each patient is essential for a care plan. This protocol is a six step strategy, fundamental each one of them, for an effective PU prevention. It has been divided into PU development risk assessment that must be done by the health professional with each patient at hospital admission, to spot high-risk individuals. Daily skin inspection, constantly looking for skin changes; with hygiene maintenance and care. Nutritional support and pressure relief, with special concern with decubitus changes and early deambulations, when possible; and educational hand-out delivery and explanations to the family members and/or caregivers. [7-10]

Interaction among health professionals, patients and family members/care takers is necessary, stressing the importance of discipline, participation and collaboration along hospital stays.

First step: PU risk assessment at admission

It is done in an objective and subjective manner, in every patient, independently of his age group. Patients must be systematically checked in the admission moment trough PU development risk assessment, and the skin must be inspected to detect PU already settled.[11,12]

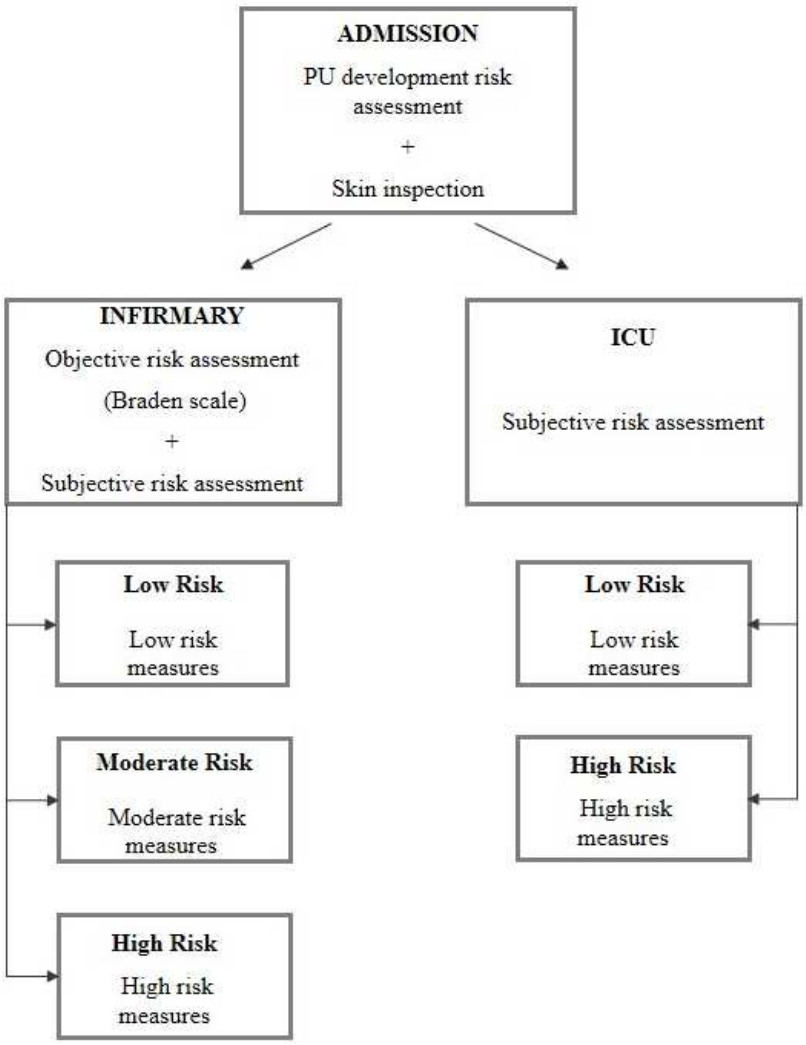
Risk objective assessment

To asses PU development risk in the hospital admission moment objectively, the nurse shall apply the predictive risk scale, validated in all the patients under internment. Braden predictive scale (Figure 3) has been adopted in this protocol. It is the most widely used one and it shall guide and shape the preventive measures for each patient, pursuant to his / her punctuation. The scale comprises the following assessment subsets: sensorial perception, moisture, activity, mobility, nutrition, friction and shearing. Skin inspection must be done on bone prominence regions, mainly on the most common PU settlement sites.[1,3]

Risk subjective assessment

Braden scale must be always applied together with the nurse clinical judgement. However, Intensive Care Centers patients displayed a poor Braden scale performance. Thus, patients admitted in such centers must be assessed concerning PU development risk only through the nurse subjective assessment, as depicted in the flowchart[3] (Figure 4).

Figure 4: Risk assessment chart



Source: the author

Second step: Skin daily inspection

The cutaneous surface daily inspection in moderate to high PU development risk (≤ 14 points in the Braden scale) patients must be done from head to toes, checking temperature, the presence of erythemas and blisters, indicators of tissue rupture. Low risk PU patients (15 to 18 points in the Braden scale) inspections must be done every 72 hours. It is worth mentioning that a great attention must be given to the high risk PU corporal areas, like heel, ischium, sacrum, buttocks, ankles, trochanter, malleolus, scapula and occipital.[3,11,12]

PU classification knowledge is key to allow the detection of early stages lesions, when there is only a non-whitening hyperemia on bone prominence sites. PU diagnostics in early stages enhances an efficient approach to avoid lesion progression.[7]

Patient decubitus must be changed and the hyperemia site must be assessed again in 15 to 30 minutes when hypermeias are detected. If it does remain, a stage 1 PU is developing. Thus, the patient and the family must be oriented and become aware of the problem. Dialogue with the family is

important to clear doubts and shows the health team compromise with the service quality.[6]

Skin changes found on patient inspection must be entered in the Patient Nursing Datasheet (Figure 5). This document contains the patient name, ulcers location, the most severe ulcer classification regarding its stage (NPUAP), its origin regarding ethiology (community or hospital) and decubitus change schedule. The document must be filled daily and filed with the patient medical records, becoming as such, a key tool to follow his evolution.

Figure 5: Patient Nursing Datasheet

Patient name:	
Severe ulcer classification (NPUAP)	( ) Stage I ( ) Stage II ( ) Stage III ( ) Stage IV ( ) Unclassified ( ) Deep tissues lesion suspicion
Ulcer localization	( ) Heels ( ) Ischium ( ) Sacrum ( ) Ankles ( ) Trochanter ( ) Malleolus ( ) Scapula ( ) Occipital ( ) Others: _____
Risk assessment (Braden Scale)	( ) Low risk ( ) Moderate risk ( ) High risk
Origin	( ) Community ( ) SCMVH
Nurse Signature _____	

Source: figure modified by the authors. Obtained at the journal: Úlceras de pressão. Rev Bras Geriatr & Gerontol, 2010;4(1):36-43.

Third step: skin hygiene and care

The skin is our largest organ, the first organism defense barrier. Factors like paralysis, numbness and old age lead to skin atrophy, thinning the protective barrier. It must receive specific care to avoid compromising, once PU is just about breaking this barrier, as a general rule it must be kept clean, well hydrated and without excessive moisture.[6] The main recommendations follow below:

. Warm water and neutral soap for bathing to reduce skin irritation and dryness. Avoid hot water and excessive skin friction.[6,12]

. Moisturizers after bathing (essential fatty acids), hydration at least once a day for old and/or dry skin patients. Dry skin is a PU development risk factor.[6]

· Do not massage the bone prominence places, nor the hyperemia sites along hydration. Hydratant must be applied smoothly, with soft moves.[6,12]

· Nursing team must pay attention to urinary and fecal incontinence, as well as to other moisture sources, as sweat and wounds exudate.[6]

Fourth step: nutritional support

There is a strict relationship between malnutrition and PU development. Pressure ulcer bearing patients or in PU development risk, must have their nutritional stage assessment trough anthropometric measures, done in the moment of the patient admission in the health institution. Those bearing ulcers or under malnutrition risks must be sent to the nutritionist, or to a multidisciplinary team in order to have a full nutritional assessment.[2,11]

The team will then shape a care plan for these individuals, to correct fortuitous nutritional deficits, as this deficiency increases vulnerability to the trauma, as well as it slows down wounds cicatrization. Energetic individualized nourishment based on medical conditions and on the subjacent activity level. If the calories or proteins ingestion is inadequate, the factors compromising such must be treated as a part of the patient integral assistance.[2,11]

Fifth step: pressure relief

One of the most important pillars for PU prevention is change the patient decubitus every 2 hours. The patients in bed must be intercalary placed in the four decubitus: ventral, dorsal and laterals in a sequence. Repositioning allows pressure distribution, reducing its scale over the vulnerable body areas, keeping the blood flowing in the major PU development risk areas.[2,11,12]

It is fundamental that the patient and his/her caregiver are aware of the preventive measures importance. Family awareness is key to unite efforts together with the medical and the nursing teams, once informed individuals have less PU development risks and less acuteness along patient condition evolution. These are the reasons why it is essential to develop and apply educational measures with those involved with the patient care, and not only with the health professionals.[6] In this study an educational hand-out has been elaborated, which will be approached in the sixth step for PU prevention.

During patient repositioning the utmost care to avoid friction moves must be taken, which means avoidance to drag the patient on bed sheets. Besides that, whenever possible, the bed headboard shall be elevated up to 30 degrees at the most, once the patient body tends to slide down, consequently causing friction and shearing moves.[7,8]

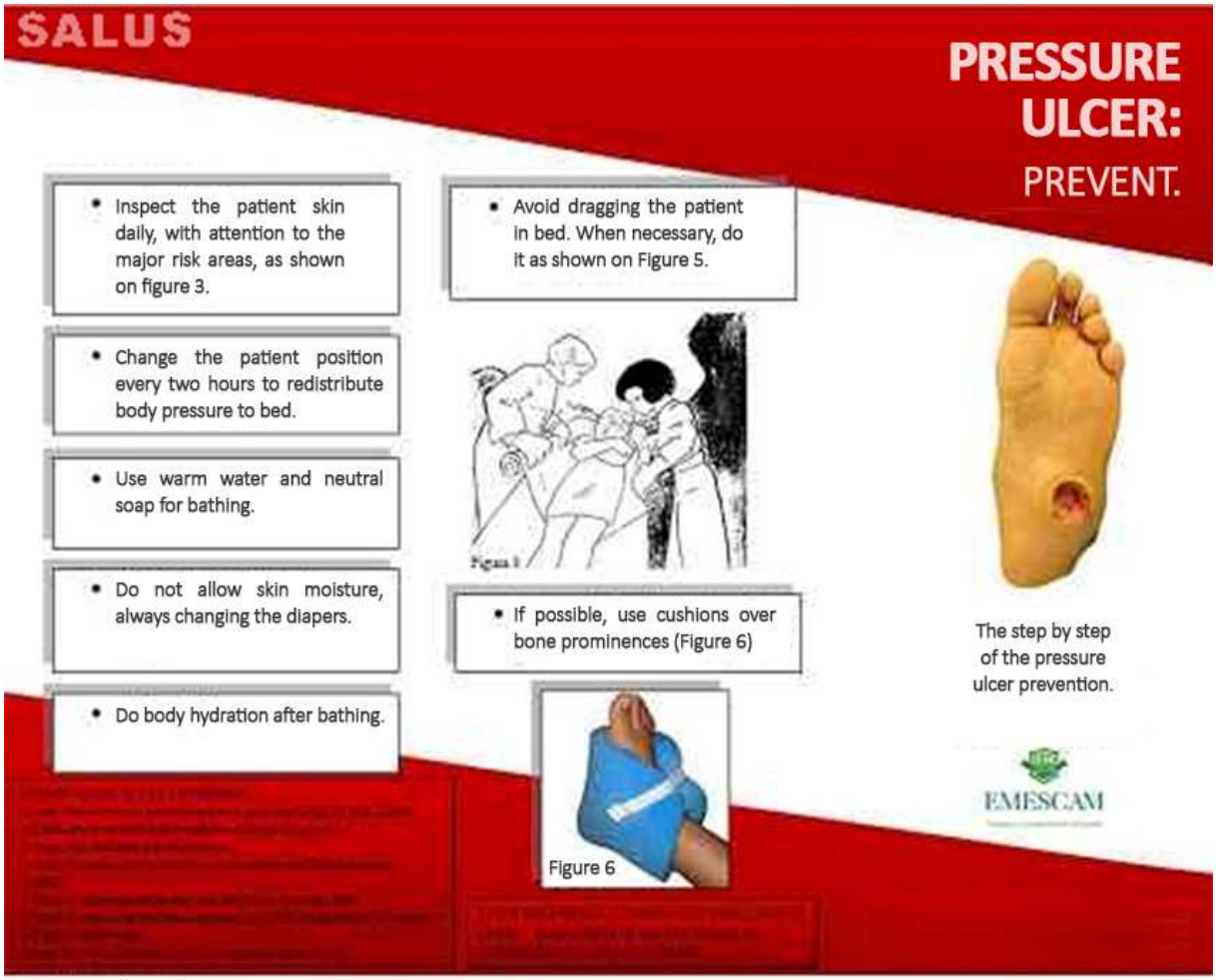
Whenever possible, high specificity reactive foam mattresses or pneumatic mattresses shall be considered for risk patients (Braden score ≤ 18) usage, in order to redistribute pressure uniformly. Although it requires larger investments, this measure is cost effective as it tends to reduce hospital stay time as it aims at PU prevention.[11] When they are not available, air mattresses might be used. Furthermore, bone prominence areas must be protected by pillows or cushions (examples: knees, heel, ankle).[7,11] Specially, heel protection is of extreme importance, whereas it is the most PU incidence site, and the extremities developed ulcers take the longest cicatrization time, rising the hospital stay costs.[5,9,11]

Sixth step: inform the caregiver with the educational hand-out delivery

Literature has corroborated educational measures adoption in PU prevention. Herein, it has been proposed the elaboration of an educational handout about PU, practical and of easy comprehension for caregivers and family members, containing concepts and relevant preventive measures.

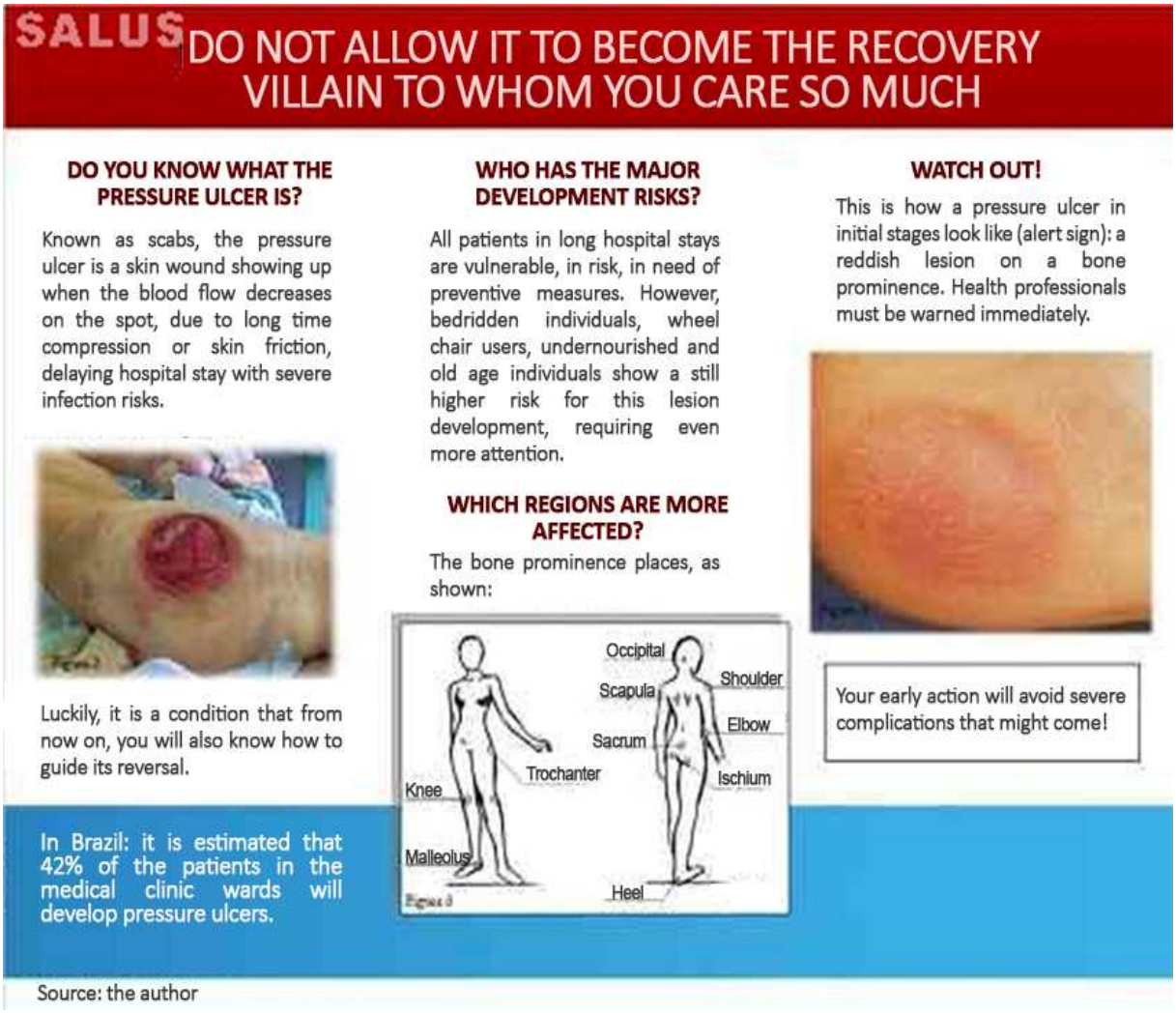
This folder (Figures 6 and 7) has been divided in 5 sections: pressure ulcer definition, development risk, most vulnerable bodily areas, early lesion identification, and at last, efficient prevention measures. The handout must be delivered to hospitalized patient caregivers, eliciting their inclusive participation in PU development preventive care. Such action requires the health professional fundamental delivery, with his/her explanation about its content, and a demonstration that it reminds the caregiver of what shall be done in patients benefit along the hospital stay

Figure 6: Educational brochure - outside



Source: the author

Figure 7: Educational brochure - inside



Source: the author

Preventive measures set

Specific preventive measures

At last, it is of fundamental importance to program an individualized prevention plan comprising the six steps previously described, making it easier for the health team to operate. The preventive measures must be risk level specific (based upon Braden scale and the patient subjective assessment) accordingly with the patient risk level met. Nurse clinical subjective assessment must be sovereign concerning the scale, facing existing risk factors and inherent PU development comorbidities, classifying the patient as a high risk one, and as such, establish the specific actions for this subgroup.[11,12] Each measure to be implemented with each specific patient group will be described further on.

Low risk patients

Preventive measures for patients within 15 to 18 Braden score: [11,12]

. Complete skin inspection every 72 hours, focused on major PU development risk areas;

. Raise awareness in patients and caregivers about preventive measures trough guidance and educational hand-out deliverance, reinforcing PU prevention importance;

. Nursing team or caregivers change patient decubitus every two hours, following the decubitus change schedule;

. Skin hygiene and hydration, keeping it always clean and dry;

. Patient nutritional stage assessment, with a valid and reliable tracking tool, to find the nutritional risk and supply individualized energetic ingestions, based on medical condition and underlying activity level;

· Calcaneus suspension devices usage.

Moderate risk patients

Preventive measures for patients within 13 to 14 Braden score: [11,12]

. Complete skin inspection every 72 hours, focused on major PU development risk areas;

. Raise awareness in patients and caregivers about preventive measures trough guidance and educational hand-out deliverance, reinforcing PU prevention importance;

. Nursing team or caregivers change patient decubitus every two hours, following the decubitus change schedule;

. Skin hygiene and hydration, keeping it always clean and dry;

. High specificity reactive foam mattresses usage;

. Patient nutritional stage assessment, with a valid and reliable tracking tool, to find the nutritional risk and supply individualized energetic ingestions, based on medical condition and underlying activity level;

· Calcaneus suspension devices usage.

. Moisture handling, with special care for urinary or fecal incontinence patients, and patients with oozing lesions;

. Shearing stress avoidance measures, like the 30 degrees bed inclination angle limit.

High risk patients

Preventive measures for patients with ≤ 12 Braden score: [11,12]

. Skin daily inspection to reassess risks and early PU detection;

. Raise awareness in patients and caregivers about preventive measures trough guidance and educational hand-out deliverance, reinforcing PU prevention importance;

. Nursing team or caregivers change patient decubitus every two hours, following the decubitus change schedule;

. High specificity reactive foam mattresses usage;

· Calcaneus suspension devices usage.

. Moisture handling, with special care for urinary or fecal incontinence patients, and for patients with oozing lesions;

. Shearing stress avoidance measures, like the 30 degrees bed inclination angle limit.

. Skin hygiene and hydration, keeping it always clean and dry;

. Patient nutritional stage assessment, with a valid and reliable tracking tool, to find the nutritional risk and supply individualized energetic ingestions, based on medical condition and underlying activity level;

. Provide and promote a fit daily ingestion of liquids for patient hydration;

. Dynamic support surfaces usage with a small air release, if possible;

. Pain handling with medicinal treatment assessment whenever necessary.

Discussion

PU development risk population tends to increase, upon factors like aging and the immobility tendency, aside from chronic maladies like diabetes, obesity and vascular diseases.[14,15] Due to this change in the population epidemiological profile, there is an urgent need to establish efficient means to prevent PU. A coordinated approach, globally focused on prevention is more promising to gain patient prognostics improvement and cost economy then

isolated changes, or modifications exclusively addressing a treatment.[14]

Intervention strategies include specific changes in PU prevention, combined with educational strategies and handling quality improvement. They point out at the importance of family, caregivers and even more, patient information and guidance. Most of the studies in the literature do demonstrate the positive effects of preventive intervention, when approached with protocol adoption and educational methods.[15]

Concerning the adoption of risk stratification scales, there are no evidences linking pressure ulcer incidence decrease of them. However, Braden Scale offers the best balance between sensitivity and specificity, aside from being the best risk estimate, more precise than nurses' clinical judgement on predicting pressure ulcer development. The stratification method has its importance, based on that precision, to early detect and adopt the fittest intervention.[16]

In the fast guides from EPUAP, NPUAP and PPPIA as of 2014, there are no recommendations to apply Braden scale to stratify patients' risk level. But, the Ministry of Health PU prevention protocol indicates Braden scale to do so, and guide the specific prevention measures.[11]

The protocol proposed in this course conclusion research paper includes Braden scale risk stratification upon its better PU risk assessment precision, easy use, its acknowledgement and the Ministry of Health protocol recommendation.[12]

Literature review shows that objective PU scale assessment tools, although important, are not routinely used by nurse teams to identify pressure ulcer risk in their clinical practice, and they also show that the nurses rely more on their own knowledge and experience than on research evidences to decide PU management.[17]

Despite the well-known benefits of prophylaxis and the accepted PU prevention directives, they are not consistently used in clinical practice.[18] There are many variables, including nursing crews improper attitudes, enhancing PU development. The most common PU prevention barriers reported in the literature are: patient condition, lack of time, lack of personnel, knowledge gaps, lack of routines and care continuity, in addition to pressure redistribution surfaces scarcity in hospitals (high density mattresses, chair cushions).[19]

It is expected PU incidence decrease with patient prognosis improvement and hospital costs lessening with this protocol adoption at Santa Casa de Misericordia de Vitória Hospital.

Conclusion

Pressure ulcer incidence may reflect the health services quality rendered, once its prevention is easy and low cost. The literature shows that PU treatment costs are substantially greater comparing to its prevention costs.[13] Frequently affects bedridden people, suggesting inadequate care, avoidable, with meaningful impacts on health systems economics.

It is observed the importance of the whole health team knowledge, also of the family and / or caregivers involved in this malady control. As such, it is concluded that it is advantageous, not only this protocol implementation, attenuating clinical procedures variability, assuring a more qualified attendance to the patient, but also the divulgation of the educational hand-out, bringing caregivers / family to the pressure ulcer prevention partnership with the health professionals.

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REVIEW ARTICLE / UPDATE

Robotic radical prostatectomy

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Abstract

Robotic radical prostatectomy when compared to the conventional (open) technique, mostly shows that the robotic has a lower rate of bleeding, lower rate of blood transfusion and shorter hospital stay. The results are, yet, controversial in the analysis of other outcomes. It seems the robotic decreases urinary incontinence and impotency, accelerates the recovery of sexual function and recovery of urinary continence. However, it has a higher cost. Randomized trials that are in progress may clarify these issues.

Introduction

The prostate cancer is treated individually, considering the patients' age, the tumor staging, the histologic degree, the prostate size, comorbidities, life expectancy, the patient's expectations and the technical resources available.[1]

The vigilant observation is an option for the located disease, but it must be used only in patients above 75 years old, with limited life expectancy and low histologic degree tumors.[1]

The radical prostatectomy is the gold pattern procedure for the treatment of located prostate cancer. It was performed via perineal by Theodor Billroth in 1867, in the Medical School of the University of Viena.[2] In 1904, Hugh Hampton Young was the first to extract the whole prostate via perineal and in 1947, Millin described the first open prostatectomy through retropubic via for the treatment of a benign prostatic hyperplasia. However, in earlier stages, several men became impotent. Thus, many preferred radiotherapy to surgery. The modern era of the radical retropubic prostatectomy began with Patrick Walsh's, according to Laviana, who described the retropubic and periprostatic anatomies in 1979. [2] This allowed Walsh to have a safe control of the dorsal venal complex, achieving less local bleeding, including the first nerve preservation and showing the erection could be maintained without compromising the cancer control.[2] In 1992, Schuessler et al performed the first laparoscopic prostatectomy.[3] In 1999, the Da Vinci surgical system, initially designed for the use of cardiac surgeons when doing coronarian bypass, started to be used by urologists. In 2000, in France, Abbou CC et al[4] reported the first robotic prostatectomy. Following this, in Germany, Binder J and Kramer[5], and in the USA, Menon et al[6] performed the first cases of robotic prostatectomy. The robotic surgery, according to the producer of the Da Vinci Surgical System, was performed in about 80% of radical prostatectomies in the USA in 2010. The use of robotics increased from 0.7% to 42% between 2003 and 2010 in the USA.[7]

The use of Robot support during prostatectomy has reduced the adversities related to the laparoscopic prostatectomy. The robotic has the following characteristics: it allows the magnification of the image by 10 times, three-dimensional imaging and a new periprostatic view, since it is fitted with a camera with endoscopic stereo lens, an increase of the wrist movements, with seven different degrees, which facilitates a vesicoureteral anastomosis and allows a better ergonomic position for the surgeon.

From 2003 to 2010, there was an increase of the number of robotic surgery equipment and, thereby, there was a decrease in hospital stay time, with readmission rates in 20 days similar to the open technique, besides allowing higher reimbursement to the hospital.[8]

Both the open access and the access via laparoscopy conducted by Robot produce alterations in urinary incontinence and erection,[9] besides other adverse events. However, some outcomes may suffer modifications with the time. The fact is the comparison between open and robotic prostatectomy for the treatment of prostate cancer is still in debate. And this is the issue to be discussed in this review.

Literature Review

Lowrance WT et al, 2010[10] critically analyzed robotic and open prostatectomy literature regarding perioperative, oncologic, functional and cost wise results of the case series type.

a- Perioperative results.

-Complications. From six quoted papers, only 1 (one) reports a higher complications frequency on patients submitted to open prostatectomy. Globally there were no significant difference between both access types. It appears that genitourinary and intestinal complications relate more towards the surgeon than to access via.

- Hospital stay time and blood loss. According to eight studies, robotics surgery is associated to less loss than open surgery.

There is no study that states otherwise. The blood transfusion rate is higher in the group of open surgery according to seven studies. Hospital stay time is lower in robotics group as well, according to three studies.

b- Oncologic results:

- Surgical margin. From eight studies, four report that surgical margin had higher positivity on open via and four other don't.

To conclude, surgeons experienced at robotic and open via are capable of obtaining a disease free margin in a high percentage of patients and, therefore, it is possible that surgical margin depends more on the surgeon than on the access via.

- Biochemical recurrence. From three studies that assessed this outcome, none detected difference on biochemical recurrence between both access via. However, the observation time was short.

c- Functional outcome

The goal of radical surgery is to heal the patient and keep continence and erectile function (trifecta).

Only 1 study validated the tools to characterize urinary continence and impotence after the robotic.

- Continence. Ficarra V, 2009, quoted by Lowrance WT et al 2010, in a prospective study, comparative, non-random, observed better urinary continence in robotic surgery than in open. These authors reported a urinary continence rate of 97% in robotic and of 88% in open (p=0.001). The patients were considered continent if they reported no urine loss in about a week or less, or none at all. The average time of continence recovery was of 25 days in robotic and 75 days in open via (p<0.001).

Ahlering et al, mentioned by Lowrance WT et al 2010, using a non-validated questionnaire, defined continence as the non-need for dippers, and reported similar continence rate between both access via (75 vs 76%).

Tewari et al, according Lowrance WT et al 2010, showed a faster continence return in robotics (44 days vs 160 days).

Krambeck et al, according Lowrance WT et al 2010, found no difference in urinary continence between both access via. Using a non-validated questionnaire, the patients were considered continents if they had no urinary loss or if they had no need for a second dipper. Urinary continence in 1 year was of 92% in robotic and 94% in open (p=0.34).

- Erectile function. Comparing robotic to open via it can be observed that data are limited by follow-up time and restricted to only a few centers.

Krambeck et al, according to Lowrance WT et al 2010, reported having no significant difference of potency between robotic and open in one year (open 63% robotic 70% p=0,08). Potency was defined as satisfactory erection for intercourse with or without 5-phosphodiesterase inhibitor.

Tewari et al, according to Lowrance WT et al 2010, using a phone interview, reported a median time shorter in recovery of potency with robotic than with open (180 vs 440 days, p<0.05). In a single study using a validated tool of potency (International Index of Erectile Dysfunction-5, IIEF-5), Ficarra et al, according to Lowrance WT et al 2010, defined potency when IIEF-5 had a score higher than 17. Limiting the analysis of at least 1 year of follow up to these patients that received a bilateral nervous preservation, the authors noted that 49% of patients that had surgery via open and 81% of patients under robotic surgery were potent according to its definition (p<0.001).

Finally, when comparing functional outcomes of robotic and open, the literature is scarce and inadequate. While there are few studies with few patients to draw definitive conclusions, robotic does not seem to be inferior to open regarding erectile function and urinary continence.

-Costs/economy: Data of costs between robotic and open are scarce.

According to Lowrance et al 2010, the costs reported by Lotan et al, Mouraviev et al, Scales et al and Bolenz et al showed that robotic has high cost when compared to open, however, these costs were related to procedure and initial duration of hospital stay. Scales et al, according to Lowrance et al 2010 reported that the cost of patients hospitalized for robotics are dependent on volumes, and the equivalent cost to open is possible in specialized centers with high volume. Bolenz et al found that the direct median cost was higher in robotics then in open (6,752 dollars vs. 4.437, $p<0.001$). Economic evaluation of robotics via goes by Da Vinci surgical system, which costs about 1.6 million dollars with annual maintenance of 120,000 dollars after the first year. The average cost of devices is approximately 1,500 dollars per case. These authors estimated the purchase of extras and robot maintenance costs by about 2,700 dollars per patient, based on an annual increase of 126 cases. This additional cost of the robot is probably overestimated in this number that will decrease with time, especially in centers of large volume.

Conclusions: The quick adoption of robot occurred without evidence level I showing superiority or equivalence to open. However, there are no randomized studies to the present. Available data points to advantages on blood loss and hospital stay time in robotics as of open. The positive surgical margin seems to be shorter with robotic, but follow-up duration of existing studies is short to evaluate the biochemical recurrence and other important oncologic aspects. Besides, it is necessary to have more studies using validated tools to define differences in functional outcomes between robotic and open. It is necessary to define if the cost increase of robotic is justified by the improvement of perioperative, oncologic and functional results and economic outcomes.

Laviana AA & Hu JC 2013[2] reviewed literature from January 2000 to April 2013 and observed a paucity of randomized controlled trials comparing the two access methods. They evaluated the outcomes: blood loss, need for blood transfusion, postoperative pain, length of hospital stay, mortality and complications. Oncologic results included surgical margin status, biochemical recurrence-free survival, and need for recovery therapy or rescue. Functional outcomes included quality of life and return to continence and potency.

Novara et al, according to Laviana AA & Hu JC 2013,[2] performed a meta-analysis of 110 studies on robotic assisted prostatectomy and reported an average operative duration of 152 minutes, blood loss of 166ml, average transfusion rate of 2%. Furthermore, the average catheterization time was of 6,3 days with average hospital stay time of 1,9 days. Complications occurred in 9% of patients under robotic and the most common were: lymphocele (3.1%) loss of urine (1.8%), and recovery (1.6%). The authors concluded that robotic can be performed with lesser blood loss and transfusion than the open.

Perioperative mortality is low on both access methods.

The operative time is influenced by the experience of the surgeon, surgeons volume and hospital volume. Krambeck et al, mentioned by Laviana AA & Hu JC 2013[2] in an initial assessment of 294 robotic, found that the operative time was longer in robotics. In the last hundred cases there was no difference ($p=0.14$).

Complications. Some studies examining the complications of robotics and conventional surgery report that the robotic produces fewer complications (rectal injury, pulmonary embolism, pneumonia, wound infection (15.7% in robotics - 1235 cases and 22.8% in conventional - 485 cases). Other studies report less readmission, ureteral injury, deep venous thrombosis, hematomas, lymphocele, wound infection, but higher likelihood of intestinal damage in robotics. The probability of reoperation, ileus, nerve damage, bladder, rectal are

similar in the two access methods. Other studies show no difference between the two access methods. Some studies show less risk of narrowing of the urethral-bladder anastomosis in robotics, probably because of the magnification of the image that robotics offers.

-Blood loss and transfusion with robotics: Tewari et al, mentioned by Laviana AA & Hu JC 2013[2] after evaluating nine studies that directly compared the three access methods, found that robotics was associated with less blood loss and blood transfusion.

Post-operative outcomes.

- Hospital stay time is shorter in robotic than in open, according to three studies and in one study there was no difference.

- There were lesser post-operative pain in robotic according to two studies and in one study there were lesser pain in open, however there was no difference in the subsequent days, as well as there were no difference in analgesic use.

Oncologic outcomes.

- Biochemical recurrence-free survival: It is limited by follow-up time, with few studies having a follow-up median of five years.

When comparing open with robotic, one meta-analysis showed positive surgical margin and seven years of recurrence-free survival similar in both groups.

- Positive surgical margin: It is associated with biochemical recurrence. Some studies point to a lower positive surgical margin in the robotic group, others show no difference. This may be because the pathologist observation bias and the development and stage of the disease. For example, in pT2 disease and Gleason score greater than 6, the surgical margins were less positive in robotic. Another study showed lower positive margin in robotic in pT2 disease, but in pT3 disease the margin was similar. In a recent meta-analysis, the margin was positive in 16.2% in robotic and 24.3% in the open, but after adjusting the score, the positive margin was similar (p = 0:19). A recent review, according Laviana AA & Hu JC 2013,[2] showed lower positive margin of safety with robotic in than to open.

Functional results.

Many studies that evaluates life quality after prostatectomy have forsaken tools (UCLA-PCI, EPIC, SHIM) in favor to dichotomous variables such as: non-use of dippers, ability to have erection enough for sexual intercourse.

- Continence recovery. It is associated with surgeon's experience, surgery technique, such as division and control of the dorsal vascular complex, anterior and posterior urethrovesical anastomosis reconstruction, preservation of the bladder neck and nerve preservation technique.

While three studies of case series type showed 95% of urinary continence recovery after open, Di Perro et al., mentioned by Laviana AA & Hu JC 2013[2] reported faster recovery of continence in three months after robotic as of open, although there was no difference after a year. Additionally, other non-randomized studies favored robotic, regarding to continence recovery.

A meta-analysis performed by Ficarra et al, mentioned by Laviana AA & Hu JC 2013,[2] of 12 studies (five robotic), using as parameter of continence the non-use of dippers, showed better continence recovery in robotic as of open (p=0.03). However, Krakembeck AE et al, mentioned by Laviana AA & Hu JC 2013,[2] in a comparative study combined with some papers, did not report continence difference between both access methods.

- Erectile recovery.

The evaluation of potency after prostatectomy varies according to obtainment technique. Potency is affected by patient age, degree of erectile dysfunction in pre-operative, comorbidities, nerve preservation technique, phosphodiesterase inhibitor drug use and exact definition of impotency.

Laviana AA & Hu JC 2013[2] state that Di Pierro et al reported better erectile recovery after robotic than the radical retropubic prostatectomy (55% vs 26%, p==0.009), that Krambeck et al demonstrated a tendency for erectile improvement in robotic as of open (p=0.08), and that Tewari et al in 2003 and Kim et al in 2011 demonstrated erectile improvement of 84% in robotic versus 47% in open.

A recent retrospective study performed by Alemozaffar et al, according to Laviana AA et al 2013, investigated the outcomes of sexual function and learning curve to attenuate neuropraxia. This research demonstrated erectile improvement in 5 months (p=0.007) and tendency for improvement in 1 year (p=0.061) and stabilization after 250-450 cases.

Malcom et al, according to Laviana AA & Hu JC 2013,[2] analyzed post-operative sexual function using a questionnaire (UCLA-PCI – University of California, Los Angeles, Prostatic Cancer Index) and verified that in approximately 3 years the sexual function was better after robotic, although did no statistic. Another study with 406 robotic versus 220 open showed no urinary and sexual function difference. Miller et al compared life quality of patients submitted to robotic with life quality of patients submitted to open surgery using a Short Form Health Survey (SF-12) questionnaire. Men submitted to robotic had higher score in the physical component from the first week, which remained up through sixth week. The physical component returned to basal earlier in robotic than in open and mental component did not differ between both access methods.

In another study, according to Laviana AA, the robotic showed fewer ill days (nauseated, tired – 11 versus 49) and in an adjusted analysis, men submitted to robotic had twice as many conditions to return to work than to men submitted to open surgery (HR 2.13, IC 95% 1.62-2.80).

Costs: The initial costs for robotic installation are bigger than U$ 1.5 million and the estimated costs for maintenance are of U$ 150.000 per year. Robot's tools cost approximately U$1.500 per case. Although shorter hospital stay, the robotic cost was significantly higher than open's (U$6.752 versus U$4.437). Lotan Y et al, according to Laviana reported an advantage of U$1.726 of open on robotic.

Conclusions: The lack of prospective randomized studies and of standardized outcomes, particularly regarding functional outcomes, limits the generalization of comparative outcomes between robotic and open. Besides, there is the heterogeneity of surgeon's experience. There is no thorough long term comparison of cancer control in both access methods. Existing studies shows that robotic produces lesser blood loss, lesser need for transfusion and lesser hospital stay time. It seems that there is also lesser anastomotic stricture, lower convalescence and faster recovery of continence and erection with robotics. While costs remain high with robotic, there is need for thorough randomized prospective studies to determine if robotic is cost-effective in centers with high volume of surgery.

Moran PS et al, 2013 compared assisted robotic radical prostatectomy with open prostatectomy or with conventional laparoscopic prostatectomy. The main outcomes were: positive surgical margin for tumors pT2 and pT3, sexual function and urinary continence in 12 months, blood loss, blood transfusion rate, complication rate, operative time in minutes and hospital stay time. Postoperative sexual function was defined as the ability to sustain erection long enough to perform intercourse with or without help of type 5 phosphodiesterase, or with use of a validated sexual function questionnaire. Urinary continence was defined as non-loss of urine, use of one or less dipper per day or through a validated continence questionnaire. The research interval was of January 2000 to March 2011.

It was included in this review the randomized controlled studies, non-randomized controlled studies and studies that compared assisted robotic radical prostatectomy with the open and with the laparoscopic. All studies were individually revised by two independent revisers and any disagreement was solved by discussion. The quality of studies was evaluated using an evaluation tool of a study previously published that was based on design and performance of individual study. The quality of the included studies was evaluated using an evaluation method developed by Hailey and modified by Ho et al in 2011.

Results: It was found 1 randomized study of a surgeon and 50 observational studies. Of the observational, 27 were comparative retrospective or studies that used historic comparing groups and 23 were observational prospective studies.

Characteristics of included studies:

A total of 37 studies compared robotic with open surgery, nine compared robotic with conventional laparoscopic surgery and five compared the three methods.

The 31 included studies involved more than one surgeon in the intervention or did not mention the number of surgeons that participated in the surgery and reported the surgeon experience. The degree of the surgeon's experience in the assisted robotic surgery was relative to his/her first case series (8 studies). 12 studies reported how the operative time was determined. Continence was defined in 15 studies (12 – non-loss of urine or use of dippers for 0-1 day, 3 – continence questionnaire). Definition of sexual potency was considered as the ability to sustain erection for intercourse with or without type 5 phosphodiesterase inhibitors aid. Complications report varied between studies: some reported only occurring complications and others categorized complications as major and minor or provided a list of registered complications.

Studies quality: Most of the studies were retrospective or prospective observational, with score of ≤ 2 points in study design. Of 51 evaluated studies, 3 were of high quality, 14 of good quality, 25 of medium quality and 9 of poor quality.

Assisted robotic surgery versus radical open prostatectomy.

Data of 15 studies with nearly 3000 patients showed that robotic surgery was associated with lesser safety margin in pT2 tumors. This result had no occurrence in pT3 tumor.

Data from nine studies with nearly two thousand patients submitted to assisted robotic prostatectomy showed that sexual function recovery in 1 year was higher in this than in open. However, these data showed high level of heterogeneity (I^2=70%). As for urinary function in 12 months, meta-analysis results from seven studies with around 1800 patients showed a significant increase of urinary function with assisted robotic prostatectomy (p=0.009).

The assisted robotic prostatectomy, in the reports of the studies in this review, was associated to lesser blood loss and transfusion rate when compared to open surgery. There is a high level of heterogeneity associated to the difference on blood loss between both procedures (I^2=98%) showing the different ways to estimate blood loss. The results of transfusion rate had higher consistency (RR 0.23, CI 95% 0.18-0.29, p<0.001, I^2=17%). The complication risk was smaller in assisted robotic surgery than in open prostatectomy (p=0.047). The operative time of assisted robotic was 40 minutes longer than the open (p<0.001).

Conclusions: Despite the increase of published articles on assisted robotic prostatectomy, the methodological quality of available evidence remain low. The long term outcomes as well as recurrence of cancer and mortality are deficient. Most evidence comes from prospective studies or retrospective and case series. This projects doubt on reliability of results, once these

studies have high risk of bias. Besides, this review shows the direction of bias tending to overestimate the benefits of assisted robotic surgery. Based on results of the present study, the assisted robotic radical prostatectomy is associated with reduced positive surgical margin for pT2 tumors as well as improves the return of sexual function in 12 months, when compared to open radical prostatectomy. Estimated blood loss and blood transfusion rate are also reduced in robotic, but operative time is longer.

Discussion

The goal of this review was to search in literature (2000-2014) for studies that verify the long term benefits of robotic surgery over open surgery in localized prostatic cancer surgery when performing radical prostatectomy. Three literature review were found, two of which included meta-analysis studies and one was a systematic literature review, and two studies that are yet to be finished.

The intraoperative bleeding is less intense in robotics[23-26,45] and decreased with the learning curve of the first 50 cases.[27] In fact there is a consensus in the literature that robotics is associated with less blood loss than open according to eight studies. There is no study that says otherwise.[10]

However, one study reported 1,6% of bleeding in robotic surgery that needed blood transfusion.[29]

The need for blood transfusion is less frequent in robotic.[11,26,28,29]According to seven studies, the transfusion rate is smaller in robotic.[10]

One study showed that there is no difference between the hospital stay time, blood transfusion rate and incidence of perioperative complications in robotic and open surgeries.[32] However, most studies states that hospital stay time is shorter in robotic.

The surgical site infection has been studied comparatively between robotic and open. The studies' results have shown that infection is less frequent in robotic surgery, and when it occurs in robotic it is taken care of quicker, without need to drain and return to surgery room, with lower probability of hospital readmission.[33]

The pain assessed in one study[34] by Likert score was lesser in robotic in the surgery day, but there was no difference in morphine sulphate dose during hospitalization between the two groups.

Patients submitted to minimally invasive surgery, including robotics, have adverse urinary and sexual events in the initial postoperative period. This may result from the surgeon's inadequate preparation[35]. Complications decreased after learning curve of 150 cases.[36]

Some measures have been proposed to prevent urinary incontinence in robotic surgery, such as: 1- preservation: the bladder neck, the puboprostatic ligament, the pubovesical complex, the neurovascular complex and extension of the urethra; 2- reconstruction: before and after and/or reinsertion of tendinous arch the bladder neck; 3-reinforcement - plication of the bladder neck and/or suspension of the neck.[37] A multi-centric, prospective, randomized study showed that the anterior retropubic suspension (puboprostatic ligament) with the subsequent reconstruction of rhabdomyo sphincter improves early return of continence without increasing complications.[38] One study showed no difference in urinary continence between robotics and open, but there is need for randomized studies to clarify this issue.[39]

Another study showed that robotic allowed faster recovery of urinary continence, reduced positive surgical margin presence and the period of urinary catheterization.[40]

The sexual potency evaluated by an index of erectile function (IIEF) and for erection hardness score (EHS), while preserving

bilateral nerves did not differ between the robot and opened. One study showed no difference in erectile function between the two access methods, one year after surgery, but the authors report the need for randomized study to clarify this issue.[39]

A positive surgical margin is an outcome of much study in radical prostatectomy. It was reported increased risk of positive margin in patients who have preserved the nerves bilaterally than when not preserved in patients with category pT2 disease, in multivariate analysis, after adjustment for confounding factors, which did not occur in patients with category pT3 disease.[41]

The assisted robotic surgery is associated to lower positive surgical margin and to lesser early cancer control because of the reduced use of antiandrogen drugs and radiotherapy in a two-year period, thus having and important effect in quality of life and health care, as well as in costs.[42] A systematic literature review study states that access method does not have clear advantages regarding oncologic results.[43]

A multi-centric study in Europe, USA and Australia reported that the surgical safety margin might be inferior after minimally invasive techniques and might be affected by the volume of surgeries in the surgical center where the robotic is performed.[44]

Another study states that the rate of positive safety margin does not differ among the access methods and that patients with high PSA levels in preoperative, in univariate analysis, as more likely to have positive safety margin.[45] Similar oncologic results may be obtained with both access methods by a surgeon experienced in robotic surgery, even in locally advanced disease.[46]

Tewari et al, 2012, in systematic literature review with meta-analysis evaluating 400 articles comparing robotic with open, observed that robotic is equivalent to open access via and laparoscopic in terms of safety margin, and suggests that robotic offers advantages specially regarding adverse events. Readmission rate, reoperation, nerve injury, rectal, deep vein thrombosis, pneumonia, hematoma, lymphocele, leaking anastomosis, fistula, surgical site infection showed significant difference among the groups, usually in favor of robotic. However, authors claim that the lack of randomized studies, use of state of margin as oncologic control and inability to compare costs are limitations of the study.[11]

In a retrospective analysis, evaluating 357 open prostatectomies and 669 robotic, safety margin of the results favored robotic, but the study has methodological limitations in T3 disease.[47] Another study shows that, in fact, there was no difference of positive surgical margin between the two access methods, and there was no difference in biochemical recurrence that has as independent predictors the preoperative PSA and the number of positive surgical margins.[48] The positive safety margin rate was more frequent in robotics that in open and laparoscopic, but no difference in pT2 disease, although the biochemical recurrence has not suffered difference between the three methods (robotic, laparoscopic and open).[49] Another study reports that there is a higher probability of positive surgical margin in robotic that in the open.[50] However, another study claims that the safety margin is similar in robotics and open in low-risk and intermediate-risk patients.[51] In a study of meta-analysis of observational studies, the authors suggested that robotics has similar risk of positive surgical margin.[52]

The positive surgical margin was lower in robotic than in open in pT2 stage and did no differ in pT3 stage, being the localization of positive surgical margin in the 3 methods the prostate apex.[53] Another literature review of 73 studies report similar surgical margin, however the functional results are difficult to be evaluated due to the studies biases.[54]

The positive surgical margin may decrease when the urologist changes from open to robotic, probably due to increased viewing

and for dissection accuracy,[55] and may decrease depending on the surgeon's experience after 30 patients.[56] Biochemical recurrence is an important outcome. It had as an independent predictor in multivariate analysis, extra prostatic extension, seminal vesicle involvement, lymph node involvement, the sum of Gleason scores and positive surgical margin.[57] This recurrence defined as PSA ≥0.1 ng/ml or PSA ≥0.05 ng/ml in patients with additional therapy did not differ between the robot and open held by a large number of surgeons.[58]

The recurrence-free survival has been compared between robotic and open. A study show that survival did not differ between both access methods at two and at four years.[59] Dariane C et al.[60] showed that recurrence-free survival has not been associated to PSA level below 4ng/ml, but to positive surgical margin and to Gleason score.[7]

When life quality is evaluated by EPIC among patients submitted to robotic surgery and open surgery for radical prostatectomy, there is no significant difference in 12 months, however patients on both groups had low response levels in twelve months, which implicates in performing other studies to clarify this issue.[61] The life quality (SF-12 version 2 of PMHSAF) evaluated in preoperative and weekly during six weeks showed higher physical score in robotic from first to sixth week, but the physical component score returned to basal earlier in robotic and mental component did not differ between both groups.[62]

The cost of the two access roads has been often compared. A recent study showed that the total cost of robotics is higher than the open, with longer anesthesia, although with robotic lower complication rate, less blood transfusion and shorter hospital stay.[63] Another retrospective study that compared 20,242 patients submitted to robotic with 9,413 patients submitted to open surgery showed that although robotic produce fewer complications and shorter hospital stay, unfortunately still has the highest cost of hospitalization.

Analyzing the results altogether, robotic when compared to open is associated with less blood loss and lower transfusion rate, shows a similar incidence of positive surgical margin and oncologic outcomes and appears to have advantages in terms of continence, potency and quality of life, but there are methodological limitations in existing studies in the literature.[64]

Other studies report no oncologic differences (positive surgical margin, progression of disease-free survival) and functional results among access methods (continence and potency).[65,66]

The Pasadena Consensus Panel in 2012, based on a systematic review concludes that robotics compared to open produces less bleeding, lower rate of blood transfusion, similar rates of complications and of positive surgical margin, advantages in the recovery of continence and potency, but there are methodological limitations on studies.[67]

In a systematic literature review comparing assisted robotic prostatectomy with open, the authors reported that assisted robotic surgery produces significant improvement in positive surgical margin for pT2 tumors and improves sexual function in 12 months, however these results should be interpreted carefully, due to evidence limitations. The studies that compares assisted robotic to open are of retrospective type, prospective case series and non-randomized, there for subject to biases.[22]

It should be noted that there are two randomized studies in literature still in development. The first is from Gardiner RA.[68] This study was initially published in 2012, but without definitive results.[69] The second is from Thompson RH and Tollefson MK.[70] Therefore, these publications should be waited to evaluate their results, which will contribute to evaluate the real benefit for robotic surgery over open during a longer period.

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CASE REPORT

Subtotal splenectomy for treatment of splenic cyst

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Keywords

Splenic Neoplasms; Spleen; Splenomegaly

Abstract

The authors describe a case of splenic cyst treated with splenectomy with preservation of the inferior pole, which is the first description in the literature of the use of this technique in human beings

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Introduction

The spleen cysts are rare, being observed in 0.075% of the autopsies. They may be classified as true cysts or pseudocysts. The true cysts have walls with cellular coating and the pseudocysts are not provided with internal coating.[1, 2, 3] The surgical treatment for spleen cysts is indicated for lesions

larger than 5cm and for symptomatic lesions.

The aim is to preserve as maximum splenic tissue as possible. The subtotal splenectomy preserving the inferior pole (SSPIP) is an alternative yet to be described for splenic cyst treatment, what justifies the present case report. [4, 5] This technique has already been described and reviewed on laboratory animals.[6]

Case report

A.K.B., 49 years old, woman, admitted to the General Surgery Service at Santa Casa de Misericórdia de Vitória Hospital in February 2001, reporting twinges of pain in the left hypochondriac region, for one year, medium-intensity, intermittent, triggered by food ingestion, associated to severe left low back pain. She said she had lost 7kg in seven months. She did not report fever, vomit, diarrhea or any other symptoms, only that she was hypertensive in regular use of propranolol.

She was in good general health status, with a palpable spleen two centimeters below the left costal margin, abdomen without pain response to superficial and deep palpation.

In the hemogram, the counter tests of hepatic function and the urinalysis were within the regular parameters.

The computed tomography of the abdomen has evidenced an enlarged spleen showing a voluminous cystic image, measuring 9.7 x 8.8 cm, of homogeneous and hypodense content, determining mild compression to the adjacent structures (See Figure 1-B).

During the surgery, a voluminous cyst was identified in the superior portion of the spleen. The SSPIP was carried out (See Figure 1-A). The yellow-citrine liquid content of the cyst was sent for neoplastic cells research, bacterioscopy and culture. The spleen portion which was extracted was sent for anatomopathological study.

The analysis of the liquid was negative for neoplastic cells. At the macroscopic evaluation: spleen with cystic formation measuring 11.5 x 10 x 5cm, with grayish corrugated external surface. The internal surface of the cyst was corrugated, presenting light grayish-brown coloration. Upon sectioning, reddish and rawish tissue.

The patient was discharged on the fifth post-operative day without any intercurrence. She was followed up weekly in the first month and, after that, monthly.

Discussion

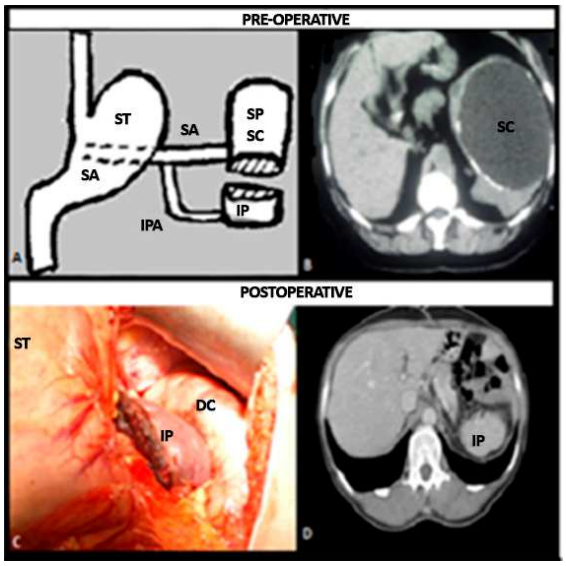
The treatment for splenic cysts is controversial. On those cysts with small diameters, with asymptomatic patients, when the lesion may remain unaltered the whole life, it is recommended radiological follow up (mainly through ultrasonography) and watchful waiting. On those with diameters larger than 5cm and/or symptomatic cysts, surgery is indicated. Some authors believe that the use of the partial splenectomy technique, which does not damage the spleen immunological functions, is the treatment of choice for cystic spleen lesions.[4]

In this case, the patient was operated for being symptomatic and because the cyst was voluminous. During the surgery, it was observed an inferior polar artery directed to the spleen. After the splenic artery ligation, it was observed a delimitation in the splenic parenchyma color, with the superior 2/3 poorly perfused, while the inferior 1/3 remained bleeding. So, we decided to preserve the parenchyma irrigated through this inferior polar vase (See Figure 1-C). The surgical procedure was uneventful, as well as the post-operatory period, being the patient discharged on the fifth day after the procedure.

On the fourth post-operative month, the patient remained clinically asymptomatic, with normal laboratorial exams. Her

computed tomography for control showed a spleen reduced in volume, normal density, without any anomalous captation areas through contrast enhancement. The color Doppler ultrasonography showed an inferior pole with regular shape and borders, preserved echotexture and reduced dimensions (51.1cm^3 volume), keeping a preserved flow, with peak systolic velocity of 35.55 cm/s.

Figure 1 – Schematic diagram of subtotal splenectomy preserving the inferior pole in patient with voluminous splenic cyst.



A – SA splenic artery; IPA – inferior polar artery; IP – inferior pole; SP – superior pole;

B– To observe pre-operatory tomography with splenic cyst (SC);

C– inferior pole preserved during surgery; ST – stomach; DC – descending colon;

D– post-operatory tomography showing the preserved inferior pole in detail.

Source: the author.

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REVISTA SALUS
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CASE REPORT AND LITERATURE REVIEW

H1N1 with acute respiratory distress syndrome and encephalopathy: a case report

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Keywords

Influenza A Virus, H1N1 Subtype; Respiratory Distress Syndrome, Adult; Encephalopathy

Abstract

This article describes a case of Influenza A H1N1 in a female patient, 52 years old, previously healthy, presenting atypical pneumonia with fast progression to acute respiratory failure and relatively late introduction of Oseltamivir. The patient has developed secondary staphylococcal pneumonia, Acute Respiratory Distress Syndrome and Posterior Reversible Encephalopathy Syndrome. This patient was not previously vaccinated for influenza as she was not included in the priority populations defined by the National Immunization Program. The present increase of severe cases and deaths from H1N1 in 2016 supports the Center for Disease Control's (CDC) guidelines to expand flu vaccination in order to reduce this disease's morbidity and mortality.

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Introduction

Flu is a universally distributed acute infection caused by the Influenza virus, which has been causing epidemies in several populations for centuries. In 2009, a new variant of this virus, the Influenza A H1N1, has started a pandemy in the Mexican city of La Gloria, Veracruz, which spread worldwide. The pandemy was declared ended in 2010 after a great number of casualties.[1]

The infection caused by the Influenza virus has a spectrum that varies from an upper respiratory tract illness without fever to a fulminant viral pneumonia. Most of the patients presents fever and cough, symptoms which may be followed by sore throat and rhinorrhea.[1, 2] The best method for initial diagnosis is still the viral RNA detection by PCR.

The main causes that lead to hospitalization and admission to an Intensive Care Unit (ICU) are diffuse pneumonia, Acute Respiratory Distress Syndrome (ARDS), sepsis and shock. There is also the possibility of affection of the Central Nervous System (CNS), less frequent.[1]

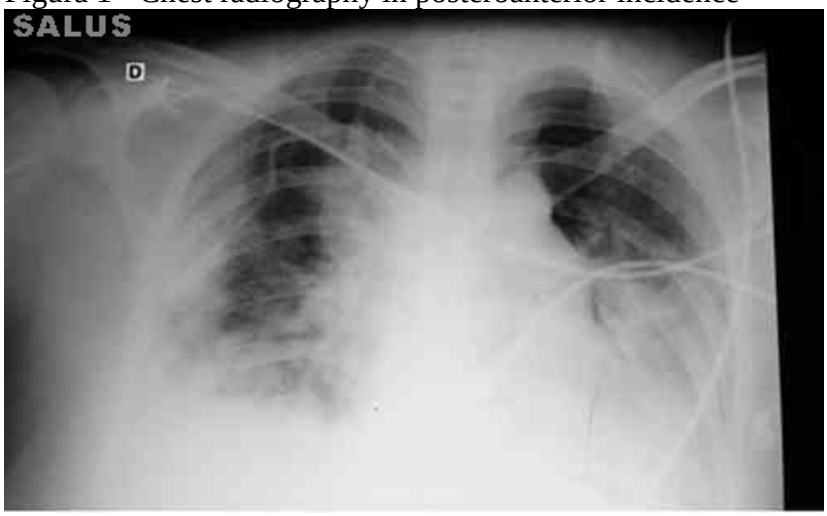
For this specific treatment, it is used Oseltamivir, an antiviral that is more effective when initiated in the first 24 hours. Due to the virus mutations, annual vaccination campaigns are recommended.[1, 2]

We report a case of a patient with influenza A (H1N1) that evolved to acute diffuse pneumonia, ARDS and Posterior Reversible Encephalopathy Syndrome (PRES).

Case report

Patient L.S.R., woman, caucasian, 52 years old, with Gastroesophageal Reflux Syndrome, in daily use of Pantoprazole, without history of smoking or alcoholism. She has complained of fever that evolved with myalgia, dry cough, earache, nausea, vomit, adynamia and hyporexia. She looked for medical care, being medicated with Azithromycin. Five days later, she was admitted to the hospital and, at the physical exam, presented a regular general health status, dehydrated, pale, anicteric, no fever (37.4ºC). Oral examination was normal, no lymphadenomegalies were detected and there was normal lung auscultation. Chest radiography (See Figure 1) showed bilateral extensive pulmonary infiltrates that were mainly basal with atelectasis and associated pleural effusion. The antibiotic therapy was changed to Levofloxacin.

Figura 1 - Chest radiography in posteroanterior incidence



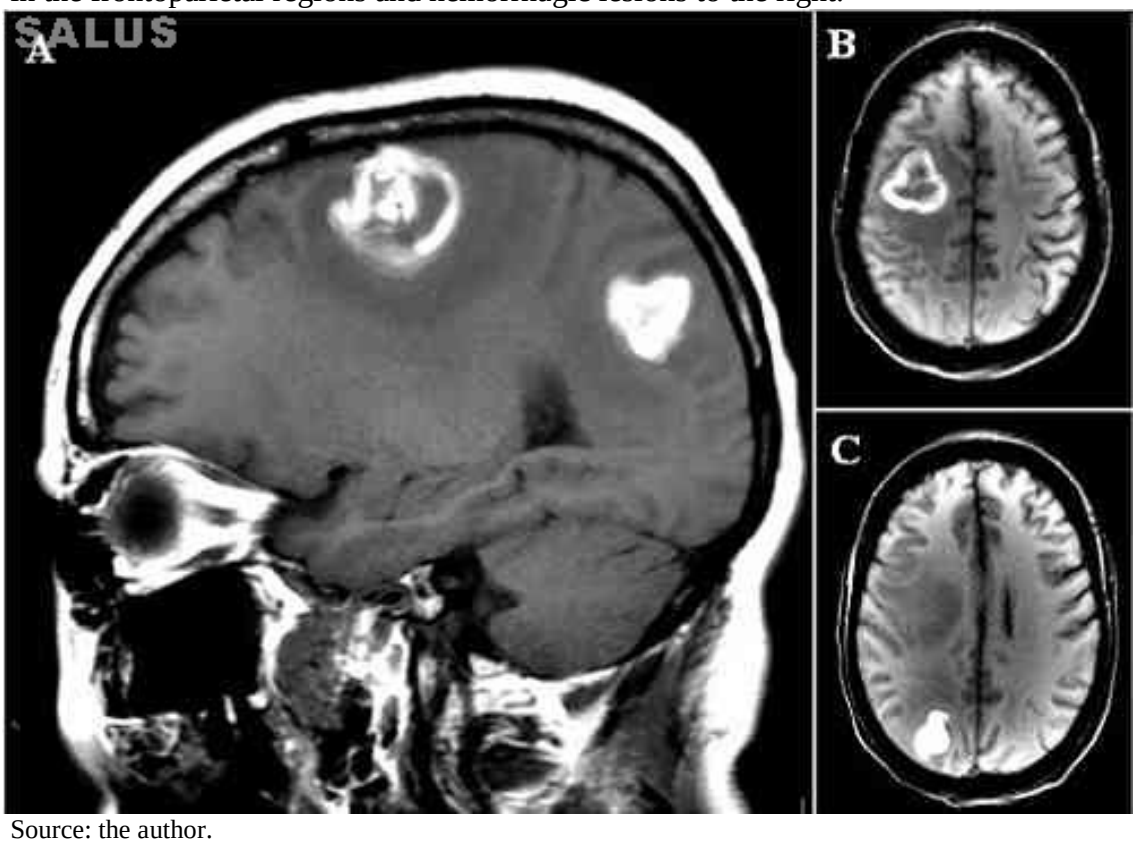
Source: the author.

The patient has evolved to severe dyspnea, was then transferred to the ICU and the antibiotic therapy was changed to Ceftriaxone, Clarithromycin and Sulfamethoxazole/Trimethoprim (SMX/TMP). She has developed septic shock and respiratory failure, so mechanical ventilation was needed and a tracheostomy was performed. Computed Tomography (CT) of the chest showed bilateral interstitial pneumonia in the right lung and left lung basis with patchy ground glass opacity, evidencing ARDS. Bacterioscopies and cultures, negative BAAR and ELISA for HIV led to the suspension of SMX/TMP and initiation of Oseltamivir.

On the eighth day of ICU, there was radiological worsening, blood cultures and cultures of trachea secretion revealed oxacillin-resistant *Staphylococcus aureus*. These findings have oriented the beginning of Vancomycin and Meropenem, with interruption of the other antibiotics. Oseltamivir was kept for only 5 days. On the tenth day, Influenza A H1N1 was confirmed by PCR done in a fluid sample collected through nasal swab at hospital admission. On the seventeenth day, she presented eye aperture and response to stimulus, without obeying to commands though. All antibiotics were stopped and the patient was put into macro ventilation.

On the twentieth day, she presented right paresis, left plegia and partial facial paralysis to the left as well. Brain CT and Magnetic Resonance Imaging - MRI (See Figure 2) showed images compatible with intraparenchymal hemorrhage in front parietal and right occipital lobes, measuring 2.2cm x 2.9cm and 1.7cm x 2.3cm respectively, with edema and blurring of adjacent sulcus.

Figure 2: MRI showing: a) Sequence in T1 with hemorrhagic lesions in the frontal and right parietal regions; B) and C) Flair sequences showing hypersignal of the white matter in the frontoparietal regions and hemorrhagic lesions to the right.



Source: the author.

Acute hemorrhagic leukoencephalitis (Weston-Hurst Syndrome) was suspected and intravenous bolus (pulse) doses with methylprednisolone was begun and kept for five days. After corticotherapy, the patient recovered the movements of the left lower limb. Arterial and venous angiographies of the skull have evidenced arterial narrowing and NRM has showed reduction of edema and hemorrhagic areas. 34 days after ICU admittance, all the respiratory support was withdrawn, leaving only the tracheostomy, with the patient being relocated to a room. The hospital discharge occurred 42 days after the admittance. Quick neurological improvement and the imaging review of MRI and CT of the skull set the diagnosis of Posterior Reversible Encephalopathy Syndrome. The patient evolved with physical therapy at home, without any motor and respiratory sequel.

Discussion

Caused by the Influenza virus, the flu is capable to cause annual recurrent epidemies and, less often, pandemies. In June 2009, four months after its outbreak in Mexico, the first Influenza pandemy of the 21st century was declared by the World Health Organization, as a "pandemy of a new virus", the Influenza A H1N1. Since August of that very year, 177 countries have reported 182,166 cases and 1,799 deaths. The end of the pandemy was declared in August 2010, but it was not before 200 million people were infected and nearly 18,500 casualties were confirmed.[1,2] From 2013 to 2014, and again in 2016, the subtype H1N1 returned, resulting in significant morbidity and mortality.

The H1N1 flu is highly contagious, being typically a mild upper respiratory tract infection associated to fever, cough, myalgia, rhinorrhea, conjunctivitis and dispnea.[1,2] Although generally self-limiting, it includes a subset of patients with unfavorable clinical course, being the severe Influenza infection normally associated to pulmonary complications.[1] Besides commonly seen in elderly adults or in the ones with high risk conditions, it is possible to state that, taking the case report as an example, the age group under 60 years old and the absence of comorbidities are not indicators of risk absence for the unfavorable evolution.[1, 2]

It is known that the evolution of the H1N1 infection depends on the form each individual pro and anti-inflammatory inner mechanisms interact. Initially, a major cytotoxic T lymphocytes stimulation occurs and is crucial for viral elimination. At the same time, a progressive increase in the production of Interleukin 10 (IL-10), a T cell inhibitor, avoids hyper stimulation of T cells. Severe and fatal cases have been linked to low and high IL-10 levels. In the first condition, cytotoxic T lymphocytes hyper stimulation, causes autoimmunity lesions; on the other hand, high inhibitory action of IL-10 on T lymphocytes compromises the protection against secondary infection.[3]

The main causes which lead to hospitalization and ICU need are pneumonia, ARDS, and, sometimes, sepsis and shock.[1] A 2009 study involving 189 ICUs conducted in Australia and New Zealand evidenced that almost half of the patients with confirmed H1N1 infection (48.8%) presented ARDS or viral pneumonitis and 20.3% were clinically diagnosed with secondary bacterial pneumonia, normally caused by *Staphylococcus aureus (often methicillin resistant), Streptococcus pneumoniae* and *Streptococcus Pyogenes*.[1,4]

Extra pulmonary manifestations, such as of the CNS, were also observed in the H1N1 infection. Occasional cases of neurological manifestation were reported, including some fulminant cases.[1,2] As it was showed, the patient presented with tetraparesis, which led to the hypothesis of Weston-Hurst Syndrome. However, a very favorable evolution, opposed to what is

normally observed in that syndrome, allied with the revision of brain MRI and CT performed strongly defined the hypothesis of PRES.[5]

Clinical suspicions and diagnosis accuracy of Influenza A H1N1 depend on whether the case is a sporadic one or occurs during a known outbreak. As described, the patient was admitted with all the Gram staining and cultures negative. However, it was posteriorly detected positive PCR to H1N1 through nasal swab, being the viral RNA identification, with this technique, the best method for the initial diagnosis.

Thus, although very important for the diagnosis, the introduction of the antiviral treatment must not wait for laboratorial confirmation. Patients with suspect clinical presentation should be treated empirically treated as soon as possible. The current AH1N1 subtype virus that circulates is still susceptible to neuraminidases inhibitors, Oseltamivir and Zanamivir, but it is very resistant to Amantadine and Rimantadine. Oseltamivir is the most used drug and it reduces hospitalization time and risk of progression to severe illness, especially when started early.[1]

As the available options for flu control are limited, it is recommended yearly prevention through vaccination. Children, pregnant women, immunosuppressed individuals, people with chronic diseases, elderly people and healthcare professionals are the priority groups. An unfavorable ending is not necessarily associated to previous debilitating conditions, but also to the individual immune response pattern during the inflammatory process, beyond the virulence of the infecting strains. The unpredictability of each particular kind of response weakens the current definition of priority groups for vaccine protection. In the present case, the patient did not fit into any criteria for vaccination coverage of the National Immunization Program of the Health Ministry. The Center for Disease Control/ USA (CDC) and some experts of World Health Organization (WHO) have recommended universal vaccination for the flu.[3,6]

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CASE REPORT

Public and private in a high complexity medical procedure

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Abstract

The care to highly complex services in Brazil is carried out by federal funding. Today, there is a link between the public and private sectors in order to provide, from the private sector part, the necessary equipment for performing high complexity services, being the public sector responsible for funding it. This article aims to understand the relations between the public and private sectors when carrying out a procedure of high complexity and, thus, a case report of a patient who underwent lung transplantation will be used.

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Introduction

Some of the high complexity health procedures, as lung transplantation for instance, are funded for the population and this subside comes typically from the Public Health Care System. In Brazil, the transplantation program, considered the

biggest in the world, exists due to public funding. In Espírito Santo, the transplantation activities were promoted through public-private agreements. Most of its funding comes from the public sector, carried out through the Health Ministry, so, it does not affect the spending cap of the states and municipalities. The State is responsible for the management of the system, regulated by the National Transplantation System.

Nowadays it is common to see articulations between the public and private sectors, in order to provide (from the private sector part) the equipment required for the realization of high complexity procedures. The public sector is responsible for the funding of the services; a true public-private mix, regarding the providing of health services in the country[1].

The government has sought strategies for reducing the obstacles to the progress of the organ transplantation program. It offers to people living in places not covered by the program the possibility of using resources from the Out-of-home Treatment program (TFD) for the transport of patients to a transplantation center. The transplantation center must have a qualified staff, specialized in the pre, intra and post-operatory handling, and formed by several different professionals who work in an interdisciplinary approach, aiming to optimize of the biological, psychological and social conditions of the patients.[2] It has been partially executed in Espírito Santo, since the patients have been taken to the Lung Transplantation Group of the Hospital Meridional Transplantation Center.

This research aims at understanding the interrelation between the public and private sectors regarding the realization of a high complexity procedure (lung transplantation). In order to do so, it presents the case of a patient with pulmonary fibrosis, here named Cachoeiro, who presented shortness of breath on mild exertion, with partial limitation of the everyday life activities, and was admitted at his city hospital almost every month. He had a private health insurance and received the TFD for undergoing the lung transplantation in Porto Alegre.

Case Report

The patient was evaluated by the multidisciplinary team of Espírito Santo and referred to the Hospital Santa Casa in Porto Alegre, where he underwent the transplant procedure. The service flow, in this case, was made in the following way: 1) social worker to evaluation of housing, social support, family and income; 2) nutritionist to evaluation of the nutritional status; 3) nurse care to evaluation and orientation of the hospital proceedings; 4) physical therapist to evaluation of the physical condition and orientation about the pulmonary rehabilitation; 5) psychiatric assessment; 6) transplantation clinical staff.

Cachoeiro is a 60-year-old man, dwelling in Cachoeiro de Itapemirim, Espírito Santo, married and living with his wife, working as a jeweller. He had completed high school. It is known that education is directly related to access to health care services, especially the private services, and, maybe because of this, to the high complexity services of the Unified Health System – SUS. According to Noronha and Andrade[3], the educational level of the family head has significant impact in the decision on looking for health care. The individuals who are attended exclusively by SUS have lower educational levels and use mostly the public health system, typically looking for medical appointments or other professionals, predominantly ambulatory service[4].

The household income of Cachoeiro was around 8-10 minimum wages and he had private health insurance. According to Ribeiro et al.,[4] only 9.2% of the patients who are attended exclusively by SUS had a per capita income higher than two minimum wages, while - among the population covered by private health insurances - this

numbers was 51.8%. It is important to emphasize that individuals who have private health insurance have 56% more chances of being admitted to a hospital, and, therefore, undergoing certain procedures than SUS patients.[3]

Discussion

It is a paradox to think that, despite the majority of the transplants carried out in Brazil are funded by the public health care system, those who have private assistance manage to be evaluated more quickly and, most likely, get transplanted, whereas SUS patients cannot undertake all the exams in the proper time, being invariably doomed to die. According to Souza (2011)[5], "in the health care sector, the imposition of the market logic has legitimated inequality in access to health care and formed an illusory share of health care service customers".

After being evaluated by the social work team, Cachoeiro has received the TFD subside in Espírito Santo. He was included in the waiting list, underwent the transplant in December, 2011 and three months late was allowed to go back home. In spite of having a private health insurance, Cachoeiro looked for public assistance when it came to a high complexity procedure, such as lung transplantation. According to Souza (2011)[5], "the private sector takes on the most profitable pathologies, associated with the most profitable therapeutic resources". The lung transplant cost is high, and about 95% of it is funded by SUS, differently from the USA, where the transplant is funded by private health insurances or direct payment made by the patient.[6]

In Brazil, the high complexity procedures are responsible for an input of federal funding for health care at great cost to the federal budget. Although there is no official data on the number of outpatient appointments for the patients who were transplanted, one may extend the analysis and gather data from other services, such as chemo, radio, hemotherapy and hemodialysis. The southeast region is responsible for 57.4% of the appointments in Brazil and 11.6% of all appointments in SUS related to these treatments, are made for people who own a private health insurance.

Thus, some high complexity procedures, such as transplants, are promoted by public-private agreements, being the federal public sector responsible for the funding, while the private sector offers the equipment and the human resources management. As it was made clear in this case report, it is unacceptable that only the part of the population who owns a private health insurance is able to get the proper agility when undertaking the required examinations for a transplant.

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