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SUMMARY

Presentation Letter

SALUS: Journal of Health Sciences - ISSN 2447-7826, Qualis Capes B4, held its first issue published on October 15, 2015. From the seventh issue, the journal will be issued as a Journal of Interdisciplinary Studies in Sciences Social and Health (REICSS) by virtue of the identification of the company holding the name used.

REICSS will keep on being the vehicle for scientific communication at the Santa Casa de Misericórdia de Vitória College of Sciences (EMESCAM), which features an undergraduate course in Medicine, for more than half a century, apart from Nursing, Physiotherapy, Social Work courses and Postgraduate Course stricto sensu, Academic Master's in Public Policy and Local Development, for over 10 years.

EMESCAM is sponsored by the Brotherhood of Santa Casa de Misericórdia in Vitória Hospital (HSCMV), ES, Brazil, a philanthropic institution. The hospital was founded in the 16th century and it is located in downtown Vitória - ES.

The journal observes the same standards, ethical and scientific rigor as journals with the most national and international academic impact, with the purpose of disseminating the production of interdisciplinary scientific knowledge in the areas of Health Sciences, Applied Social Sciences and Public Policies.

Editorial policy and administrative procedures will be supervised by Editora Emescam, affiliated to the Brazilian Association of University Publishers from the second half of 2019.

We desire to rely on the scientific community support, granting us prestige by providing the opportunity to divulge the results of quality research. The purpose is to completely abolish the endogeny inevitably noticed in this first issue.

Success for all of us!

Valmin Ramos da Silva, MD, PhD

Editor

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ESTUDOS INTERDISCIPLINARES EM CIÊNCIAS SOCIAIS E DA SAÚDE
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Original Article

LACK OF ASSOCIATION SNP+45T>G WITH CARDIOVASCULAR DISEASES IN OBESE PATIENTS

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Keywords

Adiponectin;
Obesity;
Polymorphism;
Single Nucleotide;
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Abstract

In order to assess whether the single nucleotide polymorphism (SNP) rs2241766 (+ 45T> G) in the adiponectin gene (ADIPOQ) is related to the presence of cardiovascular diseases (CVD) in overweight patients, it was carried out a survey of CVDs in patients (IMC ≥ 25 kg / m2) from the clinical database of the Molecular Genetics Laboratory of EMESCAM. It took place the extraction of genomic DNA from peripheral blood, amplified by the Polymerase Chain Reaction technique, followed by enzyme digestion and polyacrylamide gel electrophoresis and staining. The genotypic and allelic frequencies were compared by the chi-square test, with p G value of the ADIPOQ gene in overweight patients, in none of the genetic inheritance models. Nevertheless, the presence of familial history had a significant association with the severity of CVD manifestation.

INTRODUCTION

Obesity is a global epidemic that brings serious health complications[1] and it is related to an increase in mortality[2]. Its prevalence has increased in recent years and it is estimated that about 58% of adults worldwide will be overweight or obese by 2030[3]. Its progression is inherent in increased risk for various diseases, mainly cardiovascular diseases (CVD) [2-5].

CVD is a group of diseases of the heart and blood vessels which are the major cause of death in the world. The Ministry of Health Data (2011) reveal that CVD represent 29.4% of all deaths recorded in Brazil, symbolizing that more than 308,000 people died mostly of heart attack and stroke. Therefore, the country is placed among the ten countries with higher CVD deaths. In the state of Espírito Santo, an analysis of listed deaths using the International Code of Diseases (ICD-10) chapter reveals that diseases of the circulatory system, including CVDs, are the leading causes of death, representing a total of 29.5% [7].

Atherosclerosis, the central characteristic of CVD, is a chronic inflammatory disease of multifactorial origin that arises in response to endothelial aggression, affecting medium- and large-caliber arteries[8]. Another important aspect is the deficiency in the release of nitric oxide (NO) from vascular endothelium and the decrease of blood flow to target tissues of insulin, contributing to insulin resistance, also known as endothelial dysfunction[1].

Endothelial function is controlled by various molecules, including adipokines or adipocytokines, cytokines secreted by

adipocytes[2]. Leptin, monocyte chemotactic protein-1 (MCP-1), plasminogen activator inhibitor -1 (PAI-1), tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6), resistin and adiponectin are some of these adipocytokines associated with endothelial dysfunction[9].

Adiponectin, the most plentiful secreted adipocytokine, has antiatherogenic, anti-inflammatory and antidiabetic properties[10]. The change in adipokine profile in the serum of obese people, such as levels of adiponectin and proinflammatory cytokines, is a contributing factor in the development of cardiometabolic alterations[3].

Low circulating levels of adiponectin (hypoadiponectinemia) are considered an independent risk factor for endothelial dysfunction,[4,1] due to an interaction of environmental factors and genetic factors such as single nucleotide polymorphisms (SNP) in the adiponectin gene (ADIPOQ). Besides, this gene has been related to various characteristics of metabolic syndrome, DM2 and DCV[11-15].

Taking into consideration that obesity is characterized by a chronic, pro-inflammatory state causing hyperplasia and fat cell hypertrophy, leading to an imbalance in adipokine release[16] and also the important regulatory role that adipokines play, in particular adiponectin, the aim of the present study was to verify if the SNP rs2241766 (+ 45T> G), present in the ADIPOQ gene, is related to the presence of cardiovascular diseases in patients with obesity as well as if the family history influences the association of the polymorphism.

METHOD

This study is part of a larger project titled "Adiponectin Gene Polymorphism and Type 2 Diabetes Risk in Obese Patients from the population of Vitória-ES", based on a sample composed of overweight patients (BMI ≥ 25 Kg / m2), for which a survey regarding CVDs was performed. Among them, are hypertension, angina, infarction and stroke (stroke). Patients with excess weight and with at least one CVD were considered as cases, and patients with excess weight and with no CVD were considered non-cases. The survey of CVD was carried out based on the sample and on the frequency of familial history. Taking into account that all cases presented hypertension, we considered as severe cases patients who had some other CVD in addition to hypertension, and with less severity those who only had hypertension. A positive family history was considered when more than one member of the family with CVD was reported. The information was acquired through medical records of each patient.

Genomic DNA was extracted from peripheral blood leukocytes as stated by the protocol of Miller et al. (1988) and intensified by the PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) technique. PCR conditions were initial denaturation for 5 minutes at 95 ° C, followed by 35 cycles of 1 minute at 95 ° C, 1 minute at 55 ° C and 40 seconds at 72 ° C; final extension for 10 minutes at 72 ° C, followed by digestion with the BspHI enzyme of 0.1 U concentration in the dry bath at 37 ° C for 8 hours. The products of the PCR reaction were analyzed by polyacrylamide gel electrophoresis (8%), visualized by 0.1% silver nitrate staining[18].

The cases (associated with the presence of CVDs) and the non-cases, which presented genotype for the SNP + 45T> G, were examined using the chi-square test. For the purpose of determining if genotype distributions were in Hardy-Weinberg equilibrium, genotypic and allelic frequencies were compared between cases and non-cases using chi-square; a p value <0.05 was considered significant.

This work was approved by the Research Ethics Committee of College of Sciences of Santa Casa de Misericórdia (EMESCAM) of Vitória - ES under nº 076/2007.

RESULTS

The genotypes were acquired for 112 patients. Most of them were women (85.7%) obese (94.6%) and with a mean age of 41.61 ± 13.12 years. With respect to the type of CVD, 80.61% (70/79) of the cases presented hypertension, 8.86% (7/79) angina, 1.26% (1/79) infarction and 1.26% (1/79) strokes. Out of the total, 70.5% (79/112) presented CVD and were considered cases (table 1). The genotype frequency in the patients was TT 24.1% (19 cases), GG 15.2% (12 cases), and TG 60.7% (48 cases). The allelic frequency was 54.4% for the T allele and 45.6% for the allele G. The allelic and genotypic frequencies were not in Hardy-Weinberg equilibrium (p = 0.0457). There was no relation of polymorphism to any cardiovascular disease in any of the genetic inheritance models (Table 2). Examining genotypes (p = 0.188) and genetic models (Dominant p = 0.128, Recessive p = 0.177 and Codominant p = 0.734), there was no significant association of severity with polymorphism (Table 4).

The family history of CVDs was related to severe and less severe forms (p = 0.003) (Table 3). On account of this result, we analyzed the cases and non-cases with less severity that presented positive family history, in search of knowing the influence of polymorphism on hypertension. However, there was no significant difference (p = 0.317).

Table 1- Frequency of Cardiovascular Diseases and genotypes between the cases.

SNP+45T>G					
		Hypertension	Angina	Infarction	CA Stroke
	n				
TT	19	15 (78.9%)	3 (15.8%)	1 (5.3%)	0 (0.0%)
TG	48	43 (89.6%)	4 (8.3%)	0 (0.0%)	1 (2.1%)
GG	12	12(100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

CA = Cerebrovascular Accident (Stroke); SNP = Single Nucleotide Polymorphisms
Resource: author

Table 2- Gentotypic and allelic distribution in genetic models between cases and non-cases.

	Cases	Non-Cases	*p*
Genotypic Distribution			
TT	19 (24.1%)	6 (18.2%)	
GG	12 (15.2%)	2 (6.1%)	
TG	48 (60.7%)	25 (75.7%)	
Allelic Distribution			
T	86 (54.4%)	37 (56.0%)	0.88
G	72 (45.6%)	29 (44.0%)	
Dominant Model			
TT	19 (17.0%)	6 (5.4%)	0.49
TG + GG	60 (53.6%)	27 (24.1%)	
Recessive Model			
GG	12 (10.7%)	2 (1.8%)	0.18
TG +TT	67 (59.8%)	31 (27.7%)	
Condominant Model			
TG	48 (42.9%)	25 (22.3%)	0.13
TT+GG	31 (27.7%)	8 (7.1%)	

Resource: author.

Table 3 – Familiar History of Cardiovascular Diseases between cases and non-cases.

	Cases	***Non-Cases***	
			p
FH positive	76 (96.20%)	26 (78.79%)	
FH negative	3 (3.80%)	7 (21.21%)	0.003
Total	79	33	

FH = Familiar History
Resource: author

Table 4 - Genotypic Distribution of SNT+45T>G in patients with severe and non-severe DCV

	Severe DVC	Non-severe DVC	
	n (%)	n (%)	*p*
Genotype			
TT	4 (5.1%)	15 (19.0%)	
GG	0 (0.0%)	12 (5.2%)	0.188
TG	5 (6.3%)	43 (54.4%)	
Dominant Model			
TT	4 (5.1%)	15 (19.0%)	0.128
TG + GG	5 (6.3%)	55 (69.6%)	
Recessive Model			
GG	9 (11.4%)	58 (73.4%)	0.177
TG +TT	0 (0.0%)	12 (15.2%)	
Condominant Model			
TG	4 (5.1%)	27 (34.2%)	0.734
TT+ GG	5 (6.3%)	43 (54.4%)	

SNP = Single Nucleotide Polymorphisms; CVD = Cardiovascular Diseases.
Resource: autohor.

DISCUSSION

Some studies indicate the association of ADIPOQ polymorphisms with CVD [13,21,23,33]. Yet, since this association is still controversial, it is important to check the prevalence of alleles in order to confirm the increased risk in different populations and to accompany risk groups to better understand the evolution and clinical management of CVD. The major purpose of this study was to analyze whether the + 45T> G polymorphism in the ADIPOQ gene is related to CVD and whether the presence of family history influences this relation.

Around 30% of all global deaths are from CVDs, with coronary heart disease at 7.4 million, and stroke at 6.7 million deaths[19]. The CVD mortality rate in Brazil is 214 per 100,000 inhabitants[20]. In the state of Espírito Santo, diseases in the circulatory system, including CVDs, are the leading causes of death, representing a total of 30.2% [7]. In the current study, 80.6% of the patients had some type of CVD, with hypertension being the most frequent, corroborating their increased prevalence in overweight patients.

In this research, the three genotypes (GG, GT, TT) were observed in subjects with hypertension, and the groups of heterozygotes and GG homozygotes corresponded to the majority of the individuals studied. We also noted that the G (+ 45T> G) allele was present in most patients with CVD, predominantly in hypertensive individuals. Nevertheless, no association was perceived between genotypes and CVD.

Oliveira et al. (2005) associated variants of the ADIPOQ gene in diabetic and non-diabetic Brazilian patients, independent of circulating adiponectin, BMI and glycemic levels. They described an association of

variants in the adiponectin gene with CVD in patients with type 2 diabetes mellitus DM2). Zhou et al. (2014) in a meta-analysis, found out the distribution of cases and controls genotypes for the + 45T> G in relation to coronary artery disease (CAD), stated associations of variants in the adiponectin gene with the risk of developing the disease in the study group. Ferrarezi et al. (2007) in

A review of evidence reported associations of allelic variants of the adiponectin gene with CVD in patients with Type 2 Diabetes Mellitus (DM2). These authors cite that GG homozygotes and TG heterozygotes when compared to TT homozygotes, are at increased risk for CAD. Another study achieved with French and Swiss patients with DM2 and CAD also noticed an association of SNP + 45T> G with CAD. Besides, susceptibility to CAD, due to SNP + 45T> G, was independent of cardiovascular risk factors classics[23].

Some studies suggest that the G allele is at risk. However, Oliveira et al. (2005) reported that adiponectin plasma levels and the interaction of diseases such as obesity, insulin resistance, DM2, and CAD showed high mRNA expression in adipose tissue, as well as total circulating adiponectin levels higher in patients with the G allele and hypothesized that this would be a protective factor.

Witberg et al. (2016) report that high levels of adiponectin were associated with increased mortality and morbidity in a young multiethnic population with CVD. Lindberg et al. (2015) eventually followed random individuals from a community and concluded that the increase in plasma adiponectin was associated with decreased risk of DM2 and subsequent cardiovascular events. Ferrarezi et al. (2007), concentrating studies of the association of ADIPOQ in patients with diabetes and CVD, notify that genotype-related effects on serum adiponectin levels are not consistently observed and explain that this is resulting from, among others, over time, with age, the effect of diabetes on this variation and adequate quantification of the globular multimers that present this adipokine, thus suggesting further investigations.

Our study observed the absence of association of SNP + 45T> G with CVD, thus corroborating the studies of Jung Jung et al. (2006), who analyzed subjects submitted to coronary angiography with chest pain as well as those of Zhang et al. (2012), in meta-analysis with eleven studies covering 4303 Chinese patients. In a meta-analysis with different populations, Zhou et al. (2014) found that the G allele of SNP + 45T> G has a low penetrating risk factor for the development of CVD in a Caucasian group.

Queiroz (2012), argues that studies in mixed populations, as in Brazil, reveal that the prevalence of obesity and related diseases, such as type 2 diabetes and hypertension, may vary in line with the ethnic group. Thus, it is important to segregate individuals by genetic ancestry. Consequently, even though there is evidence of absence of association in other studies, sample size and miscegenation may have been limiting factors for the present study, since the population of Espírito Santo is composed of the sum of native Indians, foreign immigration of Africans and European migration from neighboring states. Saletto (2000), in his survey of the Capixaba ethnic composition, illustrates this miscegenation as a "racial cauldron".

Hardy Weinberg's balance is a significant principle of population genetics. Deviation from this equilibrium has been considered as an indicator that the alleles have not been independently segregated, which may denote a non-random cross, small sample number, or a recent mutation that has not

yet reached equilibrium, as identified by Namvaran et al., (2011). In the current study, the imbalance can be explained by the small sample size and by the ethnic diversity of the population.

The presence of familial history in our study population was an important risk factor for CVD, as was observed by Schildkraut et al. (1989) three decades ago. We attribute this fact to the strong contribution of several genetic polymorphisms linked to the familial history, when compared to the contribution of only one SNP (+ 45T> G).

Stumvoll et al., (2002) found that adiponectin polymorphism increased the risk of obesity and the insulin resistance in individuals without familial history for T2DM and also justified the absence of these associations in individuals with a family history, declaring that family predisposition would represent a genetic load much stronger than the presence of the PNS alone. Thus, in individuals who already have other genetic factors, the small effect of SNP on the phenotype may be difficult to detect.

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CONCLUSION

In the analyzed patients there was no association of CVD with the SNP + 45T> G of the ADIPOQ gene in any of the genetic inheritance models. The presence of familial history is an important marker of risk for CVD.

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ESTUDOS INTERDISCIPLINARES EM CIÊNCIAS SOCIAIS E DA SAÚDE
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Original Article

THE MANNHEIM PERITONITIS INDEX TO PREDICT THE OUTCOME OF POST-SURGERY OF PERITONITIS.

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Keywords

Peritonitis;
Sepsis;
Prognosis;
Hospital Mortality.

Abstract

Objective: To evaluate the effectiveness of the Manhein peritonitis index (MPI) in order to predict mortality in patients with peritonitis at Hospital Santa Casa de Misericórdia de Vitória (HSCMV). **Method:** Retrospective longitudinal cohort with a sample of 75 patients diagnosed with peritonitis from January 2010 to December 2, 2015 at the HSCMV, with all the necessary criteria for the calculation of MPI. **Results:** A profile of the patients was found. Among them, 33 females and 42 males, mean age 42 years, 11 deaths and 14.67% mortality rate. Comparing the

MPI variables in two groups (surviving and deceased), it was found that age greater than 50 years, presence of malignancy and patients with organ dysfunction had statistical significance for mortality, with p <0.05. The IPM varied between 4 and 41 points, with an average of 21.2 points. Nevertheless, among the deceased the score ranged from 23 to 41 points, with an average of 32.8. As a result, the cut-off point of 27 points was established through the evaluation of the best value of the Kappa Index of agreement, and through it were calculated: sensitivity of 90.90% and specificity of 78.13% through the ROC curve. **Conclusion:** According to these results, it was noticed that MPI was efficient in estimating the risk of death, which was identified when the index reached values ≥ 27 points. Classifying patients in different risk groups is important to determine a better prognosis and to define the operative risk, which contributes to the choice of the nature of the operative procedure.

INTRODUCTION

Peritonitis is an inflammatory process of the peritoneum caused by any agents, such as bacteria, fungi, viruses, drugs, digestive secretions, granulomas, and foreign bodies. The clinical spectrum of peritonitis may also be categorized in accordance with the pathogenesis as primary, secondary or tertiary peritonitis.[1]

Besides, Peritonitis is one of the most significant infectious problems for the surgeon. In spite of the progress in antimicrobial agents and of the intensive care treatment, the peritonitis mortality rate exceeds 10 to 20%, which remains a high figure.[2]

Consequently, it is required to reproduce scoring systems that permit to determine the intra-abdominal infection severity, to ratify the effectiveness of the treatment in order to assist in the calculation of an individual risk of selecting patients who may need a more aggressive approach and, also, to get sufficient data for a prognosis.

Acute Physiology and Chronic Health Disease Classification System II (APACHEII) is widely used in patients in the emergency room and it considers many clinical parameters. The literature describes a good correlation of this score with mortality in perforated peritonitis, including indicators such as the type of peritonitis and causes of perforation. Yet, its outcome is complex and it can only be calculated after 24 hours in the intensive care unit. In the meantime, MPI has demonstrated similar efficacy in a similar series of patients with good precision, as well as offering a very simple way of handling the clinical parameters required, since they are routinely requested and registered in the surgical.[2,3]

Simplified Acute Physiology Score (SAPSII), Multiple Organ Dysfunction Score (MODS), Sepsis-Related Organ Failure Assessment Score (SOFA), Multiple Organ Failure Score (MOF) are scores suitable to predict mortality in patients with peritonitis who are unable to

forecast" ongoing infection that require a relaparotomy. The SAPS II score is determined from 12 physiological variables and 3 disease-related variables and ranges from 0 to 163 points. MODS score is calculated by using a score ranging from 0 to 4 for each of the respiratory, hematological, hepatic, cardiovascular, renal parameters as well as by the Glasgow Coma Scale, with a final score varying from 0 to 24 points.

SOFA is also calculated by using a score ranging from 0 to 4 for each of the respiratory, cardiovascular, hepatic, hematological, renal and Glasgow Coma Scale parameters, with a final score varying from 0 to 24 points. MOF Index is calculated by using a score ranging from 0 to 2 points (0: normal function, 1: organ dysfunction, 2: organ failure) for each of the respiratory, cardiovascular, renal, hepatic, hematologic, gastrointestinal and central nervous system, with a final score varying from 0 to 14 points. Higher scores are related to an increased risk of morbidity and mortality.[4]

In 1983, Wacha and Linder developed the Mannheim Peritonitis Index (MPI) in a retrospective study of 1253 patients with peritonitis, in which 20 possible risk factors were considered. Out of these factors, only eight proved to be of prognostic importance and were placed in the IPM, classified according to their predictive power. IPM had as aim to classify the severity of peritonitis or intra-abdominal infections and to identify patients requiring rapid intervention and aggressive treatment, using easily collectible parameters through clinical examination and surgical exploration. IPM score takes into account: age; sex; organ dysfunction; presence of malignancy; source; evolution time> 24h; and peritoneal exudate characteristics, and for each parameter different values were assigned, with a final score varying from 0 to 47 (Annex A). Patients with a score greater than 26 were defined as having a high mortality rate for severe peritonitis with good specificity (79%), sensitivity (84%) and accuracy (81%).

The use of MPI is effective in reducing complications as well as in improving the success of the individualized therapeutic approach. Thus, the current study was performed to evaluate the efficacy of MPI in the prognosis of patients with peritonitis in HSCMV, taking into account that there are few published studies to evaluate the validity of this prognostic index at the national level.

This study aims to evaluate the effectiveness of MPI to predict mortality in patients with peritonitis in HSCMV. Specific objectives are to verify the prevalence of risk factors for mortality of patients with peritonitis; to identify the peritonitis mortality rate; to relate hospitalization time to the patients score in the score and to evaluate the IPM score of patients with peritonitis who died or survived.

METHOD

A retrospective cohort study was conducted after the approval of the Ethics Committee in Research (CEP) with human beings of EMESCAM, under the number 50831415.0.0000.5065. Patients of both sexes, over 15 years of age, admitted to the HSCMV from January 2010 to December 2, 2015, were selected to perform procedures: exploratory laparotomy (code 0407040161), appendectomy (code 0407020039), videolaparoscopic appendectomy code 0407020047), surgical treatment of diverticulum of the digestive tract (code 0407010289), partial gastrectomy with or without vagotomy (code 0407010130).

The online medical record system MV2000 was deployed at the HSCMV in 2010, but

the search for medical records in this system is only allowed from codes of procedures performed, not through diagnosis. Thus, a number of 1285 of patients was obtained through the aforementioned codes research, however, only 75 fit the diagnosis of peritonitis with all the following inclusion criteria contained in the collection form as in Annex B. The inclusion criteria are: male and female older than 15 years; a surgical description documented in the chart confirming the diagnosis of peritonitis and with characteristic of the exudate; origin of non-colonic sepsis; extension of peritonitis; presence or absence of malignancy; presence or absence of organ dysfunction (bowel obstruction / paralysis ≥24 h or complete mechanical obstruction, oliguria <20 mL / h, creatinine> 177 μmol / L or 2.32 mg / dL, urea> 167 mmol / L or 467.8 mg / dL, hypodinamic or hyperdynamic shock, pO2 <50 mmHg, pCO2> 50 mmHg) and time of evolution> 24h.

After analyzing all inclusion parameters, merely 32 patients met all the criteria. By virtue of the small numbers obtained, it was necessary to include patients who did not obtain arterial blood gas analysis at admission, however, were stable at physical examination and with other laboratory tests within normal limits, excluding a possible organ dysfunction. Patients with peritonitis who did not present all the data required to calculate MPI in the medical records, as those who died within the first 24 hours of hospitalization were excluded from the study.

The analyzed data were stored in an Excel 2013 worksheet in which are included the following data: patient´s care code, age, sex, urea, creatinine, oliguria, pO2, pCO2, presence of shock, bowel obstruction > 24h, presence or absence of malignancy, non-colonic origin, extension of peritonitis (localized or diffuse), characteristics of exudate (clear, purulent or fecal), status (discharge or death), date of admission and hospital discharge / death, days of stay and IPM score.

The smallest possible score for MPI is 0 when there are no risk factors, and the highest is 47 when there are all risk factors. Regarding the MPI score, the patients were divided into two groups, based on the cut-off point obtained in which there was a greater significance in predicting mortality by the HSCMV profile.

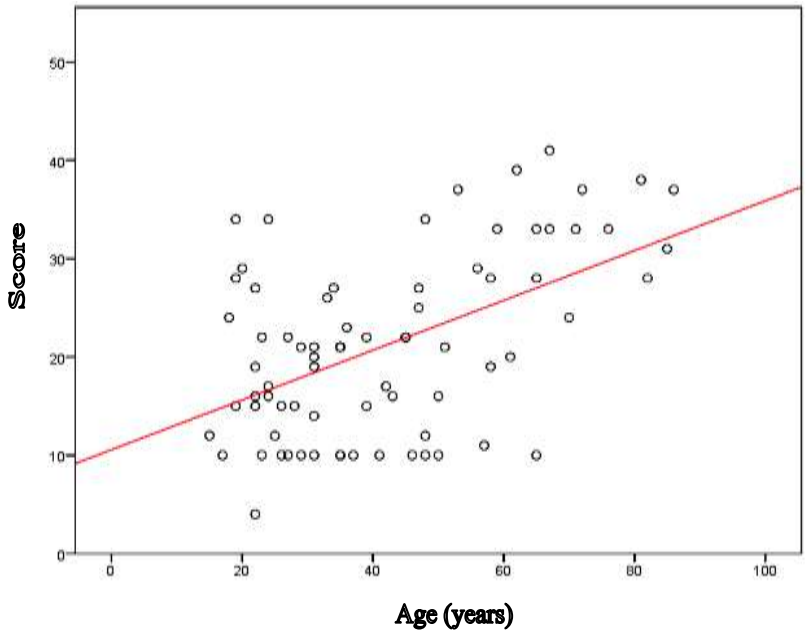
The Chi-square or Fisher's exact test (when at least one score is expected to be less than 5) was used to verify association between qualitative variables. However, the Spearman correlation coefficient was used to verify association between quantitative variables. The comparison between groups was achieved by the non-parametric Mann-Whitney test. In order to calculate Specificity and Sensibility, a ROC curve was performed.

After the analyses of the scores with mortality, specificity and sensitivity, the best cutoff point was chosen by comparing all scores. Statistical analysis was achieved with SPSS software version 23, with a significance level of 5%.

RESULTS

Out of 75 patients diagnosed with peritonitis enrolled in the medical chart, and filling in the inclusion factors, were selected for this study. The ages of these patients ranged from 15 to 86 years, with a mean age of approximately 42 years, with a standard deviation of 18.9 years. It was observed that 42 patients were male, corresponding to 56%, and 33 females, corresponding to 44%. Of this total of patients, 11 were deaths, showing a mortality rate of 14.67%.

As stated by Graph 1, it is possible to identify a linear and positive relationship between age and the score, that is, for higher age values there are higher values of the score with a correlation coefficient of 0.418 and p-value = 0.000.



Graph 1 – Age dispersion in relation to IPM
Resource: author.

When observing the causes, Acute Inflammatory Abdomen was the most prevalent with 58 cases (77.33%). Among them, patients with acute appendicitis were found in degrees III, IV and V, with 9 cases (12.00%), 44 cases (58.67%), 2 cases (2.67%), and 1 case of acute cholecystitis and 1 case of pelvic inflammatory disease (DIPA) with 1.33% each. The second most prevalent cause was Acute Perforation Abdomen with 14 cases (18.67%), 1 case of Perforated Diverticulitis (1.33%), 8 cases of postoperative peritonitis (10.67%), 1 case of rupture (1.33%), 1 case of firearm trauma (FAP) (1.33%) and 3 cases of perforated ulcer (4.00%). The other causes are displayed in Table 1 and 2. The main death factor was postoperative peritonitis with five deaths, corresponding to 45.5% of the total deceased

Table 1 – Distribution of peritonitis causes

Causes	Frequency	%
Acute Inflammatory Abdomen	58	77,33
Acute Hemorrhagic Abdomen	1	1,33
Obstractive Acute Abdomen	1	1,33
Acute Abdomen Drilling	14	18,67
Post-Puncture Contamination	1	1,33
Total	**75**	**100%**

Resource: author.

Table 2 – Distribution of peritonitis specific causes

Causes	Frequency	%
Acute Inflamatory Abdomen		
Appendicitis grade III	9	12,00
Appendicitis grade IV	44	58,67
Appendicitis grade V	2	2,67
Acute Cholecystitis	2	2,67
DIPA	1	1,33
Acute Hemorrhagic Abdomen		
Ruptured ovarian cyst	1	1,33
Obstractive Acute Abdomen		
Neoplasia	1	1,33
Acute Abdomen Drilling		
Perforated diverticulitis	1	1,33
Postoperative	8	10,67
Ruptured bladder	1	1,33
Perforated ulcer	3	4,00
Trauma	1	1,33
Post-puncture contamination		
Peritoneal dialysis	1	1,33

Total	**75**	**100,00**

Resource: author.

Preoperative duration was greater than 24 hours in 61 cases (81.30%). Purulent exudate was the most frequent, corresponding to 58 cases (77.30%). The extent of peritonitis, commonly found in the current study, was diffuse with 48 cases (64.00%). In only 9 cases (12%), peritonitis was of non-colonic origin. With regard to the organic dysfunction, 31 cases (41.33%) and only 7 cases (9.30%) of oncological patients prevailed, conforming Table 3.

Table 3- Distribution of IPM variables among patients who died and those who survived.

Risk Factor	Total (n = 75)	Total (%)	Discharge (%)	Death (%)	*p*
Age > 50 years	22	29,33	59,1	40,9	0,000
Female	33	44	81,8	18,2	0,520
Dysfunction of Organs	31	41,33	35,5	64,5	0,000
Malignancy	7	9,30	14,3	85,7	0,000
Duration > 24h	61	81,30	83,6	16,4	0,678
Non-colonic Origin	9	12,00	66,7	33,3	0,121
Difuse peritonitis Exudate	48	64,00	79,2	20,8	0,085
Clear	1	1,30	100	0	
Purulent	58	77,30	84,5	15,5	0,876
Fecal	16	21,30	87,5	12,5	

Resource: author

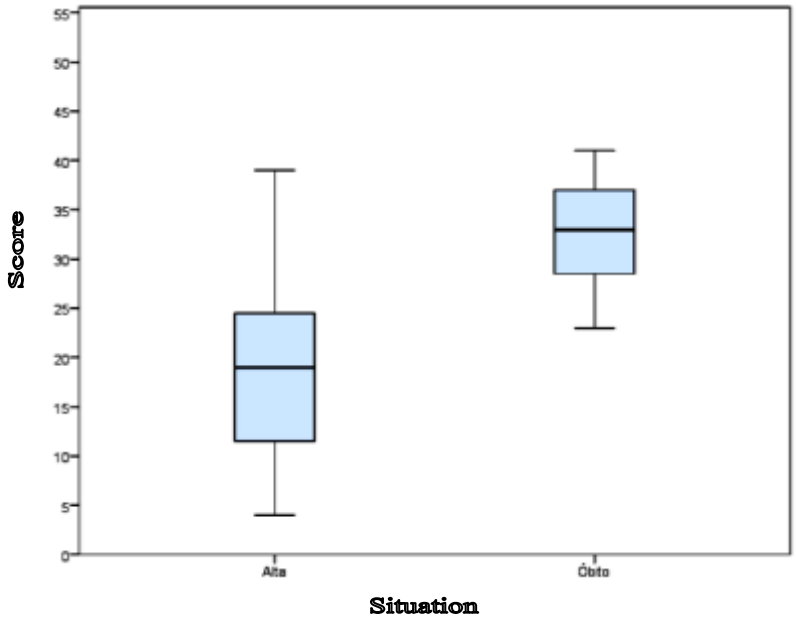
Comparando as variáveis do IPM nos dois grupos (sobreviventes e falecidos) constatou-se que idade maior do que 50 anos, presença de malignidade e pacientes com disfunção de órgãos tiveram significância estatística, com $P < 0,05$.

O IPM variou entre os 75 pacientes de 4 a 41 pontos, com média de 21,2 pontos, mediana de 21. No entanto, entre os 11 (14,67%) pacientes que foram a óbito o escore variou de 23 a 41, com média de 32,8, mediana de 33. Entre os 64 (85,33%) pacientes que sobreviveram o IPM variou de 4 a 39, com média de 19,2 e mediana 19 (Tabela 4 e Gráfico 2).

Table 4- MPI Variation in relation to the situation (discharge or death)

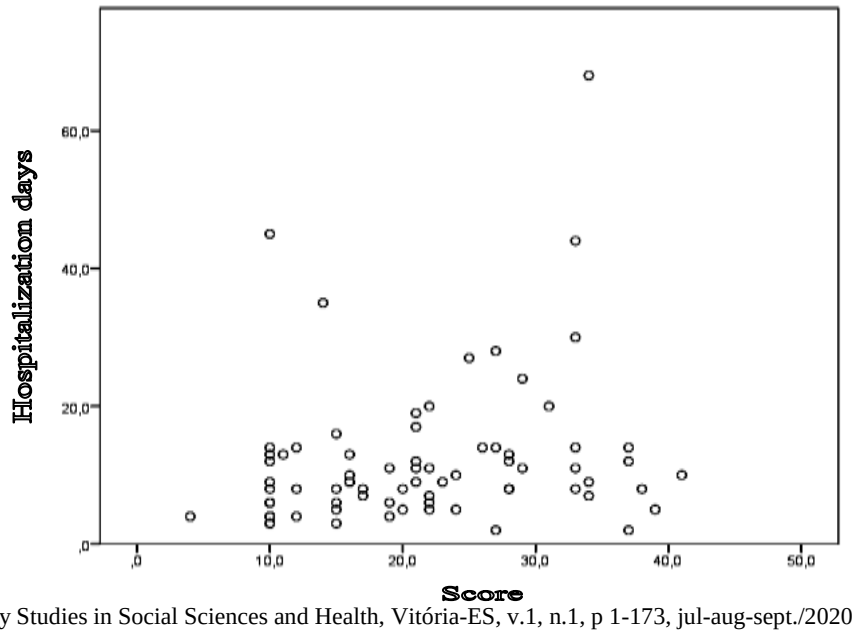
	Score					
	Minimum	Maximum	Average	Mean	Standard Deviation Padrão	Total

						(n= 75)
Discharge	4,0	39,0	19,2	19,0	8,2	64
Death	23,0	41,0	32,8	33,0	5,6	11



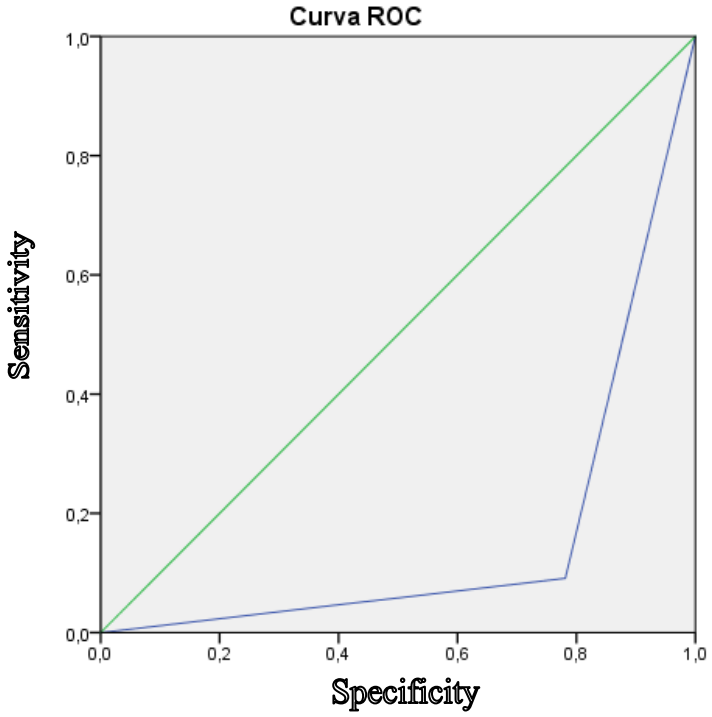
Graph 2 – Median of MPI in relation to the situation (discharge or death) through the no-parametric Mann-Whitney test, which showed statistical significance with p=0.000.
Resource: Author

Among all patients, it was noted that the average length of hospital stay was roughly 12 days, with a minimum stay of 2 days and a maximum of 68 days. As reported by Spearman's nonparametric correlation, there was a positive and a weak association with a coefficient of 0.281 and a value of p = 0.015 indicating an expressive but non-linear correlation.



Graph 3 – Dispersion of hospitalization days in relation to MPI through Spearman´s nonparametric correlation, which showed statistical significance with p = 0.015.
Resource: Author.

The outcome agrees with the score (<27 and ≥ 27) on a regular basis, the Kappa's value index is 0.464, considerably greater than zero, (p-value = 0.000). The cut-off point of 27 points was acquired by evaluating the Kappa Index of concordance. By means of this best cut-off point, we calculated: sensitivity of 90.90% and specificity of 78.13% through the ROC curve (Graph 4). The Positive Predictive Value of the IPM was 71.40%, that is, this is the probability of an individual evaluated with a score ≥27 presenting a death situation. The Negative Predictive Value of 98.00%, that is, the probability of an individual with a score <27 to be high is 98.00%.

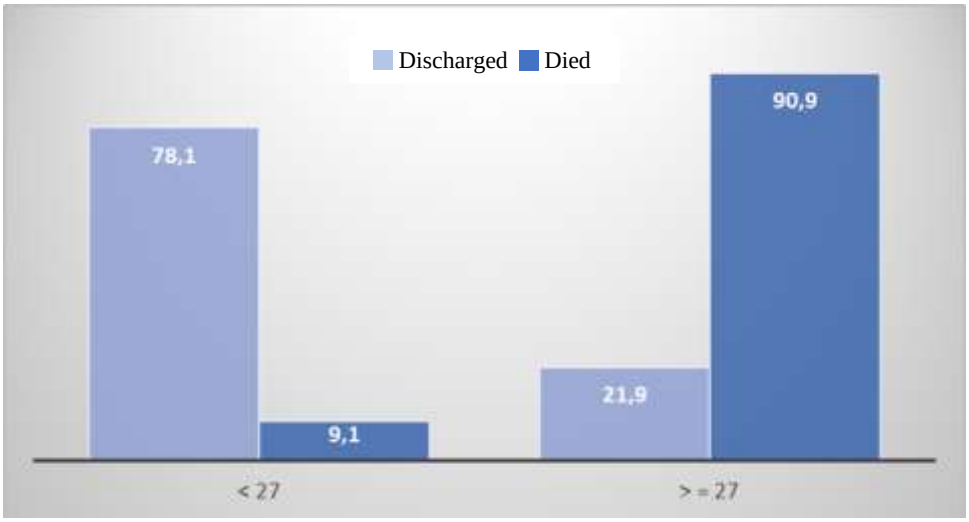


The percentage of mortality of patients with a score below 27 wa 9.10% ando f patients with a score ≥ 27 was 90.90% (Table 5 and Graph 5).

Table 5 – IPM Scores Distribution in relation to the situation (discharge or death)

Score		Situation		
		Discharge	Death	**Total**
< 27	**n**	50	1	51
	%	78,1%	9,1%	68,0%
≥ 27	**n**	14	10	24
	%	21,9%	90,9%	32,0%
Total	**n**	64	11	75
	%	100,0%	100,0%	100,0%

Resource: author.



Graph 5 – IPM Scores in relation to the situation (discharge or death)
Resource: author

DISCUSSION

Multicenter studies have corroborated that in-hospital mortality of peritonitis continues to be high, nearly 19.5% 7 although some studies reach 60% .[8,9,10]

Many factors influence the prognosis and outcome of peritonitis, possibly ranging from a specific disease to patient-related factors and therapeutic interventions. Nevertheless, the outcome is difficult to predict in most of these patients.

The precocious classification of peritonitis severity may help to determine surgical and medical conduct. Yet, scoring systems, such as the Mannheim Peritonitis Index, are required to aid in risk stratification and evaluation of new diagnostic modalities

and therapeutic advances, as in comparing treatment outcomes from different clinics.

When assessing all risk factors in patients with peritonitis in the HSCMV from 2010 to 2015, it was possible to delineate a profile indicating higher mortality. By observing the age risk factor, it was calculated that the mean age among the deceased in this study was roughly 64 years. This result was consistent with the average of 60 years of other studies.[11,12]

For the patients who survived, the WPI of this study ranged from 4 to 39 points, with an average of 19.2, higher than the average of previous studies.[2,11,12] Yet, it was equivalent to another reference.[9]

Comparing this work with other literature,[2,9,11,12] an equivalence was noted in the MPI values of patients who died. The current study observed that these values ranged from 23 to 41 points, with an average of 32.8 points. When analyzing the mortality rate of the studies, it presented 14.67% of mortality, similar to the rate of 11.70% noted in another article[11]. Nonetheless, it was divergent from others, since these studies[9,10] used samples with a higher risk profile for mortality, selecting cancer patients and the Intensive Care Unit, respectively.

Age greater than 50 years and presence of malignancy and organ dysfunction were statistically meaningful, all with p = 0.000. Of those who died, 81.8% were aged> 50 years old with a 40.9% mortality rate. As a result, mortality was proportional to the increase in age.

In relation to malignancy and to mortality, the statistical significance was also verified. Of those 11 deaths in this study, 54.5% were cancer patients. This relationship had already been found in other studies.[2,12]

The presence of organ dysfunction increases the risk of death in patients with peritonitis (p = 0.000), considering that in this study all patients who died had organ dysfunction. This result is similar to the one found in other literature.[2,12,10]

Mortality was not affected by sex and duration of peritonitis, which was longer than 24 hours. All patients who had a disease duration greater than 24h died, which was found in other studies.[2,12]

The risk of death in patients with non-colonic origin peritonitis is higher than in those with colonic origin, conforming another reference.[2] The non-colonic origin is a risk factor for IPM. However, in this study, this relationship has not been proven, as in other previous studies.[10,12]

It was possible to observe that 48 patients had diffuse peritonitis, of which 10 died and 38 were discharged. However, of all 11 deaths, 90.9% had diffuse peritonitis. Yet, there was no significant difference between extension and mortality, as in another article.[2] In contrast, other studies[10,12] presented a meaningful relation.

In the current study, 77.30% of patients presented purulent exudate, found in 81.8% of those who died. Other surveys also presented this profile.[2,10]

The mean length of hospital stay for patients who were discharged was approximately 11 days, for those who died, approximately 14 days, which disagreed with another study that analyzed only cases of patients in intensive care.[9] The total mean value was approximately 12 days. There was a statistical significance between days of hospitalization and score, as stated by another literature.[9] After analysis of Graph 2, it was noted that this association was not linear, but positive. Probably, the higher the score, the greater the severity of the patient, the more likely he or she will be to die, to stay less hospitalized or to stay longer on account of complications.

After comparing the data for each number of points of the score, one verified that the patients who died, 90.90% scored higher than or equal to 27 for the MPI. Of those who did not die, merely 21.90% presented this score. Nevertheless, one infers that the cut-off point for predicting mortality with MPI, found in the profile of patients who were under observation in the HSCMV, in the period from 2010 to 2015, is 27 points. The sensitivity for mortality is 90.90% and the specificity is 78.13%, similar to those found in another study, [2] with sensitivity of 95.90% and specificity of 80%. Reference literature[7] found sensitivity of 86.00%, specificity of 74% and accuracy of 76%. In the study[10] conducted at the National Cancer Institute (INCA), the cut-off point found was 21, which evaluated the oncology patients whose risk of mortality was highest. Their sensitivity was 87.30% and their specificity was 41.20%.

The cut-off point 27, demonstrated in the current study, revealed a statistical significance. Nonetheless, the use of it for prognostic evaluation in HSCMV patients is recommended.

CONCLUSION

Based on this study, it is possible to presume that the main causes of peritonitis were of non-colonic origin. One may note that the most frequent specific diagnosis in HSCMV patients was acute appendicitis, but it was not the main factor of death. The main cause of death was postoperative peritonitis. Of the risk factors assessed, age greater than 50 years, organ dysfunction and presence of malignancy were statistically significant. There was a positive and non-linear correlation with the patients' score, regarding hospitalization time, making this time a risk factor. However, there is no relation directly proportional to the score. It was also possible to indicate a percentage of peritonitis mortality in the HSCMV, consistent with other literature.

The expressive majority of confirmed deaths had MPI $\geq$ 27 points is in accordance with other literature, indicating that MPI was efficient in estimating the risk of death and in categorizing patients into risk groups. This stratification assists in the determination of a prognosis, in the selection of patients for intensive care and in the definition of operative risk, contributing, this way, to the choice of the nature of the operative procedure, such as damage control or definitive procedure.

Nevertheless, when this scoring range is reached, a more aggressive and fast approach must be established, possible complications must be observed, and an individualized and precise behavior must be adopted.

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Conflict of Interest: None.

ANNEXES

ANNEX A – The score system used to calculate the Mannheim Peritonitis Index (MPI)

FACTORS	ADVERSE	POINTS	FAVORABLE	POINTS
Age	>50	5	<50	0
Sexo	male	5	female	0
Organic Dysfunction*	present	7	absent	0
Malignancy	present	4	absent	0
Time of evolution	> 24 horas	4	< 24 horas	0
Origin	non-colonic	4	colonic	0
Extension of peritonitis	generalized	6	localized	0
Peritoneal Exudate	fecal	12	clear	0
	purulent	6		

Resource: Correia, 2001.

ORGANIC DYSFUNCTION*	
KIDNEY	Creatinine > 177umol/L
	Urea > 167mmol/L
	Oliguria < 20mL/h
LUNG	PO2<50mmHg
	PCO2<mmHg
SHOCK	Hypodynamic or Hyperdynamic
BOWEL OBSTRUCTION	Paralysis >24 hours or complete mechanical obstruction

Resource: Correia, 2001.

ANNEX B – Data sheet used to collect data from patients selected in the study.

Patient	Age	Sex	Cr	Ur	Oliguria	pO_2	pCO_2	Schok

Bowel Obstruction	Oncolo-gical	< 24h	Origin Non-colonic	Extension	Exsudato 1- clear 2- purulent 3- fecal	Situation 1- discharge 2- death	Date of admission	Departure date

No images were not uploaded by the author.

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ESTUDOS INTERDISCIPLINARES EM CIÊNCIAS SOCIAIS E DA SAÚDE
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Original Article

THERAPEUTIC BENEFITS OF DRY NEEDLING IN ADULT PATIENTS WITH CHRONIC LOW BACK PAIN

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Keywords

Spine;
Low Back Pain;
Chronic Pain;
Trigger Points;
Microwaves.

Abstract

Objective: To evaluate the therapeutic benefits of dry needling in adult patients with chronic low back pain. **Methods:** A pilot study of a randomized clinical trial with blind evaluator was conducted in a convenience sample composed of 10 patients who underwent an initial questionnaire and the application of scales by the blind evaluator through the following instruments: Initial questionnaire, Roland Morris Questionnaire and Visual Analogue Pain Scale - EVA. After application of the scale and questionnaires, the patients were randomly divided into two groups: one group being submitted to the protocol involving dry needling and another group that underwent manual myofascial release therapy. **Results:** The majority of the individuals were female (60%), with a mean age of

44.90 ± 12.26 years. There was a considerable improvement in pain evaluated in the visual analogue scale (VAS), before and after the study, merely in the group treated with dry needling p = 0.041. There was no significance in the Manual Myofascial Release group test for pain assessment. The functional incapacity of the patients in the dry needling group and in the control group did not present important results. **Conclusion:** Although further studies would be necessary on the therapeutic benefits of dry needling, it is plausible that this technique provides a considerable reduction of pain in patients with chronic low back pain. Although not showing any meaning regarding functional incapacity, we observed a trend in favor of dry needling.

INTRODUCTION

The sensation of pain is essential for survival, since it is the first indicator of any tissue injury[5]. By the 1950s and 1960s, the concepts of pain underwent deep modifications, [14] converting itself from a simple neurophysiological signal to a psychophysiological phenomenon. This change occurred in new studies, indicating that the severity of the pain is probably related to specific physiological symptoms, added to the effect of one or more psychological variables[6], the same way a chronic low back pain has been associated with psychophysiological factors due to its duration, affecting the social life of man. [3,7]

Lumbar pain, known as a disability by the WHO, translates itself into a disadvantage that limits or impedes the full performance of physical activities[11]. The International Association for Pain Study (IASP), [14] considers chronic low back pain, when it lasts for more than three months.

Considering that chronic low back pain does not come from specific diseases, but from a set of elements, it is important to take into account the profile of the individual with chronic low back pain. The psychological and socio-demographic components (age, sex, income and schooling) play a meaningful role in the onset of low back pain, contributing for a good response to treatment [2,7,16].

Patients who have low back pain spend a great deal of time and resource searching for a treatment. Physical therapy is a crucial resource in the rehabilitation of the patient with chronic low back pain and its main objective is to allow him to return to work and daily activities. Thus, functional restoration should be started as early as possible in order to minimize the effects of immobilization and to protect the lumbar spine from problems [3,6].

Several painful problems, including chronic low back pain, resulting from abnormal stresses that the fascia supports, are commonly not so severe pains and generally bearable. However, its duration, persistence, and frequent recurrences rapidly become intolerable[1]. Trigger points are located in these areas of tension, which are a common source of pain, and they have been commonly related to chronic low back pain[15]. Consequently, dry needling comes as an essential resource in the treatment of chronic low back pain, as it is narrowly defined as an "intramuscular" procedure involving the isolated treatment of "trigger points" [10].

Dry needling involves the introduction of needles into areas of the muscle that have motor alterations in an effort to relieve pain, decrease muscle tension, and restore normal muscle function[2]. The dry needling technique has been associated with intramuscular electrical stimulation, and it is essential to observe that this association with intramuscular electrostimulation permits the electrostimulation to reach target tissues in a deeper way because of the needles used[4].

This theme was developed because of the increase in patients with chronic low back pain in search of a faster and more effective treatment. This study is a descriptive and transversal applied research, performed in two moments: first, with a bibliographical review and then a field research, through a case series study. Accordingly, we sought to verify the therapeutic benefits of dry needling in adult patients with chronic low back pain.

METHODS

A pilot study of a randomized clinical trial with blind evaluator was conducted at the Clinic of Physiotherapy School of the Santa Casa de Misericórdia School of Science (EMESCAM) from June 2016 to December 2016, in a sample of convenience constituted by 10 patients. Initially, it was applied a questionnaire through an interview with blind evaluator, who did not participate in the choice of patients. The following were included: patients with complaints of mechanical postural low back pain; with pain in the region of the iliocostal muscles and in the longest of the chest in the chronic period greater than 12 weeks; patients of both genders and those aged between 18 and 65 years, who agreed to sign the EHIC. Patients diagnosed with chronic low back pain or who had a diagnosis of lumbosacatalgia; patients with fear of insurmountable needles; with allergy to nickel (needles are made of this metal), with coagulation problems (even if you are on anticoagulant therapy, there is risk of bleeding) and people with lymph nodes removed (because of the risk of lymphedema) were excluded.

Those who fulfilled the inclusion criteria submitted themselves to an initial, questionnaire and to a scale application by the blind evaluator through the following instruments: Initial Questionnaire, Roland Morris Questionnaire and Visual Analog Pain Scale - EVA. The interviews were individual and the study supervisor previously trained the researchers for the application of the instruments.

An initial questionnaire was utilized with the purpose of tracing the patients' profile. Data such as name, telephone, age, sex, marital status, occupation, socioeconomic / cultural history and life habits were obtained. This questionnaire was applied on their first day just before treatment was started.

The functional disability of the patients was corroborated through the Roland-Morris questionnaire, a specific instrument that allows the disability evaluation in individuals with low back pain. It consists of 24 items related to daily life activities and the questions have a dichotomous answer (yes or no). Its score was calculated through the total number of questions, ranging from zero (absence of disability) to 24 (severe disability). The Roland Morris questionnaire was applied through the blind assessor on the first and last day of treatment and the initial score was compared to the final score.

The Visual Analogue Scale (VAS) utilized to assess patients' pain, provided a measure of pain intensity in the patient. This instrument proved to be important to verify if the treatment was effective as well as to know which procedures have given better results, according to the degree of

improvement or worsening of pain. To assess the patient's degree of pain, such questions as, "Do you have pain? How do you rate your pain?" were asked. There was an account of the observations about what they said. In order to the patient's pain intensity, a score of 0 to 10 was used, distributed as follows: 0 to 2 mild pain, 3 to 7 moderate pain, 8 to 10 intense pain and 10 is the maximum pain level that can be tolerated by the patient.

After the application of the scale and the questionnaires, the patients were randomly divided into two groups with selection using envelopes numbered from 1 to 10. Group A (5 patients), who was submitted to the protocol involving dry needling, and group B (5 patients) who underwent manual myofascial release therapy. The treatment was carried out in a reserved environment resulting from the exposure of the patient's chest.

In the Treatment Protocol of group A, the patients were submitted to the technique of dry needling of the iliocostal and very long muscles of the thorax bilaterally at trigger points, using needles (DONGBANG ®) of 0.3 x 0.6 mm. After locating an active trigger point, the overlapping skin was cleaned with 70% alcohol, and the needle was subsequently inserted, penetrating skin and muscle to a depth of nearly 20 and 25 mm at the trigger point. The patient was always in the prone position. Once inserted at the trigger point, the needle was moved in multiple directions until the first local contraction response was obtained. The needles were coupled to electrostimulation through the SIKURO® device with a frequency of 4HZ, for 10 minutes, dosed in intensity according to the patient's perception. Patients were advised to report pain or any increase in their symptoms after the intervention. Subsequent to the application of the technique, the needles, as soon as they were withdrawn from the patient, were discarded in the Descarpack, a safe and resistant picker of sharp materials, guaranteeing, this way, the total protection against perforations and leaks of contaminated fluids. The treatment of patients took place in the morning, twice a week - lasting 30 minutes each, for four weeks, with the supervision of two therapists.

The patients in the B group were submitted to the manual myofascial release technique in the region of the iliochalost muscles and very long of the thorax bilaterally, for 10 minutes. Subsequently, deep heat was performed with microwaves in the lumbar region, for 10 minutes with a frequency of 60%. The treatment of these patients occurred in the morning, twice a week - lasting 30 minutes each, for four weeks, along with group A, with the supervision of two therapists.

The descriptive analysis of data collected was achieved taking into account frequencies and percentage for qualitative variables and data summary measures as mean, median and standard deviation for the quantitative variables. The Wilcoxon test was used to verify the association between initial and final VAS, and Roland Morris initial and final in an intragroup way as well as between the myofascial release and dry needling groups. The Mann-Whitney test was used to compare age in both groups. The values were considered statistically expressive when the value was $p < 0.05$. The research was approved by the Ethics Committee (CEP) of the Superior School of Sciences of the Santa Casa de Misericórdia de Vitória (EMESCAM), under the number of opinion 1,612,115 on June 28, 2016.

RESULTS

The sample of this study consisted of 10 patients from the physical therapy school of EMESCAM, where 6 were female (60%) and 4 male (40%), with a mean age of ± 12,26 years.

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Table 1. Mean age and sex distribution between groups of patients treated with Dry Needle and Manual Myofascial Release

Age	44,90 ± 12,26
Sex	6(F) / 4(M)

The initial pain data did not present different values. This shows that the groups had the same pain index at the beginning of the study. When compared intra-group, we observed that there was an improvement in the indicator evaluated in the visual analogue scale (VAS) before and after the study only in the group treated with dry needling, according to table 2.

Table 2. Mean of the initial and final Visual Analog Scale between groups of patients treated with Dry Needling and Manual Myofascial Release

	Dry Needling Group	Value p	Myofascial Release Group	Value p
Initial VAS	8±0	*0,041	7±2	0,888
Final VAS	6±1		7±0	

*p<0,05 considered significant in the Wilcoxon test

Initial data from the patients' disability assessment did not present different values, which shows that the groups had the same disability index at the beginning of the study. When compared intra-group, there was no improvement in the indicator evaluated in the Roland Morris Questionnaire before and after the study, as stated in table 3.

Table 3. Mean of the initial and final Roland Morris Questionnaire between groups of patients treated with Dry Needling and Manual Myofascial Release

	Needling Dry Group	Value p	Myofascial Release	Value p
Inicial Roland	14±5	0,068	14±4	0,465
Final Roland	10±4		11±7	

*p<0,05 considered significant in the Wilcoxon test.

DISCUSSION

Women present a higher prevalence of chronic low back pain than men, due to anatomic-functional peculiarities added to other aspects that potentiate this risk[16,8,11]. These data corroborate with those found in this study, where we verified a frequency of 60%. The degenerative changes and overloads in the work explain these findings[16]. In relation to age, there was a higher frequency of individuals over the age of 40 years, similar to the study by Masiero et al.8 where the mean age was 48.1 years.

Previous studies have investigated the effect of dry needling in patients with low back pain and have shown that it is possible that dry needling is effective in some patients[2,9]. Our results showed that only in the dry needling group there was significant improvement, before and after the study, and for a short period of treatment. The results of the present study are consistent with the data found in a study conducted by Kietris et al.14 that in 4 weeks of treatment dry needling had a strong positive effect when compared to other treatments. The Manual Myofascial Release control group showed no difference in the visual analogue scale (VAS) before and after the studies.

When related to the function, there was no significant difference in both the dry needling group and in the Manual Myofascial Release therapy group. Even so, there was a tendency for a better result in the dry needling group with the p-value reaching close to the significance, compared to the control group. These data go according to the results found in a study conducted by RAYNEI.C. E, et al.4, where patients were able to resume their functionality and return to their recreational and professional activities after dry needling therapy without pain.

CONCLUSION

There was an improvement in pain in the patients treated with dry needling.

Even though not significant, the data found tended to have a clinical relevance of significant improvement in aspects of functional disability in favor of dry needling.

Despite the fact that a larger and more in-depth study is needed on the therapeutic benefits of dry needling, it is plausible that this technique provides a considerable reduction of pain in patients with chronic low back pain, emphasizing the technique of manual myofascial release therapy.

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ESTUDOS INTERDISCIPLINARES EM CIÊNCIAS SOCIAIS E DA SAÚDE
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Original Article

INFLUENCE OF MEDULAR INJURY AND WHEELCHAIR TIME IN RESPIRATORY AND TOSSE MUSCLE FORCE

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Keywords

Spinal Cord Injuries;
Maximal Respiratory Pressures;
Cough

Abstract

Objective: To evaluate respiratory muscle strength and peak cough flow in patients with spinal cord injury and correlate muscle strength and peak cough flow over time in a wheelchair and the level and severity of spinal cord injury. METHODS: This is a case series cross-sectional study of 23 participants. The profile data of the individuals were collected through a questionnaire developed by the researchers, the spinal cord injury was assessed by the American Spinal Injury Association (ASIA) scale, respiratory muscle strength was measured by a manovacuometer and peak cough flow by a Peak Flow. Results: All participants had weakness of the expiratory musculature and the data suggest that

the higher the level of the lesion, the greater the weakness of the inspiratory musculature. The quadriplegic patients had reduced inspiratory muscle strength and cough when compared to paraplegics. In addition, the relationship between wheelchair time and peak cough flow was negative and statistically significant ($r = -0.45$, $p = 0.01$). Conclusion: The higher the level of the spinal cord lesion and wheelchair time, the greater the impact on the respiratory muscles and the efficacy of the cough. Therefore, physical therapy acts in an essential way in rehabilitation, reducing complications and consequently improving the quality of life.

INTRODUCTION

It is estimated that there are worldwide nine in fifty cases of spinal cord injury per million inhabitants[1,3] per year, and that, according to Vall et al[3], in Brazil, alone, there are more than 130,000 people with such injury.

The importance of the medulla is due to the conduction of information between the periphery and the brain. An injury to this structure may determine changes in sensitivity, motor function and respiratory muscles, with resulting impairment of lung function. As well the respiratory changes that is possible to be observed according to the injured spinal cord level, the patient usually uses the wheelchair, which does not allow him to maintain an auspicious posture for respiratory mechanics[4-8].

The area of lung capacity deficits will be determined by the level and extent of injury, and the dissimilar structures of the respiratory tract affected. The greater the extent of the injury, the greater will be the reduction in lung volume and capacity, and cough strength, as a consequence of respiratory muscle fragility[9-12].

The leading sources of morbidity and mortality, either in the acute or chronic phase of spinal cord injury, are the respiratory complications. In relation to the general population, the life expectancy of these patients can be lowered by up to 3 times[5,13,14].

Physical therapy in assisting individuals with spinal cord injury is important because it holds resources that can promote progress in respiratory function, thus reducing complications and hospitalizations, improving the quality of life[15]. The objective was to assess respiratory muscle strength (MIP and MEP) and peak cough flow (PFT) in patients with chronic spinal cord injury. There are not enough studies in the state and, therefore, it is understood that the expansion of knowledge and possible scientific evidence may contribute to the creation of new strategies for monitoring this population.

METHOD

The current study is an observational and cross-sectional research. It was marked by a case series study, endorsed by the Ethics Committee (CEP) of Santa Casa de Misericórdia de Vitória School of Sciences (EMESCAM), within the opinion number 1.310.183, on November 5, 2015. The research was held in individuals who were under monitoring at the Espírito Santo Physical Rehabilitation Center (CREFES)

in 2015, with a diagnosis of spinal cord injury, with an exception to those with associated cardiopulmonary disease, tracheostomy, cardiopulmonar, decompensation, surgical intervention or hospitalization, past three months, not located or not agreeing to engage in the survey.

For the purpose of characterizing the sample through a questionnaire created by the researchers, data regarding age, gender, race, smoking, wheelchair time and injury time were collected. Measurement of inspiratory and expiratory muscle strength was conducted by measuring MIP and MEP, respectively, with nasal occlusion using a commercial manometer. The MIP was measured from the residual volume, requesting the subject to exhale as much as possible and then to inhale through the mouthpiece. PEmax was measured from total lung capacity, requiring the individual to inhale as much as possible and then exhale through the mouthpiece[16], in agreement with Souza[17] reference values, which use the following formulas as a basis: MIP = 104 + (0.51x age) MIP = 170 + (1.03 x age).

During unaided spontaneous cough with nasal occlusion using a Respironics® Peak Flow, cough effectiveness was measured by cough flow (PFT). Measurements of respiratory muscle strength and cough effectiveness were held in the sitting and supported posture, with three consecutive measurements and considered the best value obtained. As reported by Barros and Medeiros, it was considered an ineffective cough, values lower than 160 liters / minute, a difficulty in eliminating secretions, values between 160 and 270 liters / minute and, above 270 liters / minute, an effective cough[18].

Concerning the level and extent of the lesion, the classification of the spinal cord injury was settled by neurological examination in accordance with the criteria of the American Spinal Injury Association (ASIA). Motor function was evaluated by assessing muscle strength, graded from 0 to 5, of the key muscles, and sensory, tactile and painful function was evaluated through the 28 bilateral dermatomes employing a cotton and two-pin distinct ends[19].

Following sensory and motor assessment, the level of the lesion was established, where the neurological level is the region with bilateral sensibility and bilateral muscle strength equal to or greater than three. The participants who were classified as level C4 to C8 were named as quadriplegic, and the ones as level T1 to L3 as paraplegic. In order to categorize the extent of the lesion, a digital touch was carried out in the anal sphincter region as well as the perception of the touch by the evaluator and / or a contraction of the anal sphincter 19.

In line with each variable, analyzes were held with mean and standard deviation, median (minimum and maximum) or frequency and percentage. For the purpose of verifying the association of wheelchair time with respiratory muscle strength and peak cough flow, the Pearson correlation test was applied. Simple linear regression analysis to verify the influence of spinal cord injury level for each of the dependent variables: peak cough flow, maximal inspiratory pressure, and maximal expiratory pressure. So as to compare the different classifications of peak cough flow and respiratory muscle strength between quadriplegic and paraplegic individuals, a chi-square test was performed. A significance level of 5% for all inferential analyzes was taken. The program applied was “SPSS version 23”.

RESULTS

Thirty patients were selected for the research. Out of them 4 were not located

and 3 did not consent to participate as a result of transport difficulties. Among the 23 individuals with spinal cord injury participating in the study, 13 were categorized as quadriplegic and 10 as paraplegic. Merely 6 participants agreed with the assessment of the extent of the lesion. A 3 were classified as a complete lesion - ASIA A and B and 3 as an incomplete lesion - ASIA D. (table 1)

Table 1 – Sample data on participants respiratory muscle strength in this study as well as their cough.

	N = 23
Age (Average ± SD)	32.4 (8.1)
Male sex N (%)	18 (78.3%)
Female sex N (%)	5 (21.7%)
Race N(%)	
White	3 (13%)
Brown	7 (30.4%)
Black	13 (55.5%)
Yellow	0 (0%)
Smoking N(%)	
Never smoke	16 (66.2%)
Former smoker	7 (30.4%)
Smoker	1 (4.3%)
Wheelchair time - median (min, max)* in months	102 (1.367)
PFT – median (min, max)	400 (160, 900)
Ineffective (<160)	1 (4.3%)
Effective / Weak (160-270)	3 (13%)
Effective / Strong (>270)	19 (82.6%)
Real PEmax l (average ± SD)	97.9 (36.5)
Forecast PEmax (average ± SD)	170.9 (0.2)
Real Plmax (average ± SD)	- 107.7 (28.58)
Forecast Plmax (average ± SD)	- 120.5 (4.1)
Lesion level N(%)	
C4-C5	7 (30.4%)
C6-C8	6 (26.1%)
T1-T6	5 (21.7%)
T7-L3	5 (21.7%)
Lesion extension N (%)	N=6
A - Complete	2 (8.7%)
B - Complete	1 (4.3%)
C - Complete	0 (0%)
D - Incomplete	3 (13%)

No significant association (p = 0.32) was revealed when correlating wheelchair time with respiratory muscle strength. It was possible to note a statistically significant negative, moderate correlation was noted between wheelchair time and peak cough flow (r = 0.45, p = 0.014), indicating that peak cough flow diminishes with as chair time enhances.

By comparing muscle strength between the different levels of injury, quadriplegic or paraplegic, it was noticed that quadriplegic patients had a mean MIP of -96.15mmhg (28.4), a MEP of 87.31mmhg (37.6) and a peak flow median of 390L / min (160.770). For paraplegics, the mean MIP was -119mmhg (26), the MEP 110mmhg (30.5) and the median Peak Flow 495L / min (240,900). These results indicate that quadriplegic patients are liable to have a maximal inspiratory pressure and a lower cough flow peak than paraplegic patients (p = 0.06 and p = 0.07 respectively).

Regarding linear regression, it did not provide statistical significance. Despite that, the MIP result implies that as the injury level decreases, the maximal inspiratory force increases. Nevertheless, the same was not observed for PFT and PEmax. (Table 2).

Table 2 - Linear regression analysis to verify the influence of spinal cord injury level on peak cough flow, maximum inspiratory pressure and maximum expiratory pressure.

	ß	sig
Constant	380.0	
PFT	153.0 L/min	0.73
Constant	-96.15 mmhg	
Pimax	-22.84	0.06
Constant	87.31 mmhg	
Pemax	22.69	0.14

The injury level explains 14% of the cough flow variance, 16% of the maximum inspiratory pressure and 10% of the maximum expiratory pressure.

Looking at Table 3, it can be seen that there is no significant difference in PFT between the different injury level classifications. Most paraplegics and quadriplegics had a strong and effective cough. Nonetheless, out of the 13 quadriplegic participants, 84.6% had lower than predicted MIP, 100% had lower than predicted MEP values. Sixty percent of paraplegics had lower than expected MIP and 100% lower than expected MIP, even though not statistically significant. (Table 4).

Table 3 - Comparison between tetraplegics and paraplegics according to different classifications of Peak Cough Flow (PFT).

PFT	Quadriplegics	Paraplegics	Total	Tests
≤ 160 L/min				
Yes	1 (7.6%)	0 (0.0%)	1 (4.4%)	
No	12 (92.3%)	10 (100%)	22 (95.6%)	x^2=1 p=0.80
total	13 (100%)	10 (100%)	23 (100%)	
160 -| 270 L/min				
Yes	1 (7.6%)	1 (10%)	3 (13%)	
No	12 (92.3%)	9 (90%)	20 (87%)	x^2=0.04 p=0.84
total	13 (100%)	10 (100%)	23 (100%)	
>270 L/min				
Yes	11 (84.6%)	9 (90%)	19 (82.6%)	
No	2 (15.4%)	1 (10%)	4 (17.4%)	x^2=0.67 p=0.41
total	13 (100%)	10 (100%)	23 (100%)	

Table 4 - Comparison between quadriplegics and paraplegics with values greater or less than the ideal value for minimum and maximum inspiratory pressure.

	Quadriplegics	Paraplegics	Total	Tests
Plmax				
>than the forecast	2 (15.4%)	4 (40%)	6 (26.1%)	x^2=1.77 p=0.18
< than the forecast	11 (84.6%)	6 (60%)	17 (73.9%)	
total	13 (100%)	10 (100%)	23 (100%)	
PEmax				
> than the forecast	0 (0.0%)	0 (0.0%)	0 (0.0%)	
< than the forecast	13 (100%)	10 (100%)	23 (100%)	x^2=0.04 p=0.84
total	13 (100%)	10 (100%)	23 (100%)	

DISCUSSION

The results of this study indicate that PFT decreases as wheelchair time increases, and further indicates that quadriplegic patients tend to present lower MIP and PFT than paraplegic patients. Thereby, the lower the lesion, the greater the inspiratory muscle strength. With regard to expiratory muscle strength, 100% of quadriplegic and paraplegic individuals had a lower than expected MEP.

Literature shows that spinal cord injuries generally occur in productive men age from 18 to 35 years[2,20,21]. Consequently, as in the current study, among all the 23 participants with spinal cord injury, 78.3% are male with a mean age of 32.4 (8.1) years.

Studies demonstrate that, after spinal cord injury, there is an increase in mortality rate resulting from loss of respiratory muscle activation innervated by spinal cord segments below the lesion, and consequent decrease in inspiratory and expiratory muscle strength[22,23]. In line with these results, this study revealed that all of participants had reduced inspiratory and expiratory muscle strength, and among of all 23 participants, 17 had below-predicted MIP and all had below-predicted MEP values.

Moreover, it was also found that 84.6% of quadriplegic patients had lower than expected MIP, while 60% of paraplegic patients had lower MIP, supporting the studies by Schilero et al and Barros; Medeiros[8,16] which reveal that the higher the level of the injury, the greater the impairment of the respiratory muscles. With reference to expiratory muscles, all quadriplegic and paraplegic presented values below expectations, denoting weakness of expiratory muscles.

Fonseca, Machado and Ferraz[24] claim that coughing involves four phases, and for the purpose of being effective, it is crucial that all structures in charge of it are intact, essentially the respiratory muscles. The debility of these muscles compromises respiratory mechanics, such that, on inspiration, the lungs do not expand to full capacity and, on exhalation, the power is not sufficient to produce lung compression and eliminate maximum air, compromising efficacy coughing[25,26].

Due to this respiratory muscles debility, patients with spinal cord injury use the wheelchair as their main means of movement, which contributes to an unfavorable position for the diaphragm[7,8,26]. The flexion of the legs presses the abdominal organs superiorly, causing the diaphragm not to descend efficiently during inspiration, suggesting a direct relationship between cough strength and wheelchair use[13,25], which corroborates the results of this study demonstrating that the longer the wheelchair time the lower the PFT.

The study by Cooper et al.[14] revealed a relationship between respiratory muscle strength and wheelchair use, besides the relationship between wheelchair use and PFT reduction. However, this was not noted in this study.

This study demonstrated reduced expiratory muscle strength in all individuals, and suggested that quadriplegics are inclined to have lower MIP and PFT than paraplegic patients, corroborating the study by Boaventura et al.[22].

Neurological and orthopedic physiotherapy foments adequate global muscle training, sensory and proprioceptive stimulation, adaptation to decubitus changes and transfers, with the intention of providing greater stimulation for mobility and independence. Over respiratory rehabilitation, specific exercises and

pulmonary resources supply to better pulmonary ventilation and elimination of tracheobronchial tree secretions, preventing respiratory complications, reduced pulmonary function and prolonged hospitalizations, with consequent improvement in quality of life[15].

It was possible to note that these individuals need regular follow-up and that, despite the high rate of cases of spinal cord injury in the state, the limitation of health services access is yet evident, resulting from the lack of awareness and transportation difficulties, which impacted on sample reduction of the current study. Given this, the scientific research is stressed in order to emphasize the needs of this population for innovation and incentive to develop strategies for better care.

CONCLUSION

Spinal cord injury may promote direct changes in respiratory muscle strength and peak cough flow values as stated in the level affected and possible secondary repercussions thanks to the use of a wheelchair. The study implies that all individuals had expiratory muscle weakness, and quadriplegics are liable to have lower MIP and PFT than paraplegics. With regard to wheelchair use, the longer the use, the lower the cough effectiveness.

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ESTUDOS INTERDISCIPLINARES EM CIÊNCIAS SOCIAIS E DA SAÚDE
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Original Article

RELATIONS FROM BLOOD COUNT PARAMETERS WITH MORTALITY AND TIME OF HOSPITALIZATION IN CRITICAL PATIENTS

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Keywords

Critical illness;
Systemic inflammation;
Biomarker;
Prognosis.

Abstract

Objective: to evaluate the association of three indices neutrophil / lymphocyte ratio (NLR), platelet / lymphocyte ratio (PLR) and lymphocyte / monocyte ratio (LMR) with mortality and length of hospital stay of critical patients, and to compare them with the prognostic indexes Simplified Acute Physiology Score (SAPS III), Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA). Method: retrospective, longitudinal study, evaluating patients hospitalized, during one year, in the general Intensive Care Unit of Hospital Unimed Vtória. Patients with diseases or conditions that induce immune

depression were excluded. The hematological and traditional indexes were evaluated in the first 24 hours of hospitalization. Results: The evaluation consisted of 447 patients, 196 men (43.8%), ranging in age from 16 to 193 years, mean of 68.4 ± 19.3 years. The length of stay in the intensive care unit ranged from 1 to 112 days, with an average of 8.4 ± 10.3 days; The hospitalization length ranged from 1 to 706 days, with an average of 23.5 ± 13 days. Thirty-three patients (7.4%) died in the intensive care unit and 64 (14.3%) died in the hospital.
Conclusion: There was an association between the traditional prognostic indexes, but not the inflammatory indexes derived from the blood count, with the length of hospital stay and mortality of critically ill patients.

INTRODUCTION

Intensive Care Units (ICUs) are costly and serve populations with very varied demographic characteristics. As a result, it is important to identify at-risk patients, which will help provide high-quality individualized care. Several indices involving laboratory and / or clinical parameters have been described. Some scores identify the presence, intensity, and characteristics of the systemic inflammatory response; indices using available parameters in the blood count have been studied extensively: neutrophil / lymphocyte ratio (NLR), platelet / lymphocyte ratio (PLR) and, more recently, lymphocyte / monocyte ratio (LMR). Retrospective surveys comparing the value of the index to hospitalization with the evolution of the patient, including hospitalization time, complications and mortality prevail.

The increase in the value of these relationships, especially NLR, is related to the prognosis in several acute conditions, including cardiovascular events[1], acute appendicitis and other forms of acute abdomen[2], trauma[3] and various critical diseases.[4,5]

Hemogram is a procedure routinely done in intensive care units and often repeated periodically according to clinical evolution and it is easy to access and inexpensive. Many publications suggest the evaluation of these indices in varied populations, as well as the identification of cutoff points for specific clinical conditions. They also suggest the investigation of the accuracy of these indices, repeated periodically, to guide the clinical evolution, indicating improvement or worsening of the condition.

The main objective was to evaluate if there was an association between the NLR, PLR and LMR indices evaluated in the first 24 hours of ICU admission, with mortality and length of hospital stay in the ICU and in the hospital, in addition to comparing them with traditional prognostic indexes.

METHOD

A retrospective, longitudinal study performed at the Hospital Unimed Vitória, in consecutive patients hospitalized at the ICU from 01/01/2015 to 12/31/2015, with care in general, which serves adults of both sexes; patients with cardiovascular diseases are treated in a specific unit. The

Research Ethics Committee of Hospital Unimed Vitória approved this study under the advice of number 65509717.9.0000.5061.

Patients were identified in EPIMED Monitor, a system for performance and quality management in intensive care units. This system has been available at Unimed Vitória Hospital for several years. There is a senior professional (nurse) dedicated exclusively to putting data into the program. Currently, this nurse works together with routine physicians who report details of the patients' clinical evolution, which are not identifiable in the medical records. Some of the parameters evaluated in the research are not available in this system, since they were obtained in another hospital management system, the MV2000i, in the module Unit Management System (PAGU).

The parameters were related to age, gender, origin (residence, first aid, other sectors of the hospital itself and other hospitals), main and secondary diagnoses, treatment characteristics (clinical, elective surgery, urgent surgery), medications and treatments prior to hospitalization. They were also related to complications such as infection, sepsis / septic shock, organ failure, prognostic indexes SAPS 3, APACHE II and SOFA, complications during hospitalization in the ICU such as pneumonia associated with mechanical ventilation, other infections, sepsis / septic shock, organ failure, bleeding and others. Hematocrit, hemoglobin, leukocytes, neutrophils, rods and segmented, lymphocytes, monocytes, eosinophils, basophils and platelets were assessed in the ICU admission. The outcomes analyzed were mortality and length of hospital stay.

Initially, all patients hospitalized in the programmed period were analyzed, corresponding to 691 patients, initially excluded those patients who died or did not have a hemogram performed within the first 24 hours of hospitalization at the unit, ICU readmissions during the same hospitalization and patients transferred from the ICU of other hospitals. There were 586 patients remaining. In addition to patients with diseases or treatment inducing immune depression or capable of interfering directly in the inflammatory response, also patients with non-neoplastic hematological diseases, hematologic cancer, antineoplastic chemotherapy and chronic glucocorticoid use, totaling 447 patients.

Primary outcomes: 1 - evaluate the association of NLR, PLR and LMP indices with mortality and length of stay in the ICU and hospital; 2 - evaluate the cutoff points of each of these indices to predict mortality; 3 – compare the SAPS 3, APACHE II and SOFA indices with the NLR, PLR and LMR indices to predict ICU and hospital mortality.

The SPSS program (Statistical Package for the Social Sciences, version 17.0; SPSS, Inc., Chicago, IL, USA) was used in the analysis. In order to evaluate the association between the NLR, PLR and LMR indices with the prognosis of critically ill patients, the values were also divided into quartiles, a method used in equivalent searches.

The normal distribution of the studied variables was not confirmed by the Kolmogorov-Smirnov test. Thus, non-parametric tests were used in all analyzes. The Pearson test was used for the study of correlations and in the predictive capacity of mortality of inflammatory indexes, the ROC (Receiver Operating Characteristics) curve. A significance level of 5% was considered in all tests.

RESULT

A total of 447 patients were included in the initial sample of 586 patients, along with196 men (43.8%) and 251 women

(56.2%); the age ranged from 16 to 103 years, with a median of 72 years, mean and standard deviation of 68.4 ± 19.3 years; 77 patients (17.2%) had cancer; 75 (18.1%) hospitalized with infection and 71 (17.1%) with sepsis. The length of ICU stay ranged from 1 to 112 days, with a median of 6 days, and mean and standard deviation of 8.4 ± 10.3 days; 28 patients (6.3%) were hospitalized in the ICU for 21 days or more, and they were classified as chronically critical. The length of hospital stay ranged from 1 to 706 days, with a median of 13 days, and mean and standard deviation of 23.5 ± 13 days. The treatment modality is related in Table 1.

Table 1. Modality of treatment of critical patients.

Treatment Modality	Number of Patients	%
Clinical	218	48,8
Elective Surgery	121	27,1
Urgent Surgery	108	24,1
Total	447	100,0

Some characteristics of hospitalized patients are in Table 1.

Table 2. Values of some parameters during hospitalization

Parameters	Values					
	Minimum	Maximum	Median	Mean	DP	N valid
SAPS 3	16,0	96,0	43,0	44,8	16,0	447
APACHE II	0,0	39,0	12,0	12,9	7,5	447
SOFA	0,0	19,0	4,0	3,9	3,6	447
Leucocytes	1394,0	59050,0	11900,0	13109,0	6913,1	447
Bats	0,0	11052,0	458,1	896,5	1322,9	447
Neutrophils	1086,0	46059,0	9450,0	10715,7	6213,4	447
Lynphocytes	139,4	13349,7	1402,2	1682,1	1314,9	447
Monocytes	0,0	2362,0	517,8	587,0	367,8	447
Platelets	0,0	779000,0	225000,0	243776,3	112203,6	447
RNL	0,6	48,0	6,8	8,6	7,0	447
RPL	0,0	1054,5	162,9	200,5	151,4	447
RLM	0,4	25,0	2,8	3,6	3,1	446

SD: Standard Deviation
SAPS 3: Simplified Acute Physiology Score
APACHE II: Acute Physiology and Chronic Health Evaluation
SOFA: Sequencial Organ Failure Assessment
NLR: Neutrophil/lynphocyte ratio

PLR: Platet/ lynphocyte ratio
LMR: lynphocyte/monocyte ratio
Out of 447 patients studied, 33 (7.4%) died in the ICU and 64 (14.3%) died in the hospital.

Out of 447 patients studied, 33 (7m4%) died in the ICU and 64 (14,3%) died in the hospital

The final evolution (survival or death) in the ICU and hospital according to the modality of treatment are shown in Tables 3 and 4, respectively.

Table 3. Final evolution in the Intensive Treatment Unit according to the treatment modality

Treatment Modality	Number of Patients	Survival		Death	
		N	%	N	%
Clinical	218	196	47,3	22	66,7
Elective Surgery	121	118	28,5	3	9,1
Urgent Surgery	108	100	24,2	8	24,2
Total	447	414	100,0	33	100,0
Value -p = 0,037					

Table 4. Final evolution in the Hospital according to the modality of treatment

Treatment Modality	Number of Patients	Survival		Death	
		N	%	N	%
Clinical	218	179	46,7	39	60,9
Elective Surgery	121	114	29,8	7	10,9
Urgent Surgery	108	90	23,5	18	28,1
Total	447	383	100,0	64	100,0
Value -p = 0,007					

The association of parameters to hospitalization according to ICU mortality (prognostic indexes and components of the hemogram) is in Table 5

Table 5. Association of some parameters to hospitalization with mortality in the Intensive Care Unit

Parameters	Mortality in the ICU	Minimum	Maximum	Median	Mean	Standard Deviation	N valid	p
SAPS 3	No	16,0	90,0	41,0	43,2	14,9	414	0,000
	Yes	32,0	96,0	64,0	64,8	16,0	33	
APACHE II	No	0,0	35,0	11,0	12,1	6,8	414	0,000
	Yes	6,0	39,0	23,0	23,6	7,5	33	
SOFA	No	0,0	19,0	4,0	3,5	3,3	414	0,000
	Yes	0,0	16,0	9,0	9,2	3,9	33	
LEUKOCYTES	No	1394,0	59050,0	11850,0	13177,9	6988,2	414	0,733
	Yes	2000,0	22700,0	12000,0	12245,1	5914,7	33	
NEUTROPHILS	No	1086,0	46059,0	9494,3	10774,3	6277,5	414	0,627
	Yes	1600,0	21565,0	8489,2	9980,8	5373,8	33	
LYNPHOCYTES	No	139,4	13349,7	1403,1	1686,3	1287,1	414	0,390
	Yes	177,5	9600,0	1393,2	1629,2	1647,0	33	
MONOCYTES	No	0,0	2362,0	525,9	590,3	366,2	414	0,299
	Yes	137,4	2140,0	462,5	544,8	391,1	33	
RNL	No	0,8	48,0	6,8	8,4	6,6	414	0,750
	Yes	0,6	47,5	6,8	10,1	10,7	33	
RPL	No	0,0	1054,5	162,7	196,9	143,0	414	0,601
	Yes	20,9	1025,4	163,4	245,9	230,8	33	
RLM	No	0,4	25,0	2,8	3,6	3,1	413	0,553
	Yes	0,7	15,0	2,5	3,4	2,8	33	

SAPS 3: Simplified Acute Physiology Score

APACHE II: Acute Physiology and Chronic Health Evaluation

SOFA: Sequencial Organ Failure Assessment

NLR: Neutrophil/lynphocyte ratio

PLR: Platet/ lynphocyte ratio

LMR: lynphocyte/monocyte ratio

The association of parameters to hospitalization according to Hospital mortality (prognostic indices and components of the hemogram) is in table 6

Table 6. Association of some parameters with mortality in the hospital

Parameters	Hospital Mortality	minimum	Maximum	Median	Mean	Standard deviation	N valid	p
SAPS 3	No	16,0	90,0	40,0	42,3	14,7	383	0,000
	Yes	31,0	96,0	59,0	59,9	15,3	64	
APACHE II	No	0,0	35,0	11,0	11,8	6,9	383	0,000
	Yes	6,0	39,0	19,0	19,8	7,7	64	
SOFA	No	0,0	16,0	3,0	3,4	3,2	383	0,000
	Yes	0,0	19,0	7,0	7,3	4,4	64	
LEUKOCYTES	No	1394,0	59050,0	12100,0	13133,7	6837,4	383	0,621
	Yes	2000,0	38680,0	11385,0	12961,4	7405,5	64	
NEUTROPHILS	No	1086,0	46059,0	9576,0	10750,1	6126,4	383	0,449
	Yes	1600,0	35198,8	8492,6	10509,7	6758,3	64	
LYNPHOCYTES	No	139,4	13349,7	1400,4	1670,2	1284,6	383	0,922
	Yes	177,5	9600,0	1438,1	1752,8	1492,5	64	
MONOCYTES	No	0,0	2362,0	518,4	582,8	357,6	383	0,989
	Yes	137,4	2298,0	498,9	611,9	426,5	64	
NLR	No	0,8	48,0	6,8	8,5	6,7	383	0,644
	Yes	0,6	47,5	6,4	8,9	8,8	64	
PLR	No	0,0	1054,5	162,9	196,9	142,5	383	0,758
	Yes	20,9	1025,4	158,1	222,2	196,4	64	
LMR	No	0,4	25,0	2,8	3,6	3,1	382	0,471
	Yes	0,7	15,0	2,6	3,4	2,7	64	

SAPS 3: Simplified Acute Physiology Score

APACHE II: Acute Physiology and Chronic Health Evaluation

SOFA: Sequencial Organ Failure Assessment

NLR: Neutrophil/lynphocyte ratio

PLR: Platet/ lynphocyte ratio

LMR: Lynphocyte/monocyte ratio

The correlation of prognostic indexes and components of the hemogram with the length of hospital stay in the ICU and Hospital are described in Tables 7 and 8, respectively.

Table 7. Correlation of ICU sty with some parameters

Parameters	Correlation coefficient Spearman	p
SAPS 3	0,441	0,000
APACHE II	0,377	0,000
SOFA	0,356	0,000
Leukocytes	0,034	0,469
Neutrophil/lynphocyte ratio	-0,003	0,954
Platet/lynphocyte ratio	0,014	0,764
Lynphocyte/momocyte ratio	0,033	0,491

SAPS 3: Simplified Acute Physiology Score
APACHE II: Acute Physiology and Chronic Health Evaluation
SOFA: Sequencial Organ Failure Assessment

Table 8. Correlation of Hospital stay time with some patients

Parâmetros	Coeficiente de correlação Spearman	p
SAPS 3	0,427	0,000
APACHE II	0,320	0,000
SOFA	0,309	0,000
Leukocytes	0,020	0,411
Neutrophil/lynphocyte ratio	-0,039	0,954
Platet/lynphocyte ratio	0,016	0,742
Lynphocyte/momocyte ratio	0,043	0,370

SAPS 3: Simplified Acute Physiology Score
APACHE II: Acute Physiology and Chronic Health Evaluation
SOFA: Sequencial Organ Failure Assessment

As there was no association of the parameters NLR, PLR and LMR, with or without distribution in quartiles, both with mortality and with the length of hospital stay, it was impossible to analyze the predictive capacity and cutoff points of each of these indexes.

DISCUSSION

The number of patients admitted to ICUs is growing, corresponding to more than five million people each year in the United States.[5] Reflecting what happens to the general population, it receives more and more elderly patients with multiple comorbidities, with acute chronic conditions that increase severity and worsen prognosis. The most salient outcome in research on this topic is mortality, which can occur in the hospital or at home. There are scores traditionally indicated to evaluate the prognosis of critical patients. Among these scores, APACHE II[6], SAPS 3[7, 8] and SOFA[9] stand out. As for the long-term outcomes beyond survival, the recovery of functional capacity and the return to normal activities are increasingly valued.[10]

Diseases treated in the units, including sepsis, have systemic inflammation as an important component of their pathophysiology. It is the result of the action of several mediators, with emphasis on cytokines (tumor necrosis factors, interleukins and interferons) and eicosanoids (prostaglandins, thromboxanes and leukotrienes). Several biomarkers, including acute phase proteins (PCR, amyloid A) and cytokines have been used to assess the presence, characteristics and intensity of the inflammatory response and, by extension, the prognosis of critically ill patients; the most efficient markers are expensive and little available in clinical practice.

Leukocytes play a key role in the pathogenesis of local and systemic inflammation. There is a tendency to increase the number of neutrophils and reduce the number of peripheral blood lymphocytes in acute aggressions. Neutrophils are present for the first 6 to 24 hours post-injury. They persist for 7 to 10 hours in the circulation and undergo apoptosis within 24 hours.[12] Activated platelets produce inflammatory mediators that can initiate or modulate the inflammatory response, in addition to interacting with system cells immune cells.[13] Monocytes exit the circulating blood and into connective tissue, they turn into macrophages, important producers of cytokines.

The hypothesis that NLR is associated with clinical outcomes is based on the physiological relationship between neutrophilia and lymphopenia with stress and systemic inflammation.[14] NLR may be indicative of the patient's response to an inflammatory insult; there is an increase in neutrophils and, when it is very high, it induces apoptosis of the lymphocytes. Studies have identified, for example, the associated presence of neutrophilia and lymphopenia in trauma victims and patients meeting the criteria for systemic inflammatory response syndrome.[5] Lymphocytes are important for the regulation of an appropriate inflammatory response and its decrease, either by apoptosis, cellular exhaustion or down-regulation can perpetuate a chronic inflammatory state. The increase in NLR can identify patients who have smaller physiological reserves, which makes them with reduced capacity to survive an inflammatory insult.[5]

Some indexes that include components of the blood count have been of increasing interest in assessing the prognosis in different clinical settings. Chronic diseases include cancer (digestive, lung, ovary and breast) [15], cardiovascular diseases[1, 16, 16] and metabolic syndrome[18]. Several studies have evaluated inflammatory indexes in critically ill patients. Higher NLR scores were found in critically ill patients than in non-critically ones.[5] NLR was associated with mortality in acute coronary syndrome and pulmonary embolism.[1] High PLR was associated with incidence of atrial fibrillation and post-operative period,

incidence of reoperations due to sternal dehiscence, length of hospital stay and mortality in patients undergoing myocardial revascularization surgery.[19]

NLR has been associated with the results of acute pancreatitis and was identified as a predictor of the need for ICU admission and prolonged hospitalization[5]. Out of the patients hospitalized for sepsis, most due to abdominal origin, the LNR was significantly higher in non-survivors. The progressive increase in their value in the first five days of hospitalization was related to late mortality[20]. NLR values are grouped in quartiles according to many studies.

By using this method (group in quartis), the authors found a positive relationship with an increase in mortality in 28 days in the general population as well as in the non-septic one. However, it was not possible to predict septic mortality[5]. Another study reported that APACHE II and NLR were independent indicators of hospital mortality at one and six months[4]. In patients with diabetic ketoacidosis, it has been shown that a PLR higher than 267.67 represents a high risk for mortality and readmission in 90 days[21].

Regardless the high availability and low cost of the blood count and the initial success of using these indices, there are restrictions that deserve alertness. The studies are usually retrospective, performed in isolated centers with a limited number of patients. Moreover, there is no cut-off point indicating a universally accepted prognostic change. As an example, in order to predict the evolution of the acute coronary syndrome, the RNL is considered elevated when superior from 1.4 to 6 in the different works (3 is the value considered by most authors) [1]. The cutoff point should vary with the situation (acute, chronic), with the diagnosis (acute cardiovascular event, acute appendicitis, etc.) and with the outcome studied. It may vary in different populations. Thus, the authors suggest that surveys be repeated in several hospitals. The present study is therefore justified as a complement to the existing literature, since there are points to be explored.

In the current study we chose to exclude patients with diseases or conditions that induce immune suppression or exaggerated inflammatory response, such as HIV, autoimmune diseases, hematologic cancer, antineoplastic chemotherapy, chronic steroid use (patients receiving glucocorticoids during ICU treatment were not excluded). Riché et al. used a similar criterion to evaluate the NLR in patients with septic shock [20].

Examining Table 2, we highlight the large range of values of laboratory tests and prognostic indices. Platelets, for example, ranged from 0 to 779,000, with mean and standard deviation of 243,776 ± 112,203; the NLR ranged from 0.6 to 48.0, with mean and standard deviation of 8.6 ± 7.0. These findings are characteristic of critical patients because of the variability of clinical settings, which makes statistical calculations difficult and requires very large samples for conclusive results. Another limiting factor also occurred in this study: a normal distribution of the analyzed parameters was not demonstrated through the Kolmogorov-Smirnov test, which justified the use of non-parametric tests.

Mortality in the ICU (7.4%) and Hospital (14.3%) was relatively low and showed that half of the deaths of critically ill patients occur after discharge from the ICU, a result described by other authors [22, 23]. It is noteworthy that this is not the total mortality, since many high-risk patients were excluded, as previously justified.

With respect to the association of some general parameters (gender, age, presence of infection or cancer, chronically critical

patients and treatment modality) with mortality, statistical significance was much more comprehensive when considering in-hospital mortality than mortality in ICU.

As regards to the association of mortality with the traditional prognostic indexes (SAPS 3, APACHE II and SOFA), to the components of the hemogram (leukocytes, neutrophils, lymphocytes, monocytes and platelets) and to the relationships originated from components of the hemogram (NLR, PLR and LMR), both in the ICU and Hospital, it was statistically significant only with the traditional prognostic indexes.

With reference to the hospitalization time, there was an association with almost all the general parameters, both in the ICU and in the hospital. There was correlation with the traditional prognostic indexes, but not with the parameters and relations derived from the hemogram.

In sum, the indices investigated in this study, NLR, PLR and LMR, were not associated with length of hospital stay and mortality in both ICU and Hospital. It is worth mentioning that important studies have shown that inflammatory indicators on admission may not guide the prognosis. For example, to create a score capable of assessing the nutritional risk of critical patients, called NUTRIC score, a Canadian group tested several markers at the start of ICU treatment. The multivariate analysis showed that PCR and procalcitonin were not able to guide the prognosis; but the IL-6 was capable to do so.[24]

The study was repeated by analyzing the NLR, PLR and LMR indices distributed in quartiles, as used in another research,[5] but the results were equivalent, that is, they remained without statistical significance. It was therefore impossible to compare these indices with SAPS 3, APACHE II and SOFA as well as to identify the cut-off point for each relation.

The research presented some limitations as it was retrospective, performed in a single center and with a relatively small number of participants; the population was very heterogeneous, as all patients admitted to a general ICU were evaluated. Nonparametric tests were used because there was no normal distribution of the analyzed variables. As there was no association of inflammatory indices with mortality and length of hospital stay, it was not possible to analyze the predictive capacity and cut-off point for each index.

The great advantage of NLR, PLR and LMR lies in the possibility of implementing these simple parameters by the use of laboratory tests already available at no additional cost.

CONCLUSION

There was an association between the traditional indexes SAPS 3, APACHE II and SOFA, but not the inflammatory indexes NLR, PLR and LMR, evaluated at admission, with length of hospital stay and mortality of critically ill patients.

The outcome of the inflammatory indexes was maintained when analyzed through quartile distribution.

As there was no association of the inflammatory indexes NLR, PLR and LMR, with mortality, it was not possible to compare them with traditional indexes or to identify a cutoff point.

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Original Article

ANALYSIS OF BACTERIAL VAGINAL MICROBIOTA IN POSTMENOPAUSAL WOMEN WHO HAVE NOT UNDERGONE HORMONE THERAPY

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Keywords

Microbiota;
Postmenopause;
Vaginosis, Bacterial

Abstract

Objective: To investigate the microorganism imbalance of the bacterial vaginal microbiota in postmenopausal women who have not undergone hormonal therapy. Method: Prospective analysis, semi-quantitative of vaginal secretion in menopausal women attended at the gynecology service of the Santa Casa de Misericórdia de Vitória Hospital. Out of 150 patients underwent specular examination and collection of secretion of the middle third of the vaginal wall with a spatula and subsequent staining by the Gram method to identify the various microorganisms of the vaginal microbiota in terms of morphology and coloration. Of these, were considered for analysis only 83 blades stained by the Gram method,

standardized on 2 centimeters of smears. Results: The presence of Lactobacillus acidophilus was found in 60.24% of the patients, Mobiluncus sp. in 13.25%, Atopobium vaginae in 8.43% and Gardnerella vaginalis in 7.22%. Of those 4.81% positive for bacterial vaginosis according to the Nugent criteria. Conclusion: It is possible to find in postmenopausal women the presence of Lactobacillus spp., the presence of bacterial vaginosis, requiring future studies related to the microbioma and biological factors of women.

INTRODUCTION

The normal vaginal microbiota consists of a great diversity of microorganisms, composed of aerobic, microaerophilic, facultative anaerobic bacteria, and strict anaerobes, which remain in equilibrium. Lactobacillus spp., also known as Döderlein bacilli, whose vaginal colonization may be influenced by the estrogenic action in this tissue, and its concentration is related to different stages of woman's life.[1]

Among the microorganisms present in the lower female genital tract are the Lactobacillus, Group B hemolytic Streptococcus, S. viridans, Enterococcus spp. Peptoestreptococcus, Prevotella spp., Clostridium spp., Bacteroides spp., Mobiluncus spp., Gardnerella vaginalis, Ureaplasma urealyticum, Atopobium vaginae, Bifidobacterium, Enterobacteriaceae microorganisms (Gram negative rodent enteric fermenters), various forms of bacteria (coccus, rods and spirals), fungi, including the genus Candida and viruses[2].

The decrease of Lactobacillus spp., due to different factors in the mucosa, may favor the increase of certain microorganisms causing infections in this environment. Therefore, this ecosystem becomes complex with more than 200 bacterial species influenced by genes, ethnic origins, environmental and behavioral factors, and normal and abnormal vaginal microbioma can undergo changes in the dependence of adverse factors.[2]

As a rule, in this type of analysis, vaginal bacterial cultures do not provide what can be judged as the cultural identification of microorganisms considered pathogenic by microbiota imbalance, mostly due to the difficulty of cultivating strict anaerobic bacteria. On that account, microscopic technologies are not based on culture, but on direct microscopy of the vaginal material revealing a complex and dynamic system, dominated largely by Lactobacillus spp., which have the capacity to form a natural biofilm covering the entire mucosa. Accordingly, they inhibit the adhesion, growth and proliferation of other microorganisms foreign to the vaginal environment.

Besides, some species of Lactobacillus produce chemical substances considered in this place, such as microbial toxins, such as hydrogen peroxide, because it inhibits the growth of strict anaerobic pathogenic microorganisms by making a selection of facultative anaerobic and strict anaerobic species that are adhered to the vaginal epithelium

The acidogenic capacity of Lactobacillus causes the vaginal pH to remain acidic, which also functions as a protective effect in view of the maintenance of which limits the growth of Streptococcus spp., Gardnerella vaginalis, Atopobiumvaginae, Mobiluncus sp. Synergism modifications

can lead to vaginal pathologies, including bacterial vaginosis (BV) [2, 3]. There are species of Lactobacillus that dominate the healthy vaginal mucosa, because they establish a defense system and favor the production of antibacterial substances, cytokines, defensins related to pathogenic bacteria. During menacing, the vaginal microbiota consists of 85 to 90% of Lactobacillus spp. In postmenopausal women, the vaginal microbiota usually has its balance maintained with about 60% of these bacilli.[4,5] In menopause, due to hypoestrogenism, a reduction in the epithelial layers as well as the vaginal mucosa also occurs, predisposing to acquisition of fissures and abrasions, which can serve as a gateway to fungi and bacteria.[6]

When the woman reaches 40, 50 years of age, the menstrual cycles become irregular and anovulatory, and they can cease after months or years. The time at which the cycles discontinue and the female sex hormones decrease is called menopause. During the reproductive life of the woman, about 400 primordial follicles grow, nevertheless, thousands of oocytes degenerate. At the age of 45, only a few primordial follicles remain to be stimulated by the Follicle Stimulating (FSH) and Luteinizing (LH) hormones.[7]

Estrogen production by the ovaries decreases as the concentration of primordial follicles decreases. When this production is below a critical level, the estrogen can no longer perform the negative feedback in the production of FSH and LH, and, therefore, the gonadotrophins become elevated, and the increase of FSH is greater than that of the hormone LH [7.8].

In consequence of hypoestrogenism, weakness of the vaginal epithelium occurs and epithelial cells are deficient in glycogen. The pH becomes more alkaline and the mucosa less thick.8 Other related symptoms are vulvar pruritus, dry vagina and dyspareunia.[9] Hence, there is a change in the vaginal microbiota of the patients, which facilitates infections such as BV.[10]

Nevertheless, an exception to hypoestrogenism in postmenopausal women is those with a Body Mass Index (BMI) greater than or equal to 25, because in obese women there is an increase in the activity of the aromatase enzyme, increasing the level of androstenedione peripheral conversion in estrone by elevating circulating estrogen.[11]

The prevailing cause of pathological vaginal discharge in women of childbearing age is imbalance. Still, the prevalence is underestimated, as 50% of women are asymptomatic. Infection in VB is mainly associated with the reduction of Lactobacillus spp., producers of hydrogen peroxide in the vaginal microbiota and the growth of obligatory or optional anaerobic microorganisms, considering that Gardnerella vaginalis is present in more than 95% of the cases.[2]

Risk factors include pregnancy, vaginal pH (which occurs in ejaculation or in the use of showers), high number of sexual partners, use of intrauterine device (IUD), use of spermicides, broad spectrum antibiotics, poor hygiene habits, vaginal douche use, coitus frequency, decreased vaginal immune response, and menopause.

According to Table 1, the evaluation of the vaginal microbiota can be based on the Nugent score, which considers the amount of morphotypes present in the vagina.[12]

Table 1. Score for each of the morphotypes

1+ = presence of at least 1 morphotype in the immersion field
2+ = presence of 1 to 4 morphotypes in the immersion field
3+ = presence of 5 to 30 morphotypes in the immersion field
4+ = presence of more than 30 morphotypes in the immersion field

Source: Gilbert, GG, Donders, MD. Definition and classification abnormal vaginal flora. **Best Practice and Research Clinical Obstetrics and Gynaecology.** Belgium, volume 21, issue 3, june 2007, pages 355-373. [12]

The Nugent criteria, created in 1991, point to identify Gram-positive bacilli suggestive of Lactobacillus, Gram-labile short bacilli indicative of Gardnerella vaginallis or gram- negative bacilli suggestive of Mobiluncus sp., as presented in Table 2.

Table 2. Nugent Diagnostic Criteria for Bacterial Vaginosis

A. *Lactobacillus acidophillus* (Gram-positive bacilli)
B. *Gardnerella vaginalis* e espécies bacteroides (Gram-short variable bacilli)
C. *Mobiluncus* sp. (Gram-negative or variable bacilli)
The total score is the sum of the weight of the amount of the three bacterial morphotypes
Score for each one of the morfotypes:
Zero = no morphotypes in the immersion field (1000x)
1+ = less than one morphotype in the immersion field (1000x)
2+ = one to four morphotypes in the immersion field (1000x)
3+ = five to thirty morphotypes in the immersion field (1000x)
4+ = more than thirty morphotypes in the immersion field (1000x)
A+ B + C = 0 a 3 4 to 6 Major 7
Normal Intermediate Bacterial Vaginosis

Source: CAMPOS, Ana Aurélia Salles et al. Estudo comparativo entre o teste do pH e do KOH versus escore de Nugent para diagnóstico da vaginose bacteriana em gestantes. *Rev. Bras. Ginecol. Obstet.* [online]. 2012, vol.34, n.5 [cited 2017-10-19], pp.209-214.[13]

The hormonal profile of postmenopausal women is characterized by hypoestrogenism, a factor that triggers a weakness of the vaginal epithelium, glycogen deficiency in the epithelial cells, an alkalinization of the vaginal pH and a decrease in the thickness of the vaginal mucosa. Accordingly, the patients usually present symptoms as vulvar pruritus, lubrication deficiency of the vagina, dyspaurenia and decreased libido.

Furthermore, there is a change in the vaginal microbiota of these

postmenopausal women due to hypoestrogenism, with a decrease in Lactobacillus spp. and proliferation of pathogenic potential bacteria, facilitating infections such as BV. Consequently, the importance of the current study is to supply a better quality of life for patients, reduce morbidity and mortality and prevent surgical complications, increase knowledge about women's health, and collaborate to reduce spending on medicines used in the hospital. [14]

Bacteria of the vaginal microbiota, considered or not pathogenic, and those collaborating for balance can participate in the various stages of a woman's life and directly or indirectly influence the development of BV. Hence, the quantitative presence of Lactobacillus is considered important. [15-17]

METHOD

This study, a prospective, semi-quantitative analysis, investigated the vaginal microbiota of 83 postmenopausal patients without hormonal therapy, who came from the spontaneous demand of the Gynecology Outpatient Clinic of the Santa Casa de Misericórdia Hospital of Vitória within a period of 6 months after approval in the committee ethics and research. The procedure took place according to the demand of the general gynecology clinic. After explaining the reasons and objectives of the research, the patient had the right not to participate in the study. The research did not jeopardize the patients' health, once the procedure performed is part of the routine of the Gynecology Outpatient Clinic of the Santa Casa de Misericórdia Hospital in Vitória.

All patients who underwent amenorrhea for more than one year, without antibiotics and specific hormones for topical (intravaginal) or systemic menopause in the last months of the study were included as inclusion criteria as well as hysterectomized patients at a menopause compatible age.

Patients who had sexual intercourse up to two days prior to collection, those who had pathological vaginal secretion, hysterectomized patients at a non-menopausal age were excluded from the sample. Women with a BMI greater than or equal to 25, for in obese women occurs an increase of the aromatase enzyme activity, increasing, thus, the level of peripheral conversion of androstenedione to estrone raising the circulating estrogen.

The smear was obtained by specular examination, from which a sample of secretion of the middle third of the vagina was collected with a spatula. A unidirectional longitudinal smear on glass slide for microscopy was done in a space of 2 cm in diameter, fixed to dry, by means of heat and later staining by the method of Gram for identification of the vaginal microbiota, totaling 150 exams.

Applied the exclusion criteria, we obtained 83 exams.

Gram-stained discharge was analyzed in the laboratory of clinical analysis of the Santa Casa de Misericórdia Hospital in Vitória, using an optical microscope with a 100-fold objective (immersion in 1000-fold increase), and was classified according to the score for each of the morphotypes (TABLE 1), derived primarily from the diagnostic criteria for bacterial vaginosis as stated by Nugent.

The technique of analysis of the data of the research was made by using hypothesis tests and level of statistical significance. Probabilities smaller than 5% ($p < 0.05$) will be considered significant and when the probability (p) of the null hypothesis is low, it will be rejected.

RESULT

Lactobacillusacidophillus Gardnerella vaginalis, Bacteroides and Mobiluncus sp were searched for Nugent criteria and found Lactobacillusacidophillus in 60.24% of patients; Gardnerella vaginalis in 7.22%, bacteroides in 8.43% and Mobiluncus sp in 13.25%. Lactobacillus acidophillus -the most frequent ones (FIGURE 1) and Mobiluncus sp. (TABLE 3). The presence of leukocytes (24.09%) and epithelial cells (42.16%) and the frequency of other microorganisms such as Gram-positive cocci (46.98%), Gram-negative coccus (14.45%), Gram-negative rods (20.48%), Atopobium vaginae (33.73%), Yeasts (2.40%) and no protozoa were observed (TABLE 4)

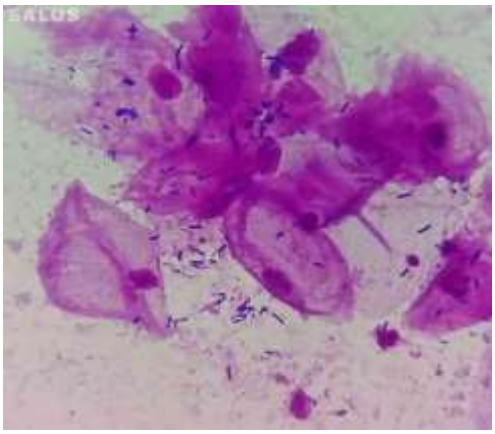


Figure 1. *Lactobacillus spp.*

Table 3. Frequency of Microorganisms found

Micro-organisms Ocorrence (nº) (%)
Lactobacillusacidophillus 50 60,24%
Gardnerella vaginalis 6 7,22%
Bacteroides 7 8,43%
Mobiluncus sp 11 13,25%

Table 4. Frequency of other microorganisms

Microorganisms Ocorrence (nº) (%)
Gram-positive Cocos 39 46,98%
Gram-negative Cocos 12 14,45%
Gram-negative Anaerobic rods.
Atopobium vaginae 28 33,73%
Yeasts 2 2,40%

When using the Nugent criteria to the results of the 83 bacterioscopies analyzed by the Gram method, 4 women with bacterial vaginosis (FIGURE 2) representing 4.82% of the sample studied were found, 32 of which were considered intermediate (38.55%), 44 normal (53.01%) and 3 impaired (3.61%) due to the suggestive infection of Chlamydia trachomatis (TABLE 5).

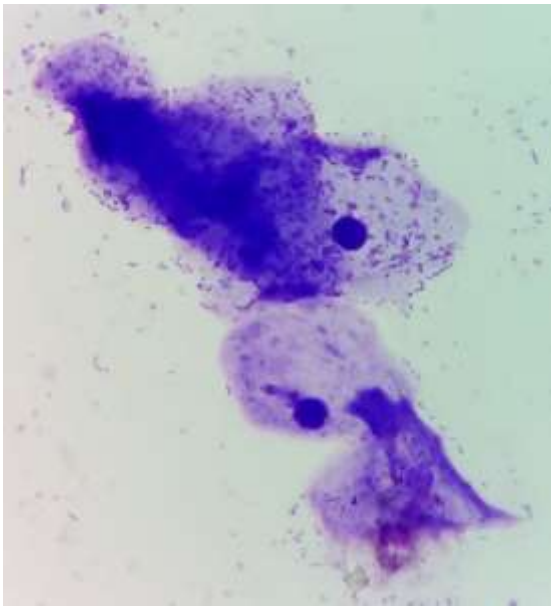


Figure 2. “Clue Cells” de *Gardnerella vaginalis*.

Table 5. Prevalence of Bacterial Vaginosis according to Nugent Criteria

Prevalence Classification (%)
Normal (0 a 3) 53,01%
Intermediate (4 a 6) 38,55%
Bacterial vaginosis (>=7) 4,81%

DISCUSSION

The bacterial microbiota of the 83 women in the current study revealed a wide variety of microorganisms, with slight variations as compared to other studies on bacterial vaginal microbiota.

There are high levels of estrogen that increase glycogen levels of epithelial cells in menacing. The metabolism of this species by some type of Lactobacillus spp. produces lactic acid, resulting in normal vaginal pH of 3.8 to 4.2, difficult range of Gardnerella vaginalis and anaerobes. Bacterial vaginosis occurs when there is a reduction in the number of Lactobacillus spp., decreasing the production of lactic acid, resulting in increased pH. This increase favors the growth of anaerobes and Gardnerella vaginalis, Mobiluncus sp.,

and Atopobium vaginae, one of the main agents causing bacterial vaginosis.[18]

Even though menopause causes reduction of glycogen levels of epithelial cells and the number of Lactobacillus spp. in the vaginal microbiota, and considered as a risk factor for bacterial vaginosis, a prevalence that was significantly higher than that found in women at menacme was not observed in this study. Nevertheless, the small sample studied does not reliably translate into the population of menopausal women, and further studies are required to cover more patients to determine if menopause actually favors infection with agents that cause bacterial vaginosis. [17-19]

In agreement with the results of the research, it will be possible to prevent surgical complications by correctly using antibiotics for procedures accomplished through manipulation of the vagina, along with reducing expenses with medications given in the treatment.

CONCLUSION

This study granted relevant information on the microbiota of menopausal women. There was no marked decrease in Lactobacillus, but the menopause remains a risk factor for favoring vaginal microbiota alteration, which was compatible with the microorganisms present in the Nugent criteria, and it is possible to easily identify and quantify the bacteria responsible for vaginosis.

Image 1

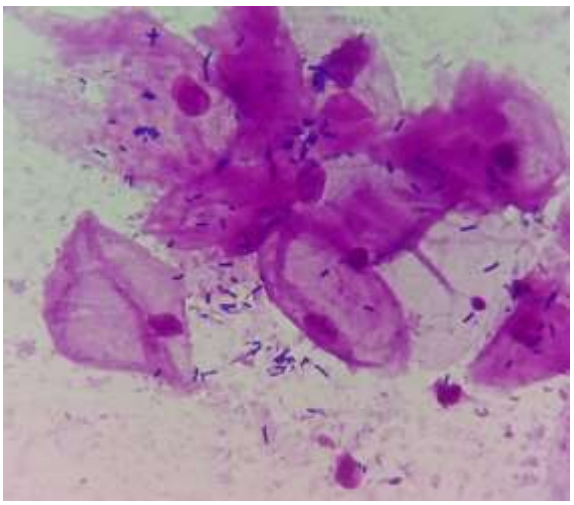
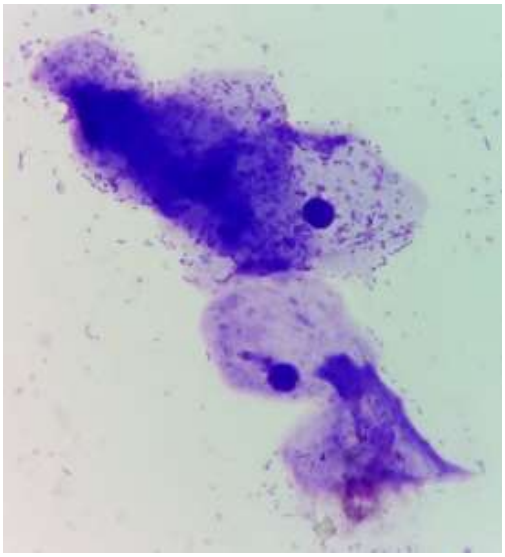


Image 2



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ESTUDOS INTERDISCIPLINARES EM CIÊNCIAS SOCIAIS E DA SAÚDE
INTERDISCIPLINARY STUDIES IN SOCIAL SCIENCES AND HEALTH

v.1, n.1, 2020

Original Article

ASSOCIATION BETWEEN QUALITY OF LIFE AND MORTALITY IN PATIENTS WITH HEART FAILURE

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Keywords

Heart Failure;
Mortality;
Quality of Life

Abstract

Objective: The central focus of this study was to estimate the association between quality of life and mid-term mortality in patients with heart failure (HF). Methods: Prospective study in which the Minnesota Living with Heart Failure Questionnaire (MLHFQ) was applied to adults assisted in a specialized center, with voluntary and secretive filling between October 2012 and March 2013, in a consecutive inclusion. After a three-year clinical follow-up, the group of patients who died was compared to the survivor ones, according to baseline clinical characteristics and initial quality of life. Results: From 76 patients initially approached and interviewed, 74 (97.4%) answered the questionnaire and had completed a 3.5 year follow-up. Comparison between groups death (n=8; 10.8%) and survivors (n=66; 89.2%) showed no difference concerning age, sex, diabetes, smoking, atrial fibrillation, body mass index, ejection fraction by echocardiogram, functional class, use of beta-blocker and use of angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist. The average index studied score was 40.2 ± 24 in the death group and 40.9 ± 21 in the survivors group (p=0.94). Conclusion: There was no association between quality of life and mid-term mortality among HF patients. The influence of quality of life over this prognosis may be complex, and the ideal measurement method for quality of life remains undetermined.

INTRODUCTION

Heart failure (HF) is a disease that results from functional myocardial changes, taking into account that with the progressive increase in life expectancy, the incidence and prevalence of this disease has been increasing.[1] Nearly 2.3% in the general population[2] presents a high mortality, and may reach up to 50% of this population within five years after the diagnosis[3].

An estimated 300,000 US deaths each year have HF as the cause[2]. Several factors such as gender, lower ejection fraction, renal dysfunction, diabetes, depression and the need for hospitalization due to decompensation are associated with higher mortality[4].

HF generally imposes great limitations on daily activities, whether due to physical or psychological symptoms, [5] which is associated with worsening quality of life.[6] It is defined as the patient's beliefs of the influence of the disease in his or her life.[3]

There are many specific instruments to measure quality of life in HF, among them the Minnesota Living with Heart Failure Questionnaire (MLHFQ), one of the most frequent used for both research and daily clinical practice.[7,8] Besides trying to estimate the quality of life in patients, this

questionnaire can also be used to estimate mortality and the need for hospitalizations.[5,7] There is an evidence that MLHFQ is an adequate and a valid instrument for measuring quality of life in HF patients, even in their different versions translated into several countries, including Brazil.[5,9]

The objective of the study was to assess the relationship between quality of life and mortality in the medium term in patients with HF with reduced ejection fraction attended by outpatients.

METHOD

This prospective cohort study was performed in adult patients with reduced ejection fraction HF who completed the MLHFQ at the time of inclusion.

Patients with HF with ejection fraction of less than 50% were transthoracic echocardiograms of both sexes, regularly followed at the HF clinic of the Santa Casa de Misericórdia Hospital de Vitória - ES.

Those under 18 years of age, those who did not accept to complete the questionnaire or who did not sign the Free and Informed Consent Term (TCLE) were excluded.

MLHFQ is a questionnaire comprised of 21 questions, reflecting the physical, emotional and socioeconomic aspects of patients. Responses range from zero to five points. The zero score shows that this aspect did not influence life in the last month, while the 5 score shows that a certain circumstance had maximum limitation. The highest score in the questionnaire is 105 points, considering that the higher the score, the worse the quality of life.

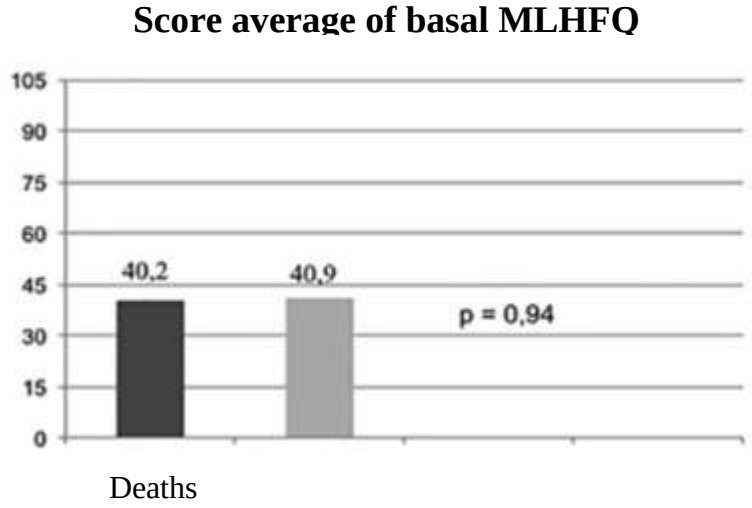
The MLHFQ version validated for Portuguese language[9] was completed in a voluntary and confidential manner between October 2012 and March 2013, in consecutive inclusion. After three-year clinical follow-up, patients who died were compared to survivors for baseline clinical features and initial quality of life.

SPSS software version 18.0 was used for statistical analysis of the data. The Pearson's chi-square test, the Fisher's test and the student's t-test were used with a significance level of 0.05. The categorical variables were expressed in frequencies and percentages, and the continuous variables, in means and standard deviations.

Research Ethics Committee of the institution approved the current study, and all participants in it completed the TCLE.

RESULT

Out of 76 patients initially treated 74 (97.4%) fulfilled the inclusion criteria in the study and answered the questionnaire completely and then with median 3.5 years of follow-up to 3.5 years (mean 3.1 ± 0.9 years). At the end of the follow-up, eight patients had died (10.8%) and 66 survived (89.2%). The final outcome is shown in figure 1.



By comparing the groups, there was no difference in baseline clinical characteristics or the rate of use of angiotensin converting enzyme (ACE) beta blockers and inhibitors or angiotensin receptor blockers (ARBs), as shown in table 1.

Table 1. Baseline clinical characteristics according to the group

Characteristics	**Deaths**	**Survivors**	**p**
Age (years), mean ± SD	54,1 ± 10	59,7 ± 12	0,16
Male gender, n (%)	3 (37,5)	39 (59,1)	0,15
Diabetes mellitus, n (%)	3 (37,5)	25 (37,8%)	0,29
Smoking, n (%)	3 (37,5)	12 (18,2%)	0,15
Atrial fibrilation, n (%)	2 (25)	22 (33,3%)	0,30
BMI mean ± SD	25,6 ± 4,5	27,5 ± 6,3	0,32
Ejection fraction, mean ± SD	39% ± 6	37% ± 8	0,41
Funcional class, mean ± SD	1,4 ± 0,7	1,6 ± 0,9	0,72
Use of ACE inhibitors or BRA, n (%)	8 (100)	65 (98,5)	0,89
Use of beta-blocker, n (%)	8 (100)	65 (98,5)	0,89

SD = standard deviation; ARB = angiotensin receptor blockers; ACEI = angiotensin converting enzyme inhibitors; BMI = body mass index.

The MLHFQ score ranged from 3 to 100, and the mean score obtained in the baseline questionnaire of the total sample was 40.4 ± 21.8, similar between the death and survivor groups (Figure 1).

Subtitle

Figure 1 - Quality of life at the time index according to clinical evolution at follow-up (death or survival) – means of Minnesota Living with Heart Failure Questionnaire (MLHFQ) socres, in which a higher score indicates lower quality of life.

DISCUSSION

Heart failure is a rising disease in our environment today, which is mainly due to population aging and, therefore, is no longer restricted to developed countries. Since is a chronic-degenerative disease, government spending on treatments increases exponentially, costing medications, hospitalizations, devices, surgeries and work incapacity; improving the quality of life of these patients may reduce mortality and the need for hospitalization has been demonstrated in other populations that.[10]

Different quality of life measurement tools may present different prognostic stratification powers in HF. Consequently, the ideal method of measuring this variable remains controversial, and literature data may differ, with general and disease-specific questionnaires available. For MLHFQ, the physical component domain seems to be related to increased long-term mortality, but adjusted analysis does not place the overall score as an independent predictor.[11]

By comparing patients who died and survivors at three years of follow-up, this study observed no difference in the mean MLHFQ scores applied at the time of inclusion. Moreover, baseline clinical characteristics were also statistically similar, as well as the rate of use of beta-blockers and ACE inhibitors / ARBs. Other prognostic factors of the studied population such as other diseases, socioeconomic conditions or unfavorable clinical evolution may have played a decisive role.

The significance of the association between quality of life and survival can be compared to other known predictors of HF mortality, such as diabetes or previous hospitalizations.[10] Frequently, the quality of life, underestimated and deprecated in relation to echocardiographic markers or laboratories, may inform valuable data to health teams, possibly in subgroups or populations yet to be defined.[12]

We identified a wide variation in the MLHFQ score, initially applied in the HF population. The mean score found in our study was similar to that of other studies.[4,11,13] The lower mortality rate in comparison with other studies was probably due to a lower risk profile with a mean ejection fraction above 30%

Spanish study found total mortality of 69.7% in seven years follow-up of HF 433 patients. Survivors had a mean MLHFQ score of 46 points, while those who died, 51 points (adjusted risk ratio = 1.26; 95% confidence interval (CI) 95% .97 - 1.64). The Netherlands conducted analysis of 152 patients with HF with follow-up of 18 months, observing mortality of 34%. In this, the mean MLHFQ score was 42 among the survivors, and 52 among those who died ($p = 0.02$), with a score> 37 presenting a relative risk of 3.24 (95% CI 1.38 - 7.62) for mortality.[4]

Another Dutch study, with 661 patients from 17 centers, observed a mortality rate of 42% in three years, with a MLHFQ mean of 44 at the time of inclusion. Comparison between surviving and non-surviving groups showed a significant difference for the MLHFQ score (42 ± 22 vs. 47 ± 19, $p = 0.010$). An increase of 10 points in the score was associated with a 7% increase in mortality.13 Alla et al. evaluated 108 patients with HF in France, showing mortality of 24% in one year and associated a worsening of 10 points in the MLHFQ score to a 23% higher risk of death ($p = 0.03$). However, after the adjusted analysis, this finding was non-significant, which was attributed to the small sample size.[14]

In the United States, an analysis of 313 patients with HF had shown that worse MLHFQ scores were associated with younger, less educated patients with lower

functional capacity. In this study, for each additional point in the MLHFQ, the risk of a cardiac event at follow-up increased to 1.6% .[15]

A Brazilian study included 101 patients with HF who were followed up in public health services and obtained a mean score of HFHR of 37.5.[2] Another recent study observed a non-specific questionnaire with a low quality of life in patients with HF, when compared to the population with no HF.[16]

The prognosis in severe and symptomatic HF is poor, with high morbidity and mortality. Quality of life is one of the notorious aspects, since new therapies present potential for increased survival. Improving symptoms and quality of life of patients with HF is a goal of treatment, which should be in association with the reduction of arrhythmic or mechanical mortality.

Although relevant and unprecedented in the local population, this study has limitations, such as the reduced sample size and the fact that the questionnaire was not applied periodically to evaluate evolutionarily the quality of life.

CONCLUSION

There was no association between quality of life by MLHFQ and mortality in the medium term among patients with HF. Heart Failure is a complex disease, with important systemic repercussions, and the best method to measure the quality of life of these patients remains uncertain. Larger studies are essential to evaluate the importance of quality of life on the prognosis and complications of HF patients.

Potential Conflict of Interest

The authors declare not to have conflicts of interest.

Financing Source

The present study had no external sources of financing.

Academic Linkage

The current study is not tied to Graduate Programs.

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ESTUDOS INTERDISCIPLINARES EM CIÊNCIAS SOCIAIS E DA SAÚDE
INTERDISCIPLINARY STUDIES IN SOCIAL SCIENCES AND HEALTH

v.1, n.1, 2020

Original Article

THE INFLUENCE OF RISK OF FALLING ON FUNCTIONAL DEPENDENCE OF HOMEBOUND ELDERLY

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Keywords

Aged Rights;
Homebound Persons;
Personal Autonomy;
Postural Balance

Abstract

Objective: Verify the influence of sociodemographic factors, caregivers and risk of falling on the functional dependency of homebound elderly. Method: Crossectional descriptive study during the participation of the PRO PET Saúde - EMESCAM. Functional dependency was assessed by the Functional independency measure, risk of falling by the TINETTI, sociodemographic and presence of caregiver by questionnaire developed by the authors. For statistical analysis were used descriptive statistics, chi square and logistic regression. Results: A total of 155 elderly participated in the present study. The results of the logistic regression suggests that a high score in the TINETTI decreases the chances of being functional dependent (OR 0,83, p

INTRODUCTION

The increase in population survival in developed countries is due to the fall in mortality, progresses in medicine, the adequate urbanization of cities, nutritional improvement, the rise in personal and environmental hygiene levels and technological advances. In developing countries, such as Brazil, this increase is associated with the fall in the fertility rate, and the increase in life expectancy, indicated by improvements in health, coupled with technological advances[1-2].

Aging is a dynamic and progressive process in which morphological, biochemical, functional changes arise[3] and also changes in the central nervous system (CNS), compromising the neuromuscular function, given by changes in balance, reduced reflex response, loss of muscle fibers, change in the percentage of contractile muscle tissue, deficit in muscle innervation and decrease in muscle strength and function, with resultant muscle atrophy, therefore increasing the loss of bone mineral density (osteoporosis and sarcopenia)[4-5]. These changes cause functional disabilities, restricting the performance of activities of daily living (ADLs), namely walking, standing, maintaining postural balance and preventing imminent falls[4].

In Brazil, about 30% of the elderly fall at a minimum once a year and the incidence of falls increases with advancing age, transpiring in more than a third of people aged 60 or over. A study carried out in 2015 showed that out of 8,142,342 deaths in Brazil, between 1997 and 2010, of people over 60 years of age, 0.61% were deaths resulting from falls, and 50.6% occurred among the population of 80 years or more[5-6-7]. The outcome is the greater demand of the elderly for health services, fostering more frequent hospitalizations, longer bed occupancy, when as against other age groups and a higher number of deaths among the elderly. Consequently, falls in the elderly represent an essential public health problem and produce health expenditures three to seven times higher than the average cost of the population, and the social assistance system. Falls can promote or emphasize morbid states, also considering their biopsychosocial consequences, in particular difficulty in

walking, fear of recurrent falls, limitations in instrumental activities of daily living, restriction at home, decreased independence, autonomy and quality of life[6-7-8], which may encourage to functional dependence. These functional disabilities and limitations in activities and participations contribute the restriction of the elderly to the domestic environment, in order to require constant help from a caregiver who helps in their activities, which is defined as functional dependence[9]. This functional dependence provides a progressive social confinement, which can lead to sedentary lifestyle, cognitive deficit, loss of self-esteem and abandonment of self-care[10] and, consequently, to the development and / or worsening of diseases and health conditions. Based on IBGE, in 2010, 12% of the inhabitants of Vitória, Espírito Santo, were 60 years old or older. Pampolim et al.[12], in 2017 noted that the prevalence of functional dependence (DF), influenced by sociodemographic and economic factors in elderly people homebound elderly, was 48%, but that there are other factors that can influence the DF of the elderly homebound elderly, and there is no evidence of how much the deficiency of balance and risk of falls influences the disability and DF of these elderly[12], which makes this knowledge significant for both health professionals and public policies, considering the need to develop prevention and education promotion programs attached to falls.

As a result, the purpose of this study is to determine the influence of sociodemographic factors, the presence of the caregiver and the risk of falls in the functional dependence of elderly people who are restricted to their home.

METHODS

This is a secondary analysis of the study database called "Socio-demographic and health profile of the homebound and bedridden elderly at a family health unit in the city of Vitória-ES", conducted by PRO-PET Saúde (National Program for the Reorientation of Professional Training in Health and the Program of Education through Work for Health), related to EMESCAM (Higher School of Sciences of Santa Casa de Misericórdia de Vitória) and the State Health Secretariat of Espírito Santo and the Municipal Health Secretariat of Vitória. It is characterized by a cross-sectional study with a quantitative approach with a convenience sample and data collection performed from April to November 2014. This study comprised individuals aged 60 years or older, homebound elderly(not bedridden, which characterizes as restricted to bed), registered in the territory of the Family Health Unit Dr. José Moysés and who accepted engage in the research 155 elderly people, by signing (of the elderly or responsible) the free and informed consent term.

The study excluded: elderly people who were unable to perform the TINETTI test; those who did not have a suitable caregiver for this purpose; who showed refusal or family restriction to participate in the study; the cases of death and / or migration to another region during data collection. This study was approved by the Research Ethics Committee of EMESCAM under protocol number 567,990.

The data were collected via face-to-face interviews, performed at the residence of the elderly by students of EMESCAM's physiotherapy, nursing and medicine courses, formerly trained by the main researcher, and monitored by ACS. All participants underwent a semi-structured interview in order to gather information concerning the socio-demographic profile, namely age, sex, race and socioeconomic

status, and afterwards the elderly were subjected to the appraisal of functional capacity and the risk of falling.

Functional capacity was evaluated by the Functional Independence Measure (FIM), a scale created in the 1980s with the purposeof developing an instrument eligible of measuring the degree of request for third-party care that patients with disabilities require to accomplish motor and cognitive, and hence toestablish what care is required to be submitted for the patient to carry out ADLs[13].

The purpose of MIF scale is to evaluate physical and cognitive functionality using 18 items, with regard to six dimensions: self-care, sphincter control, transfers, locomotion, communication and social cognition. For each dimension, the elderly person is assessed with a score from 0 to 7, with a value of 0 according to total dependence and a value of 7 corresponding to performing tasks independently. The MIF score has total scores ranging from 18 to 126 points. Once the assessment was performed in the elderly's own home, there was no reason to use any special resource to simulate daily living conditions, nevertheless it is appropriate mentioning that, as instructed by the Ministry of Health, when an item could not be evaluated / answered, a score of 1 was given. The total FIM result set the presence or absence of DF[14-15-16]. Individuals with scores $\leq$ 103 points were assumed dependent, where lower scores indicate functional dependence[13-16].

The risk of falls was assessed by the TINETTI test, which has been applied to assess balance and gait abnormalities. The test is composed of 16 items, 9 of which are for body balance and 7 for walking. The TINETTI Test categorizes aspects of walking such as speed, stride distance, symmetry and balance while standing, turning and also changes with eyes closed. The score for each exercise ranges from 0 to 1 or 0 to 2, with a lower score denoting poorer physical ability. The total score is the sum of the body balance and gait scores. The maximum score is 12 points for walking, 16 for body balance and 28 for total[16-17].

Data analysis was accomplished using the statistics program (IBM, SPSS 20.0). The descriptive characteristics of the elderly were presented as mean and standard deviation for continuous variables and as frequency and percentage for ordinal and nominal variables. In order to determine the influence of sociodemographic factors, presence of caregiver, risk of falling, and gait in functional dependence, an ordinal regression analysis was implemented, where the level of functional dependence (0 independent or 1 dependent) is the dependent variable and the variables sociodemographic (age, sex, race, elderly income, family income) risk of falling (low, moderate and high), gait capacity and caregiver presence as independent variables. A significance level of 5% was selected for all analysis.

RESULTS

The total elderly population recorded at the Dr. José Moyses Health Unit, in February 2014, was 4,832, among them 212 participated in the data collection, of which 167 were restricted to their home. After analyzing the inclusion criteria, the sample of the current study is 155 elderly people restricted to their home. Table 1 illustrates the sample's sociodemographic characteristics. It can be detectable that 54.8% of the sample is aged between 81 and 90 years old, with a statistically significant correlation with the risk of falls, 78.6% being female, and predominantly white with 72, 2%. Of the 155 participants, 79.6% had a caregiver and 35.1% of the elderly participants lived with only one person. Concerning the risk of falls, 27.7%

had a moderate to high risk of falls with a score between 19 and 22 or 0 and 18, respectively. The elderly was classified as reported by the functional independence scale (FIM) in dependents, portraying 30.32% of the sample and independent, representing 67.09%.

Table 1 - Sociodemographic characteristics of elderly people restricted to the home assigned to USF José Moysés related to TINETTI and MIF scale.

	Total Sample (n=155)	Independent (n=104)	Dependent (n=47)	Value of p
		n (%)		
Age range				
60-70	11 (7,1)	6 (5,7)	5 (10,2)	
71-80	43 (27,7)	26 (24,5)	17 (34,7)	0,085
81-90	85 (54,8)	63 (59,4)	22 (44,9)	
>90	16 (10,3)	11 (10,4)	5 (10,2)	
Fourth age				
Yes	101 (65,2)	74 (69,8)	27 (55,1)	0.055*
No	54 (34,8)	32 (30,2)	22 (44,9)	
Sex				
Female	121 (78,6)	90 (84,9)	31 (64,6)	0,005*
Male	33 (21,4)	16 (15,1)	17 (35,4)	
Race				
Brown	28 (18,5)	18 (17,3)	10 (21,3)	
White	109 (72,2)	75 (72,1)	34 (72,3)	0,33
Black	11 (7,3)	8 (7,7)	3 6,4)	
Yellow	3 (2)	3 (2,9)	0 (0)	
Education				
Illiterate	36 (25,9)	25 (26)	11 (25,6)	
Up to 4 years	43 (30.9)	30 (31,3)	13 (30,2)	
From 5 to 8 years	35 (25,2)	26 (27,1)	9 (20,9)	0,28
From 9 to 11 years	16 (11,5)	10 (10,4)	6 (14)	
Over 11 years	9 (6,5)	5 (5,2)	4 (9,3)	
Marital status				
Married	39 (25,2)	24 (22,6)	15 (30,6)	0,07

Single	15 (9,7)	12 (11,3)	3 (6,1)	
Widower / widow	94 (60,6)	66 (62,3)	28 (57,1)	
divorced /Separated	7 (4,5)	4 (3,8)	3 (6,1)	
Presence of children				
Yes	137 (88,4)	95 (89,6)	42 (85,7)	0,32
No	18 (11,6)	11(10,4)	7 (14,3)	
Family income				
Up to 1 minimum wage	14 (13,5)	13 (18,8)	1 (2,9)	0,010*
From 1 to 4 min. wages	51 (49)	32 (46,4)	19 (54,3)	
Entre 4 e 10 min. wages	28 (26,9)	14 (20,3)	14 (40)	
Above 10 min. wages	11 (10,6)	10 (14,5)	1 (2,9)	
Elderly income				
No income	2 (1,6)	1 (1,2)	1 (2,6)	
Up to 1 minimum wage	64 (51,2)	47 (54,7)	17 (43,6)	0,44
Above 4 min. wages	59 (47,2)	38 (44,2)	21 (53,8)	
Residents				
Alone	18 (11,7)	14 (13,3)	4 (8,2)	
1 person	54 (35,1)	35 (33,3)	19 (38,8)	0,6
Above 2 people	82 9 (53,2)	56 (53,3)	26 (53,1)	
Elderly caregiver				
Yes	117 (79,6)	72 (72,7)	45 (93,8)	0,002*
No	30 (20,4)	27 (27,3)	3 (6,3)	
Risk of falls				
Low	28 (18,1)	23 (21,7)	5 (10,2)	<0,001*
Moderate/High	43 (27,7)	37 (34,9)	6 (12,2)	

Table 2 – Sociodemographic characteristics of elderly people restricted to the home assigned to USF José Moysés related to TINETTI and MIF scale.

Variables	Total Sample (n=155)	Independent (n=104)	Dependent (n=47)	Value of p
	Median (min,max)			
Age	82.9 ± 7.5	83 (64,100)	83 (63, 103)	0,28
Tinetti Balance	10.26 ± 3.5	11 (2,16)	7 (1,16)	
Walking	6.88 ± 3.37	8 (2,12)	4 (0,12)	< 0,001*
Total	17.2 ± 6.4	20 (7,28)	12 (1,28)	
MIF				
Cognitive	28.33 ± 8.69	34 (18,35)	20 (5, 35)	
Motor	74.44 ± 19.39	85 (69, 91)	56 (13, 88)	< 0,001*
Total	102.77 ± 25.43	116 (104, 126)	79 (18,102)	

*p<0,05
USF = Family Health Unit

In table 3, when the results of the Binary Logistic Regression analysis were verified, we observed that the factors that most influence the functional dependence of the elderly are the elderly's own income (p 0.039), Tinetti's gait domain (p 0.037), the presence of caregiver (p 0.019). In contrast, the other independent variables such as gender, age, race, children, education, marital status, number of residents in the household, family income and Tinetti balance did not exhibit statistically significant influence.

Table 3 - Binary Logistic Regression between socio-demographic and economic variables and the presence of functional dependence in elderly people restricted to the home, assigned to the Family Health Unit.

Independent Variables	OR	IC95%	p
Age	0.83	0,68 – 1,01	0,063
Sex	0,13	0,01 – 1,53	0.106
Race			
White (Reference)			
Brown	3,33	0,50 – 22,08	0,210
Black	0,47	0,01 – 13,45	0,661
Other	0,00	0,00 – 0,00	1
Children	0,22	0,00 – 7,17	0,39
Education			
Illiterate (Reference)			
Up to 4 years	0,38	0,05 – 3,26	0,38
From 5 to 8 years	0,70	0,06 – 7,89	0,77
From 9 to 11 years	0,026	0,00 – 2,08	0,10
Above 11 yeares	0,06	0,00 – 2,82	0,15
Marital Status			
Married (Reference)			
Widower	2,24	0,22 – 22,51	0,494
Single	0,44	0,00 – 47,7	0,734
Other	2,58	0,04 – 153,50	0,649
Number of residents in the Household	0,70	0,17 – 2,92	0,63
Elderly Income	8,52	1,11 – 65,30	0,039
Family Income	3,07	0,75 – 12,59	0,119
Presence of a caregiver	95,0	2,10 – 4298,90	0,019
Tinetti gait	0.55	0,31 – 0,96	0,037
Tinetti Balance			
Low risk of falls (Reference)			
Moderate risk of falls	1,14	0,02 – 58,20	0,94
High risk of falls	0,33	0,00 – 50,98	0,67

OR – OddsRatio; IC – Confidence Interval; SM = Minimum Wage * $p < 0,05$

DISCUSSION

Usually, the profile of the elderly in this study composed of: elderly between 81 and 90 years old, female, self-declared white, with low education, widowed, with children and caregiver, with low income and living in houses with less than two people. Those characteristics reiterate what has already been evidenced in the literature, underscoring the increase in longevity and the feminization of aging[18-19].

Nevertheless, we identified that the vast majority (78.6%) of the elderly studied were female, corroborating with the studies by Lopes et al., 2014[19] and Clares et al., 2011[20]. When comparing the groups, the elderly women were stillthe majority. Though, we noted a decrease in the frequency of women in the dependent elderly group, and this difference was statistically significant (p = 0.005). Gomes, Nascimento and Araújo 2007[20] present that women take better care of themselves, carry out almost all domestic activities, take care of their children and are more active, which may be contributing to a more active, healthy and independent aging.

With respect to age, it was noted that the fourth age (≥ 80 years) elderly had considerably greater functional dependence (p = 0.055), a result previously expected, since the aging process represents an overburden for all systems, which may be leaving the elderly vulnerable to falls and other functional impairments[21]. It was also observed that the gradual decline in functional capacity is concerned to the progressive enhance in age. Studies by Alves, Leite and Machado 2012[23] showed that the probability of elderly present impairment of functional capacity increases considerably with advancing age.

The study of Mello, Engstrom and Alves 2014[24] characterized functional dependence with the fact that a person requires help or assistance to execute an activity, or if a person is unable to perform a task. Changes pertinent to the aging process appear as a result of advancing age and, occasionally the presence of the caregiver becomes important[24].

Nevertheless, in some cases, the presence of the caregiver can hustle the natural functional decline to the aging process, considering that the elderly can be accommodated, gradually leading them to interrupt their activities, as stated by Pampolim et al., 201712. Macedo et al., 2012 declare that, in some situations, the dependence of the elderly is associated with the ability to perform a task, as well as the expectations of other people in relation to what the elderly person is capable of doing, besides the opportunities given to these elderly. In this sense, a very protective environment, which does not encourage the independence of the elderly, and where family members / caregivers end up performing tasks that the elderly would still be able to execute alone or with little assistance, helps in their functional decline.

This study identified that the presence of the caregiver in the group of dependent elderly people was significantly (p = 0.002) higher. Amendola, Oliveira and Alvarenga 2011[25] highlighted the importance of the caregiver knowing how to identify and deal with the degree of dependence of the elderly, in order to help only in what is really necessary and avoid overprotection and increased dependence on the elderly[25]. According to Ursine; Lamb; Moraes 2011,[26] the restriction to the home - which can be promoted by family overprotection and the presence of the caregiver - is an insidious and dynamic process, which can be modified or prevented, if there is adaptation of the environment and adequate intervention in its risk factors. The restriction of the

elderly to the domestic environment combines functional dependence with an increased risk of comorbidities and loss of autonomy[26].

Recognizing that falls may lead to worsen health in the elderly, contributing to increased morbidity and mortality, family members decide for the presence of the caregiver in order to prevent complications. In agreement to Machado et al. 2009[27] and Soares et al. 2011[28], falls may affect the functional capacity, autonomy and the level of dependency of the elderly, as it is related to anatomical changes based onthe natural aging process and on several pathologies that may head the elderly to need help. Thus, the prevention of falls is an essential item for the health of the elderly, and also a situation that involves caregivers, family members and health professionals, taking into account that this situation can directly influence the functionality of the elderly[27-28-29].

Ribeiro et al. 2015[5] stated that the assessment of the of the elderly functionality is asignificant parameter in the practice of gerontology, as it offers relevant information about their health and the need for help from third parties to perform the activities of daily living. Functional assessment can be implemented using a variety of instruments, including the Functional Independence Measure (FIM). We identified that 47 elderly people were classified as dependent. Based on the FIM, 93.8% have a caregiver, manifesting that dependence can be a predictor for the presence of a caregiver, corroborating the studies carried out by Alves et al. 2007[30] and Colomé et al. 2011[31] who demonstrate a strong influence of chronic diseases concerned the elderly on functional capacity, and that when they compromise autonomy, the presence of a caregiver may be necessary to provide assistance[5-30-31].

The Logistic Regression analysis results derived from this study demonstrate that the most influential factors in the functional dependence of the elderly are: the elderly's income (p = 0.039), Tinetti's gait domain (p = 0.037), the presence of a caregiver (p = 0.019) the work of Pampolim et al, 2017, who found an influence of 48% of the sociodemographic factors of the elderly's functional dependence on the presence of the caregiver, which is a strong and significant predictor of this outcome. In the current study, we observed that furthermore these sociodemographic factors, the risk of falls also favors functional dependence by an additional 27.7% [12].

Functionality means the integrity of structures, the individual's physical and mental functions, enabling them to accomplish activities and take part in a social context in anautonomous way. The disability of the elderly has significant implications for the family, the community, the health system as well as their own life, considering that it leads to greater vulnerability and dependency, besides the reduction of the well-being, and the quality of life of the elderly[32]

After checking the relationship between functional capacity and income, we identified that when the elderly person has a higher income, is much unlikely that he will present a poor functional capacity.Education, in contrast, presented itself as a protective factor. This fact is justified by the principle that elderly individuals with a higher educational level are less likely to be exposed to risk factors for diseases and to submit to inadequate working conditions.

Thus, the dependence of the elderly may take place due to the natural aging process, the great family protection, the presence of a caregiver and mainly due to the increased risk of falls. Aging, dependence and the presence of the caregiver request new

forms of assistance from health professionals. It is understood that the risk for falls increases proportionally with the number of risk factors, as it is an event that is hardly the result of an isolated factor. Hence the importance of Physiotherapy acting preventively in relation to falls and consequently contributing to the independence of the elderly, seeking to act on the greatest possible number of these factors[33].

CONCLUSION

The sociodemographic factors and the presence of the caregiver enhance the functional dependence of the elderly homebound elderly and the risk of falls further increases this situation.

The population growth has been occurring through a continuous process of automation of daily practices and technological advances, where the release of muscle groups is increasingly observed in basic daily activities, such as remote control, elevators, access the help of third parties, among others.It demonstrates that there is a gap in scientific knowledge, avid for new research that intends to emphasize and rectify the main negative interventions that may interfere in the active, healthy and vital aging process.

The rehabilitation operates by performing muscle strengthening, gait training - on stable and unstable ground, as well as promoting improved posture and the proprioceptive adaptive response. When associated with other pathological conditions, it is crucial that the intervention is geared towards the patient's cognitive, motor and sensory readjustment. Other significant strategies implicate improving flexibility and preventing deformities.

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Original Article

ANALYSES OF THE HEPATOTOXIC EFFECTS RELATED TO MTX USE IN PSORIASIS TREATMENT

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Keywords

Psoriasis;
Methotrexate;
Liver;
Transaminases.

Abstract

Objective: Analyze the use of methotrexate and its possible hepatotoxic effects in psoriasis patients at the outpatient dermatology clinic of the Santa Casa de Misericórdia de Vitória Hospital. Method: The present study is cross-sectional, retrospective, descriptive, elucidative and quantitative. All data were collected by analyzing medical records of patients with moderate to severe psoriasis who used methotrexate from 2006 to 2016 at the outpatient dermatology clinic of the Santa Casa de Misericórdia de Vitória Hospital. Results: Of a 50 patients sample, 13 (26%) developed deranged transaminases, and methotrexate withdrawal was necessary in only 6 (12%) patients, which presented transaminases value greater than twice the upper limit of the normal range. There was no development of hepatic cirrhosis related to drug use in any case. Conclusion: Methotrexate can be used with safety and effectiveness as a long-term therapy as long as there is a careful selection of patients prior to therapy initiation and regular laboratory follow-up to assess the development of liver abnormalities.

INTRODUCTION

Psoriasis is a chronic inflammatory disease that affects the skin and joints. It is immune-mediated, of genetic base, with great polymorphism of clinical expression. Current studies propose that the onset of psoriasis is multifactorial in origin, alleging as factors firmly concerned the onset or exacerbation of the pathology infections, metabolic changes, emotional exacerbation, physical trauma, drugs, smoking and alcoholism. The disease has a universal occurrence between sexes and age, with peaks of incidence in the second and fifth decades of life. It is a common dermatosis in clinical practice and it is usually manifested by well-defined erythematous-scaly plaques, occasionally pruritic, in areas of constant trauma to the skin, such as elbows, knees, pre-tibial region, scalp and region sacred. The size and number of plaques are variable, with the possibility of affecting the entire skin, and in 8% of moderate to severe psoriasis, joint manifestations may occur. Among the cutaneous forms it can mentioned: guttate psoriasis, psoriasis vulgaris or plaque, palmoplantar psoriasis, nail psoriasis, pustular psoriasis and erythrodermic psoriasis.[1,2]

Psoriasis was previously considered an exclusive skin disease, and healing of skin lesions was considered the primary goal of treatment. Nevertheless, the knowledge of dermatological disease has advanced a lot in the last decades, and it is now recognized as a multisystemic disease, strongly related to inflammatory bowel disease, uveitis, psychiatric disorders, and, more recently, osteoporosis / osteopenia, chronic obstructive pulmonary disease and apnea obstructive sleep. In recent years, metabolic syndrome and its isolated components (hypertension, type 2 diabetes mellitus, obesity and dyslipidemia) have also been related to psoriasis. The Understanding of these associations in

clinical practice implies a new attitude of the dermatologist in face of this disease.[1,3]

The diagnosis of psoriasis is clinical, confirmed through histopathology (skin biopsy) in less typical cases. Considering that it is an immune-mediated, genetic-based disease with an increase in inflammatory mediators, particularly the tumor necrosis factor (TNF) -alpha, psoriasis has no cure, however it has good control in most cases. The treatment of the disease relies on the clinical form, age, sex, severity and extent of the lesions, the patient's clinical condition and socioeconomic status. It is important to consider the representation of psoriasis in the impairment of the patient's quality of life, as the disease can be understood as stigmatizing by the individual, in a very different way from non-dermatological diseases.[1,2]

Consequently, among the topical control medications are: corticosteroids, coaltar (variable concentration of 1 to 5% of tar in the form of pastes, ointments, gels, lotions and shampoos, in the latter, in the form of liquor carbonis detergens), Goeckerman's method (association of coaltar with ultraviolet B radiation), anthralin or dithranol and analogues of vitamin D. Topical corticosteroid is considered the gold standard medicine in the treatment of thicker lesions, with clobetazole propionate being the most used. The topical-systemic medication used when the lesions cannot be controlled by topical medication or when the extent / severity of the condition so requires, is the association of psoralen and ultraviolet A radiation (PUVA), highly effective in psoriasis and, obtaining whitening of the lesions, can be used as maintenance therapy. Systemic medications include methotrexate, acitretin, cyclosporine A and immunobiological drugs.[2]

Methotrexate is a derivative of aminopterin used for the first time by Farber, in 1948, in children with acute lymphocytic leukemia. In 1951, Gubner et. al published the first evidence on the action of the precursor drug methotrexate, considering it effective in the treatment of psoriasis. The FDA approved methotrexate for the treatment of psoriasis in 1972. The drug has an antiproliferative, anti-inflammatory and immunosuppressive mechanism of action. The compound is structurally similar to folic acid, and binds competitively and irreversibly to dihydrofolate reductase. This connection inhibits the conversion of dihydrofolate to tetrahydrofolate, which is the cofactor necessary for the transfer of carbon atoms, which are fundamental to the formation of the nucleotides purine and thymidine for the synthesis of DNA and RNA. MTX (methotrexate) also acts by increasing the concentration of adenosine, mediating the secretion of cytokines in macrophages and neutrophils and in the expression of adhesion molecules (L sectin, beta2 integrin and CD11b)

Methotrexate is the drug of choice for systemic psoriasis therapy. Its use is indicated in erythrodermic psoriasis, psoriatic arthritis, moderate to severe, acute pustular psoriasis (generalized or localized) and severe or disabling plaque psoriasis. The drug is especially used in patients who fail to improve after topical therapy and phototherapy, or in cases where these therapies are contraindicated. Methotrexate is also indicated as an element of combination therapy with other immunosuppressive drugs, mainly in combination with immunobiological drugs. The drug is available as 2.5 mg tablets or as a 2 ml solution for injection (50 mg MTX), for intramuscular (IM) or subcutaneous (SC) use. Taking the medication can be prescribed in a single weekly dose or subdivided into three doses, with an interval of 12 hours.[4]

The incidence of adverse reactions involved in MTX connected with psoriasis is calculated to be nearly 78%. Adverse symptoms arise with variable severity, with a pronounced tendency to decrease after dose reduction or with discontinuation of treatment. The most serious complication concerned MTX therapy is myelosuppression. Leukopenia and thrombocytopenia can emerge at any stage of treatment, though, they usually occur between the 7th and 10th day. Gastrointestinal intolerance to MTX, characterized by nausea, vomiting, diarrhea and anorexia is the most common effect. The adverse liver effects are roughly due to the extended use of the drug, which can scope from a simple elevation of liver enzymes to steatosis, fibrosis and liver cirrhosis. Recently, liver damage induced by methotrexate is clinically and histologically similar to hepatic steatosis, and there is an increased risk of progression to non-alcoholic steatohepatitis (NASH) with higher cumulative doses or in the presence of risk. Evidence demonstrates that folic acid supplementation is eligible to reduce hematological and gastrointestinal side effects, and also to encourage reduction in the absolute risk of hepatotoxicity without, however, decreasing the effectiveness of the drug.[4-7]

An essential element related to MTX therapy is the problem with the drug's interactions with other drugs, and periodic scrutiny of this possibility should be exercised, particularly in the elderly. Drugs which have the same target organ as methotrexate, such as systemic retinoids and alcohol, can synergistically increase hepatotoxicity.[4]

The selection of patients for the use of MTX must consider the criteria of absolute and relative contraindication, listed in Table 1. The relative contraindications should be carefully considered about the risk-benefit context and discussed with the patient. Besides a careful history and clinical examination, the candidate for MTX therapy must undergo the following pre-treatment laboratory evaluation: complete blood count, including platelet count; urea and creatinine, type I urine (and in the elderly, creatinine clearance); alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total proteins and fractions, gammaglutamyltransferase (gamma-GT), beta- HCG (women). Based on patient's epidemiological history, serology for hepatitis A, B and C and determination of antibodies to the acquired immunodeficiency virus (HIV) may be requested. While some experts defend the need to order serology for hepatitis in all patients prior to methotrexate therapy, others do not obtain viral titers unless there is further evidence of viral hepatitis, such as elevated liver function tests.[4,8]

Understanding concerned liver disease in psoriasis has risen. The presence of other possible mechanisms that promote the development of steatosis, fibrosis and cirrhosis in psoriatic patients has been revealed. Obesity, arterial hypertension, dyslipidemia and type 2 diabetes mellitus (usually related to metabolic syndrome) are common in individuals with psoriasis and are known to be precursors of NASH, a precursor of fibrosis. Alcohol abuse, another hepatotoxin, was also noted in individuals with psoriasis, enhancing the development of liver fibrosis.[7]

Liver biopsy is the gold standard test for the diagnosis of liver fibrosis and, for this reason, it is important for drawing causal conclusions. The clinical scenario of each patient must rule its need. The updated guidelines indicate that patients considered for methotrexate therapy should be divided into two groups on the bases of their risk factors for liver injury (Table 2).[8]

Patients with no risk factors for liver injury are probably to have a low risk of hepatotoxicity and progression to fibrosis. Hence, the follow-up criteria for MTX as reported by the guidelines of the American College of Rheumatology (ACR) and the British Society for Rheumatology (BSR), demonstrated in Table 3, can be applied to these patients. This approach was validated and exhibited a safe reduction in the number of biopsies conducted.[8]

There is a consensus that patients with one or more risk factors for hepatotoxicity should follow the stricter guidelines previously published, presented in Table 4.[8]

In patients selected for a liver biopsy, on the bases of the conditions considered above, the relative decision to continue or discontinue methotrexate is made after analyzing the biopsy results. The recommendations are in accordance with liver abnormalities using the Roenigk scale and are shown in Table 5.[8]

It is important to note that this procedure has real morbidity and occasional mortality, and cannot be indicated, or should be postponed, if the risks of performing it exceed the benefits for the patient. In recent years, the dosage of the pro-collagen III aminoterminal peptide (PIIINP), which is still poorly available in Brazil, has been used as a potential marker for detecting liver fibrosis. A recent study compared the guidelines of the American Academy of Dermatology (AAD) of 1998 and the guidelines developed in Manchester for the use of PIIINP and showed seven times less biopsies in this last group. Another study revealed that liver biopsies could be avoided entirely if the use of PIIINP was consolidated. Most dermatologists in the UK use this test to monitor liver fibrosis.[8]

It is recommended that patients using MTX be monitored in the laboratory throughout the treatment period. The complete blood count with platelet count should be performed 7 to 14 days after starting treatment or after increasing the dose of MTX, and every 2 to 4 weeks in the first months, then approximately every 1 to 3 months, depending on the number of leukocytes and the stability of the patient. Patients with risk factors for hematological toxicity need closer monitoring, particularly at the beginning of therapy and after increasing doses. Liver assessment should be performed every one or two months, with measurement of liver enzymes and albumin levels, every six months.[4,8]

This study was conducted in order to analyze the use of MTX, and its possible hepatoxic effects, in patients with moderate to severe psoriasis, at the dermatology outpatient clinic of Santa Casa de Misericórdia de Vitória Hospital.

METHODS

This study is cross-sectional, retrospective, descriptive, elucidative and quantitative. At first, a literature review was conducted and the sources used for bibliographic research were articles from Pubmed, Medline and Scielo. The following keywords were used: “psoriasis”, “methotrexate”, “liver”, “transaminases”, published between 2000 and 2016, in English and Portuguese.

Second stage, a retrospective cohort study was carried out, composed of a simple random sample of 50 patients undergoing psoriasis using MTX. Inclusion criteria were patients using MTX and patients of both sexes. Exclusion criteria were defined as patients who had laboratory-proven liver changes prior to starting treatment with the drug.

Data were collected via analyzing medical records of patients with moderate to severe psoriasis that used MTX from 2006 to 2016 (duration of 10 years), from the dermatology outpatient clinic of Hospital Santa Casa de Misericórdia de Vitória, accomplished by the medical team of Dermatology. Individual assessment of patients and details of changes in biochemistry and liver function (transaminases, bilirubins, alkaline phosphatase, gamma glutamyltransferase, albumin and prothrombin activity time), blood count and serology of hepatitis A, B and C viruses and ultrasound of abdomen when possible, in addition to excluding the use of other hepatotoxic drugs.

Data analysis was conducted in the SPSS version 23 program, using descriptive statistics methods to characterize the profile of patients using MTX, percentage analysis of the sample concerning the route of medication administration, initial dose of MTX, ultrasound of abdomen, serology, skin biopsy and presence of comorbidities. The prevalence of laboratory liver disorders in patients using MTX was calculated, the mean and standard deviations of: age, age at diagnosis of psoriasis and initial MTX dose, in addition to the mean, standard deviation, median and minimum and maximum dose values cumulative MTX to hepatotoxicity.

RESULTS

The results are on the basis of the analysis of medical records of 50 psoriasis patients using MTX, over a 10-year period (2006 to 2016). Demographic data and clinical characteristics of the patients are demonstrated in Table 6. Only 2 (4%) patients in the sample underwent skin biopsy for the purpose of corroborating the diagnosis of psoriasis, the remaining patients were clinically diagnosed.

The initial dose of MTX varied from 5 mg to 15 mg weekly when oral (VO) and from 20 mg to 25 mg weekly when SC, with an average of 9.7 ± 4.1 mg. In the sample, 3 patients (6%) used the SC medication, 45 (90%) patients used MTX VO and 2 (4%) patients used both presentations.

Out of 50 patients in the sample, 13 (26%) developed changes in transaminases. AST normal values between 12-38 U / L and ALT between 7-41 U / L were considered as reference. Among patients with changes in transaminases, 7 (54%) had an alteration less than or equal to twice the ULN (upper limit of the normal range) (values found for AST between 52-76 and ALT between 48-79), 4 (31%) had an alteration greater than twice and less than five times the ULN (values found for AST between 80-122 and ALT between 96-134) and 2 (15%) presented changes in transaminases greater than 5 times the ULN (values AST between 244-415 and ALT 258). Thus, it was stablished that MTX withdrawal was necessary only in patients with transaminase changes greater than twice the ULN, that is, in 6 (12%) patients. For the remaining 7, it was possible to continue treatment at the same dose or at a reduced dose value, with regular monitoring of liver function and biochemical tests. The average cumulative dose of MTX until reaching hepatotoxicity was 781.9 ± 753.9 mg, with a median of 710 mg and minimum and maximum values 45mg and 2615mg, respectively. Serologies for the investigation of viral hepatitis were performed in 19 (38%) patients, all of whom had non-reactive serologies. Among these, 8 patients had hepatoxicity, thus excluding, in these patients, changes in transaminases concerned viral hepatitis.

Among the 13 patients with transaminase disorders, in our sample, 5 (38%) had comorbidities such as type 2 diabetes mellitus, arterial hypertension, dyslipidemia or obesity. Eight (16%)

patients in the study had undergone abdominal ultrasound. Among them, 2 presented USG (ultrasonography) of the abdomen with hepatic steatosis, without transaminase alterations and 3 presented USG with hepatic steatosis and transaminase alteration. It should be pointed out that out of the 5 patients with abdominal ultrasound with a pattern of hepatic steatosis, 3 were patients with a metabolic syndrome profile, with 2 of these showing alteration of associated liver biochemistry. No patient underwent liver biopsy.

DISCUSSION

Psoriasis is a quiet common, chronic, immune-mediated skin disease of unfamiliar cause, predisposed to genetically determined disease. Such predisposition was proven through research in monozygotic twins, where 95% of psoriasis was demonstrated in both. At present, studies indicate that the onset of psoriasis is of multifactorial origin. Factors firmly concerned the onset or exacerbation of the disease are bacterial and / or viral infections (streptococcal infection and HIV), metabolic changes (puberty, pregnancy and menopause), emotional stress, physical trauma, excessive sun exposure, smoking, alcoholism and use of some drugs such as lithium, beta blockers, antimalarials, non-steroidal anti-inflammatory drugs and even the abrupt withdrawal of systemic corticosteroids. It is noteworthy that environmental, geographic and ethnic aspects can interfere with its incidence, nevertheless, in Brazil, there are no studies on its prevalence, considering that 1% of the population is affected. Psoriasis can occur in any age group, with peaks of incidence in the second and fifth decades of life.[1,2] The average age at diagnosis of psoriasis in our sample was 41.2 ± 16.9 years of age. In our sample, there was a preponderance of males, with a male-to-female ratio of 1.38: 1.00, which is very close when in comparison with the study by Ng, Lee, Lee, Wong[9], in which a total of 66 psoriasis patients who received MTX during the study period, with a male to female ratio of 1.44: 1.00.

In recent years, progress has been made in identifying the inflammatory mechanisms involved in the pathogenesis of psoriasis. A large number of inflammatory molecules are produced in skin lesions of patients with psoriasis, such as TNF, IL (interleukin) -1, IL-6, IL-8, IL-17, IL-22, IL-23, growth factor vascular endothelial, interferon-γ. It is understood that they are released into the systemic circulation based on the severity and extent of skin lesions.[11]

Experimental and epidemiological studies have correlated certain interleukins, cytokines and hormones (adipokines) with cardiovascular disease, metabolic syndrome, obesity and type 2 diabetes mellitus, making psoriasis a risk factor in the systemic development of these comorbidities. Furthermore inflammation, other factors should be taken into account to explain this association, such as common risk factors (e.g. smoking and alcohol consumption), treatment (e.g. use of immunosuppressive agents or drugs that altered the lipid profile) or genetic inheritance of susceptibility loci.[10] A recent meta-analysis revealed that in psoriasis patients have a higher prevalence of metabolic syndrome compared to the general population, and in patients with more severe psoriasis, the chances are even greater.[11]

In a large population-based study in the United Kingdom, Langan et al[12] found a 22% increase in the chances of developing the metabolic syndrome in people with mild psoriasis, a 56% increase in those with moderate disease, and a 98% increase in patients with severe psoriasis. Insulin resistance was found in non-obese patients

with psoriasis and correlated with the severity of the disease, increasing the risk of developing diabetes. In vitro evidence shows a common inflammatory relationship between psoriasis and dyslipidemia. Cytokines such as IL-1, IL-6 and TNF-α, which mediate psoriasis, can alter the function of hepatocytes and arterial smooth muscle cells, leading to the development of arterial plaques. Besides, these interleukins increase lipid levels. Psoriasis is related to increased oxidative stress, with oxidized LDL elevated in severe psoriasis.[9]

Accordingly, it should be pointed out that in our study 14 patients had comorbidities, 6 (12%) with type 2 diabetes mellitus, 11 (22%) with systemic arterial hypertension, 6 (12%) with dyslipidemia, 2 (4%) with metabolic syndrome and 2 (4%) with obesity. Nevertheless, we were unable to establish when such comorbidities were diagnosed with regard to the diagnosis of psoriasis, by virtue of the lack of prior medical monitoring by these patients. The recommendation is that all patients with psoriasis undergo a detailed medical evaluation and receive specific treatment for different comorbidities. Physicians should be aware of the increased potential risk of psoriasis, in particular, of moderate to severe forms, for the development of metabolic syndrome and therefore cardiovascular disease and increased risk of mortality.[10]

The approval of methotrexate for the treatment of psoriasis by the FDA and the publication of the initial guidelines in 1972 happened simultaneously. The Brazilian Consensus on Psoriasis recommends the prescription of MTX in a single weekly dose or subdivided into three doses, with an interval of 12 hours. As a result of the greater toxicity, the dose should not be divided into daily doses. It recommends an initial dose of 5.0 to 7.5 mg, with a gradual weekly increase (2.5 to 5.0 mg, every week), in accordance with the results of the control tests or starting with a dose of 15 mg / week besides performing weekly controls until dose security is achieved in that particular patient. For patients who do not respond or need doses greater than 15 mg, a change from VO to SC or IM should be an alternative. The total weekly dose should not exceed 25 mg.[1]

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Out of 50 patients in our sample, 13 (26%) developed changes in transaminases. Nonetheless, merely 6 patients (12%) had MTX discontinuation, since they had an elevation greater than 2 times the ULN. This result is very similar if compared to the study by Ng, Lee, Lee, Wong[9], in which of the 66 patients in the sample, removal of MTX as a result of severe hepatotoxicity was necessary in only 6 (9%) patients. Thirty-two (48.5%) patients developed moderate liver enzyme changes and they were able to continue treatment with the same dose or with a reduced dose value, which is against our study, in which only 7 (14%) patients had moderate

changes and, therefore, it was not required to withdraw the medication.

In that same study, the initial dose of MTX ranged from 5 mg to 10 mg weekly, with an average of 8.3 ± 3.02 mg, while in our study the initial dose had an average of 9.7 ± 4.1 mg, quite approximate data. The cumulative dose of MTX related to altered transaminases in the study by Ng, Lee, Lee, Wong[9] was 552.3 ± 596.1 mg, while ours was slightly higher, with a value of 781.9 ± 753.9 mg. Conversely, Heydendael et al[13] performed a study with a total of 43 patients with moderate to severe psoriasis selected at random, receiving treatment for 16 weeks with methotrexate (initial dose 15 mg per week). The treatment had to be stopped in 12 (27.9%) of the patients as a result of the increased levels of liver enzymes (the highest level found was ALT 198 U / L). These laboratory changes were transient and the values reverted to normal within four to eight weeks after stopping treatment.

In the current study, folic acid supplementation was not conducted in all patients, contrary the patients in our sample, in which all of them received folic acid by mouth. There are no evident recommendations on the optimal dose of folic acid that should be administered with MTX. The main purpose of supplementation is to prevent adverse reactions from the hematopoietic system and decrease hepatotoxicity. The broadly recommended dose of folic acid is 15 mg per week, administered at least 12 hours (usually 24-48 hours) after the last dose of MTX. Another option is to use 1-5 mg of folic acid per day (except on the days of MTX use).[8]

Another study by Warren et al,[14] consisted of a sample of 330 psoriasis patients who had completed at least 3 months of methotrexate therapy, revealed that 65 (19.7%) of the patients using MTX developed hepatotoxicity. Haustein and Rytter[15] carried out a study with 157 patients with the forms of plaque psoriasis: disseminated, erythrodermic, pustular and psoriatic arthritis. Patients were treated with a low dose of methotrexate (15-20 mg maximum weekly dose, most for long periods). It was demonstrated that 40 (25%) of the patients developed an increase in liver enzyme levels or signs were identified by ultrasound or liver biopsy of hepatotoxicity. Nonetheless, in only 22 cases (14%) the medication needed to be discontinued. There was no case of liver cirrhosis concerned the MTX treatment, as in our study. The study by Conway, Low, Coughlan, O'Donnell, Careyl[16] showed that the use of methotrexate is actually connected with na increased risk of liver enzyme changes in patients with rheumatoid arthritis, psoriasis, psoriatic arthritis and inflammatory bowel disease. Even though the majority of transaminase increases were minimal (7.9%), the most significant increases occurred in 3.3%. However, this did not translate into an increased risk of developing fibrosis, cirrhosis, liver failure or death related to liver disease.

The histopathological characteristics of methotrexate-induced liver toxicity are similar to NASH, a liver histological pattern noted in a large proportion of obese, dyslipidemic or diabetic people with non-alcoholic fatty liver disease. It is common knowledge that patients with psoriasis have a higher incidence of these comorbidities, whose presence is considered to be a risk factor for the development of liver disorders with a lower cumulative dose of MTX, and probable worsening of pre-existing NASH with the use of methotrexate.[8] In in our sample, 5 patients who underwent abdominal USG had a pattern of mild hepatic steatosis, supporting the data that MTX can be considered a steatogenic drug. Out of these 5 patients, 3 had a metabolic

syndrome profile, and 2 of them also developed liver biochemical changes.

Liver biopsy is the gold standard procedure for diagnosing liver fibrosis, however it is not an innocuous procedure. The risk of advanced fibrosis must be balanced with the risk of liver biopsy complications. hopefully, in patients with psoriasis the risks tend to be lower than in patients with other diseases. These risks include subcapsular hemorrhage, perforation of the gallbladder, pneumothorax and hemoperitoneum. Most harmful events emerge in patients with changes concerned other diseases.[8] In this study, no patient underwent liver biopsy, for economic reasons, since the study was performed in a public hospital, and because the risk was considered higher that the benefit in cases that evolved with hepatotoxicity with MTX use.

Psoriasis patients have a higher rate of alcohol consumption, depression and suicide than the general population. The disease can present a considerable impact on social relationships, self-image and self-esteem. It is crucial that psychosocial aspects are always considered when evaluating therapeutic options.[1] In our group of patients, 1 (2%) were alcohol abuse and 3 (6%) had symptoms of depression, nervousness or anxiety.

CONCLUSION

Psoriasis is a relevant disease and, therefore, the number of patients using methotrexate, a hepatotoxic drug, is significant. In our sample, we found 26% of patients with transaminase changes after using methotrexate, concluding that the event of hepatotoxicity, involved in the use of medication, is a relatively ordinary event. Regardless these results, discontinuation of the medication was required in only 12% of the patients, who had a transaminase value twice as high as the ULN. These data corroborate the current literature, which illustrates that most cases of hepatotoxicity related to the use of MTX do not translate into an increased risk of developing fibrosis, cirrhosis, liver failure or death concerned liver disease.

Consequently, we are aware that MTX, used as a systemic therapy for the treatment of psoriasis, is an effective and relatively safe medication, which can cause liver damage, overall, from mild to moderate degree. Cautious selection of the candidate patient for MTX treatment is crucial. The criteria of absolute and relative contraindication concerned the use of the drug must be taken into account, and the relative contraindications must be considered in the risk-benefit context and discussed with the patient. All patients taking the medication should receive regular laboratory follow-up to evaluate the development of liver disorders, particularly those with associated risk factors, in which abdominal USG may be required throughout the treatment for better assessment and liver biopsy.

Accordingly, the current study demonstrates that the treatment of a chronic disease will always be a challenge for the physician, since administering drugs for continuous use is frequently an uncomfortable situation. For the purpose of being successful in MTX therapy, it is highly important to follow this patient closely, maintaining a good doctor-patient relationship to ensure adherence to treatment, always advising on possible, but avoidable liver damage or other adverse events concerned damn it.

Table 1 - Relative and absolute contraindications in therapy with metrodexate

Relative contraindications	Absolute contraindications
Patient's inability to understand or follow the drug guidelines	Pregnancy and lactation
Altered kidney function	Hepatical cirrhosis
Alcohol abuse	Active hepatical infection
Associated metabolic diseases such as: diabetes and obesity	Liver failure
Liver disease characterized by abnormal liver enzymes, abnormal liver function tests, history of liver disease	
Hematological changes	
Associated metabolic diseases such as: diabetes and obesity	
Men and women planning to conceive	
Active infectious disease or history of disease with potential for recurrence (tuberculosis, for example)	

Source: Brazilian consensus on psoriasis, 2012

Table 2 – Risk factors for methotrexate liver toxicity

History or current consumption of alcohol
Persistently abnormal liver biochemistry values
History of liver disease, including chronic hepatitis B or C
Family history of hereditary liver disease
Diabetes mellitus
Obesity
History of significant exposure to drugs or chemicals with liver toxicity
Lack of folate supplementation
Hyperlipidemia

Fonte: Kalb, 2009

Table 3 – Monitoring of hepatotoxicity in low-risk patients

Without baseline liver biopsy Monitor liver function tests monthly for the first 6 months, and then every 1 to 2 months. For small elevations (<2 times the LSN), repeat in 2 to 4 weeks. For moderate elevations (> 2 times, but <3 times the ULN), monitor more closely, repeat in 2-4 weeks, and dose reduction if necessary. For persistent elevations in 5 of 9 AST levels over a 12-month period or if there is a decline in serum albumin (in the context of normal nutritional status) below the normal range in a well-controlled disease scenario, liver biopsy should be performed. Consider continuing follow-up according to the ACR guidelines above without biopsy. Or Consider liver biopsy after a total cumulative dose of 3.5-4.0 g. Or Consider switching to another agent or discontinuing therapy after a total cumulative dose of 3.5-4.0 g.

LSN, Upper limit of the normal range; AST, Aspartate Aminotransferase;
ACR, American College of Rheumatology
Source: Kalb, 2009

Table 4 – Monitoring of hepatotoxicity in high-risk patients

Consider using a different systemic agent. Consider late baseline liver biopsy (2 to 6 months after starting therapy to determine medication effectiveness and tolerability). Repeat liver biopsies after approximately 1.0 to 1.5 g of cumulative doses of MTX.

Source: Kalb, 2009

Tabela 5 – Recommendations based on liver biopsy results regarding the decision to decision to continue or discontinue methotrexate

Patients with grade I or II of alteration can continue to receive methotrexate. Patients with grade III-A changes may continue to receive methotrexate therapy, but liver biopsy should be repeated after approximately 6 months of methotrexate therapy. Alternative to systemic therapy should be considered. Patients with grade III-B changes should be discontinued on methotrexate. Exceptional circumstances, however, may require continued therapy with methotrexate, with minimal follow-up through liver biopsy.

Grade I - Normal liver tissue, or mild fatty infiltration and mild inflammation of the portal space;
Grade II – Moderate to severe fatty infiltration; moderate to severe inflammation of the portal space;
Grade IIIA - Presence of mild fibrosis;
Grade IIIB - Presence of moderate to severe fibrosis;
Grade IV - Presence of liver cirrhosis;
Source: Kalb, 2009

Table 6 - Demographic data and clinical characteristics of patients with psoriasis using methotrexate.

Variables	All cases (n=50)
Age (years)	
Average ±SD	52,8 ± 15,7
Variation	13-80
Sex n(%)	
Female	21 (42%)
Male	29 (58%)
Diagnostic age (years)	
Average ±SD	41,2 ± 16,9
Variation	13-80
Comorbidities n (%)	
Type 2 diabetes mellitus	6 (12%)
Arterial hypertension	11 22%)
Dyspipidemia	6 (12%)
Metabolic syndrome	2 (4%)
Obesity	2 (4%)
Alcoholism	1 (2%)
Crohn's disease	1 (2%)
Idiopathic Ulcerative Retocolitis	1 (2%)
Depression / anxiety / nervousness	3 (6%)

N, número; DP, desvio padrão.
Fonte: Próprios autors.

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Original Article

CADMIUM EXPOSURE EFFECTS ON THE BLOOD PRESSURE AND MYOCARDIAL CONTRACTILITY.

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Keywords

Cadmium;
Blood pressure;
Heart.

Abstract

Objective: To develop a literature review on the effects of cadmium exposure in the heart and blood pressure. Methods: The search approach was based on a narrative review for selection of studies and interpretation of information. To this end, a review study was conducted in books, theses, dissertations, magazines and papers acquired from databases: LILACS, PUBMED, MEDLINE and SCIELO. **Results**: The studies suggest that cadmium exposure is involved in the development of hypertension, associating the deleterious effects of cadmium on vascular endothelium as the main cause in the genesis of hypertension. **Conclusion**: There is a need for more studies in order to elucidate the mechanisms involved in these changes promoted by cadmium, particularly in the heart. Nevertheless, it is important to recognize the risks of intoxication by this metal because it has been associated with increased mortality from cardiovascular diseases.

INTRODUCTION

Cadmium (Cd) is a metal extremely toxic to man, even in low concentrations, and not essential to human metabolism. There are a number of different modes of environmental contamination by Cadmium, but they include contamination from the use of pesticides and agricultural fertilizers, as well as the disposal of industrial wastes derived from the production of polyvinyl chloride (PVC), plastics, glass and batteries[1]. With this widespread use of the metal, vegetables, seeds and tobacco leaves accumulate high levels of cadmium from the soil[1]. Thus, tobacco smoking has become the main form of non-occupational exposure to cadmium[2].

A large number of scientific evidences relates this metal to the increased blood pressure in humans and the development of hypertension, atherosclerosis and other cardiovascular diseases[3,4,5].

Smoking is considered a source of exposure to cadmium, considering that the presence of this and other heavy metals in cigarettes has been identified as a causative agent of cardiovascular disease induced by smoking[6,7,8,9].

It is important to note that hypertension is an important risk factor for various cardiovascular diseases and that, since the 1960s, these diseases represent the leading cause of death in Brazil[10]. Therefore, this article aimed to build a review of the blood pressure and cardiac effects of exposure to cadmium, based on a collection of data from the scientific literature

METHODOLOGY

For the selection of studies and interpretation of information on the toxic effects of Cadmium on blood pressure and the heart, a narrative review was adopted. Consequently, for the construction of knowledge, a descriptive-discursive type survey of scientific production data was performed.

This review was based on studies that pointed to the toxic effects of cadmium on the heart and blood pressure. Based on the

data presented, a critical discourse on the exposed theme will be presented.

The analysis of this study was carried out through the search of electronic bibliographic data of available literature in theses, dissertations, journals and scientific articles acquired from the LILACS (Latin American and Caribbean Literature) and MEDLINE (National Library of Medicine, U.S). The electronic search was done from the combination of the descriptors: cadmium; arterial pressure; heart.

The articles were separated according to importance and insertion in the context of the topic addressed, based on a critical analysis performed from the considerations presented by reading the researched content.

RESULTS/DISCUSSION

Even though it is known that heavy metals are harmful to the functioning of the organism and to the maintenance of health, it is not yet fully known what are exactly the specific mechanisms involved by which metals produce their effects. However, there is evidence that many of these effects may result from interactions of cardiovascular system components.

3.1 Exposure to cadmium and hypertension

The World Health Organization (WHO) considers cardiovascular diseases as the central cause of morbidity and mortality in the world. In addition, the appearance or aggravation of these diseases has been related to the exposure of heavy metals considered toxic to the organism, such as cadmium[11]. Considering that about 17 million people died as a result of cardiovascular diseases in the world in 2011, the WHO estimates that in 2030 more than 23 million individuals will die from cardiovascular causes[11].

Hypertension is considered one of the main risk factors for the development of cardiovascular diseases. It is estimated that 20% of the world population is hypertensive and that in Brazil 40% of the Brazilian population can become hypertensive[12].

Since the twentieth century, cadmium has been associated with cardiovascular effects, when Asberg and Schwertze proposed changing coloration in the testicles of animals exposed to this metal. Subsequently, they attributed this effect of cadmium to the rupture of the junctions between endothelial cells and testicular capillaries, promoting edema, hemorrhage and necrosis[14,15].

According to Téllez-Plaza et al.[5], there is an association between peripheral arterial disease and the presence of cadmium in the urine, by means of the ankle-brachial index evaluation capable of detecting variations in flow in the arterial circuit caused by stenosis in the vascular bed. This study observed that individuals with a higher level of urinary cadmium were at higher risk for peripheral arterial disease. Houtman[16] noted that hypertensive individuals had higher amounts of cadmium in the urine and also noted that populations living in areas of higher cadmium contamination had higher incidences of atherosclerosis.

An increase in blood pressure was observed in animals exposed to cadmium in the diet for 3, 5, 10 and 14 months, where systolic blood pressure was 15 to 20 mmHg higher than the control group in all models of exposure[17]. Other studies have associated increased blood pressure, reduced body mass gain, and increased levels of malondialdehyde on exposure to cadmium[18,19,20]. Taking into account that malondialdehyde is a marker of lipid peroxidation, it may be the factor involved in the reduction in body mass gain and also can be viewed as a pro-atherosclerotic

factor in a model of cadmium intoxication[20].

3.2 Exposure to cadmium and endothelial dysfunction

It is believed that the mechanisms involved in the pathogenesis of cadmium-induced hypertension are multifactorial, even though they have not been clarified yet. Some authors suggest that cadmium-induced glutathione depletion leads to oxidative stress and lipid peroxidation, which are hypertensive factors[21], while others suggest interactions with calcium channels[22], sympathetic stimulation[23] and reduction of the release of vasodilatory agents[24].

It is suggested that endothelial dysfunction is involved with hypertension, considering that it may contribute to the increase of vascular resistance, favoring the onset or the aggravation of the hypertensive process[25,26,27]. Overall, some studies claim that endothelium is the primary target of cadmium intoxication with respect to the cardiovascular system, and that the interaction between the metal and the endothelium may result in imbalance of the production of vasodilator and vasoconstrictor substances and consequently, increased vascular tone[28,29,30].

Reducing the bioavailability of nitric oxide (NO) is considered one of the most important factors associated to vascular disease.[31,32,33] One of the main mechanisms involved in this process would be the increase in the production of superoxide anion and the consequent reduction of the bioavailability of NO and the production of peroxynitrite, a potent oxidizing agent.[31,32,33]

A recent study performed in our laboratory by ALMENARA and collaborators[34] demonstrated in an experimental model of exposure for 30 days in drinking water that cadmium promotes increased blood pressure from the first week of exposure. In this study, the endothelial dysfunction caused by the metal occurs due to the increase of superoxide anion production and, consequently, decrease of the bioavailability of nitric oxide. In addition, the metal promotes an increased reactivity to phenylephrine in isolated aortic rings.[34]

In another metal exposure model, 0.5 mg / kg / day for 120 days i.m., Tzotzes and collaborators[35] did not observe a change in the contractile response to phenylephrine. Nevertheless, in mice exposed to cadmium for 8 weeks via drinking water 100 mg / L, there was a reduction of the reactivity to phenylephrine.[19,30] The different results reported suggest that the effects of cadmium on vascular reactivity depends on the time of exposure as well as on the concentration of the metal.[34]

Cadmium, likewise other heavy metals, appears to be involved in an increased oxidative stress. This increase has been associated with an increased NADPH oxidase activity, increased expression of NOX-2 and the production of hydrogen peroxide, with consequent increase in the production of reactive oxygen species.[34] Other studies have also reported increased bioavailability of superoxide anion in animals exposed to cadmium.[19,30]

Changes in SOD expression reveal an important mechanism of action of oxidative stress, considering that this enzyme plays the leading role in cellular antioxidant defense. Using COS-7 culture cells exposed to cadmium, Obara et al.[36] demonstrated reduced expression of the extracellular isoform of SOD, and Ozturk et al.[37] observed an increase in SOD enzyme activity in rats treated with 15 mg / kg / day by gavage during 60 days.

3.3 Exposure to cadmium and cardiac contractility

An association between the exposure of some populations to dietary cadmium and mortality rates from cardiovascular disease has been described[38]. Alterations such as cardiac conduction system disorders, changes in blood pressure and heart rate were observed in a population of elderly women exposed to cadmium through food[39]. Besides, Wronska-Nofer et al[40] revealed rhythmic changes, such as ventricular fibrillation, in an individual after ingestion of 25 mg / kg of cadmium.

The cytotoxic effects of cadmium apparently affect the heart, because when exposed to low doses it has caused accumulation of metal in cardiac tissue, reduction of myocardial contractility[41], damage to the intercalated discs, leading to structural changes of the heart muscle[42]. Furthermore, exposure to cadmium impairs mitochondrial respiration of cardiomyocytes, inhibiting the transfer of electrons, resulting in an increase in the formation of reactive oxygen species[43,44].

Turckan et al.,[45] utilizing an animal exposure model of 100 mg L-1 of CdCl2 via drinking water, established the presence of fibrosis in the myocardium only in animals that received a lipid-rich diet, and indicated that cadmium induces apoptosis after 96 hours of exposure. They also observed that cadmium intoxication associated with moderate hypercholesterolemia or normal cholesterol levels induces the development of cardiac fibrosis and, consequently, the reduction of cardiac contractility and, thus, the deposition of cadmium in cardiac tissue in animals seems to be dependent on high levels of cholesterol[45].

Not only does cadmium affect tissue structure and cardiac muscle integrity, but also it interferes with the cardiac conduction system[46]. The metal blocks the L-type calcium channels and changes the potassium current in the ventricular myocytes, causing changes in the physiological and biochemical processes[47,48].

Using an experimental model of exposure to cadmium for 30 days in drinking water plus 100 mg L-1 of CdCl2, Vescovi[49] demonstrated that the metal was involved in increasing peripheral vascular resistance by increasing sympathetic activity, resulting in an elevated blood pressure and cardiac inotropism. Even so, by in vitro evaluation after 30 days of exposure, he observed that cadmium did not promote increased contraction force of isolated papillary muscles, nor did it modify transarcolemal calcium influx, nor did it promote changes in β-adrenergic stimulation, thus suggesting the intervention of neurohumoral regulation in the mechanisms involved[49].

Cadmium is a transition metal and it is commonly associated with zinc, lead and copper ore in the environment. [50] Like lead, cadmium is a bivalent, toxic metal and has no physiological function in the body. [2,51]

When investigating the effects of lead on myocardial contractility, Vassalo et al[52] reported a reduction in strength developed at concentrations above 30 μmol L^{-1}. They attributed the reduction in strength promoted by acute exposure to lead to lower transarcolemal calcium influx and reduction in the activity of the myosin ATPase enzyme, without altering the activity of the sarcoplasmic reticulum[39]. Since lead, like cadmium, is a bivalent heavy metal, the results demonstrated may contribute to the clarification of the mechanisms involved in the alterations of the "cardiac contractile machinery" in the exposure to cadmium.

FINAL CONSIDERATIONS

Cadmium is a metal toxic to the body and it plays an important role in vascular system changes, such as the onset or impairment of hypertension, peripheral arterial disease and other cardiovascular diseases.

It is known that exposure to cadmium is related to the development of arterial hypertension, increasing the mortality rate due to cardiovascular diseases. It is worth noting that the evidence suggests the deleterious effects of cadmium on the vascular endothelium as the main cause in the genesis of hypertension promoted by this metal as a result of imbalance in the production of vasodilator and vasoconstrictor substances. The endothelial dysfunction caused by the metal can occur due to the increase in the production of superoxide anions and consequently the decrease of the bioavailability of the nitric oxide, besides causing structural changes in the cardiac tissue.

Although the effects of cadmium on the heart are already known, little is comprehended about these effects, and much research is still needed to elucidate the mechanisms involved in these changes. Thus, it is necessary to recognize the risks of cadmium poisoning and to certify a reassessment by competent authorities of the effects of exposure to cadmium in the population, especially the occupationally exposed population, and in smokers.

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ESTUDOS INTERDISCIPLINARES EM CIÊNCIAS SOCIAIS E DA SAÚDE
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Original Article

REFRACTORY DIGESTIVE HEMORRAGY BY USE OF DIRECT ANTICOAGULANT IN OCTAGENARY PATIENT WITH CHRONIC ATRIAL FIBRILLATION: CASE REPORT

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Keywords

Anticoagulants;
Atrial fibrillation;
Hemorrhage;
Elderly aged 80 years or more.

Abstract

Fibrilação atrial é a arritmia cardíaca sustentada mais prevalente do mundo, cuja incidência aumenta progressivamente com o envelhecimento humano, apresenta elevada morbimortalidade, especialmente o acidente vascular cerebral, muito comum na população idosa. A terapia preconizada para reduzir eventos tromboembólicos são os dos anticoagulantes orais; atualmente a varfarina vem sendo substituída pelos novos anticoagulantes orais (NACOs), pela facilidade de manejo terapêutico. Apresentamos o caso de um senhor de 88 anos de idade, portador de insuficiência coronariana crônica com histórico recente de fibrilação atrial sustentada, que

foi introduzido um inibidor direto da trombina, a dabigratana 110mg duas vezes ao dia, como estratégica preventiva. Ele apresentou um quadro de hemorragia digestiva volumosa após seis meses de uso do NACO. Internou com necessidade de várias transfusões sanguíneas e evoluiu por duas semanas sem estabilizar o quadro clínico. Não foi detectado o local do sangramento pela endoscopia digestiva alta e a colonoscopia demonstrava um sangramento ativo procedente do intestino delgado. Através de angiotomografia abdominal foi detectado, em topografia em terminal de intestino delgado, o possível local de sangramento. Foi indicada intervenção cirúrgica no 16º dia de internação, a qual, por meio do método de transluscência de íleo terminal, confirmou o local de sangramento, com enterectomia do segmento comprometido. O exame histopatológico demonstrou epitélio atrófico com vasos congestos.

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in the world, and its significant management and knowledge is mostly a result of the great connection with high morbidity and mortality events, namely stroke, especially ischemic stroke. Accordingly, therapy should be established to diminish the risk of thromboembolic event. In the past 5 years, the guidelines have replaced warfarin with Direct Oral Anticoagulants (DOACs) for anticoagulation in cases of non-valve AF, in response to a broad therapeutic window; onset of rapid action; no need for regular laboratory monitoring (no control with INR); pharmacokinetics and predictable pharmacodynamics; short half-life; little food and medication interaction (no restrictions on some foods); more favorable dosage; among other benefits.3

DOACs class has different action mechanisms between their drugs. The Dabigatran is an anticoagulant that acts as direct thrombin inhibitor. Studies have indicates that Dabigatran, at a dosage of 110 mg, had rates of stroke and systemic embolism similar to warfarin, besides lower rates of severe bleeding. The 150mg dosage was relatable with lower occurrences of stroke and systemic embolism, but similar to severe bleeding in comparison with warfarin.[1] Other study reported that, in patients under the age of 75, the doses of dabigatran, in contrast to warfarin, have a lower risk of intracranial and extracranial bleeding. In patients aged 75 years or older, the risk of intracranial bleeding is lower, but the risk of extracranial bleeding is similar or even greater when comparing the doses of dabigatran with warfarin.[2]

Hemorrhage is a common complication to the use of Dabigatran, nevertheless, it is barely required to resort to surgical intervention to contain the condition. Small bleeding has a short half-life and, therefore, can be resolved only by discontinuing the medication. More severe cases submit a good response to hemodialysis, given that the binding to plasma proteins is weak and has predominantly renal metabolism. Other ways of conduction of hemorrhage are the use of activated charcoal, although it is contraindicated in situations of digestive

hemorrhage, administration of Fresh Frozen Plasma and Concentrate of Prothrombin Complexes, especially in situations of severe hemorrhage. Since they are not currently available in the Unified Health System (SUS), there are reversers of the action of DOACs, with Idarucizumab being specific for Dabigatran. Surgery is indicated for specific cases, as exemplified in this report.[4]

CASE REPORT

Male patient, 88 years old, with paroxysmal atrial fibrillation (FAP), CHADVASC 4 (risk of high thromboembolism), HASBLED 3 (risk of moderate bleeding), coronary artery disease (CAD) and acute myocardial infarction event (AMI) with implantation of 2 stents 17 years ago, besides heart failure with an ejection fraction of 40%. Smoker for 50 years, with ½ pack a day. He is in use of omeprazole, enalapril, simvastatin, carvedilol, buffered acetyl salicylic acid and dabigatran 110mg every 12 hours.

Regularly monitored in the cardiology and geriatrics sector at Hospital Santa Casa de Misericórdia de Vitória (HSCMV). He was admitted to the emergency room of the institution with digestive hemorrhage, and referred to symptoms of asthenia, vertigo, postural hypotension and melena, the latter being present for 1 week. On admission, he presented Hb 4.8, TAP 30%, negative urine culture and mild leukocytosis. A diagnostic hypothesis of an adverse event was performed using dabigatran. By virtue of significant anemia, transfusion of 2 red blood cell concentrates, 3 fresh frozen plasmas, and suspension of ASA and dabigatran was prescribed as an initial approach.

The patient was hospitalized for 28 days, and the medication suspension was continued for the entire time, in addition to the specific oral diet for CKD. On the second day of hospitalization, an upper digestive endoscopy (EDA) with biopsy was conducted, showing mild atrophic pangastritis. The melena episodes continued; the TAP continued broad. On the sixth day, colonoscopy was performed (complete examination until terminal ileum), resulting in a large amount of clots and indication of probable digestive hemorrhage in a supracolic site (jejunum or ileum), which cannot be identified by the method. In the first week of hospitalization, a total of 4 transfusions of packed red blood cells and 3 fresh frozen plasmas were conducted, with no clinical improvement.

In the second week of hospitalization, examinations of abdominal angiotomography, chest CT and abdominal CT were performed. In the abdominal CT, an area of hyper-enhancement in the arterial phase was identified, seen next to the small intestine loop wall, at the entrance of the pelvis, on the right, apparently in projection of the ileum, measuring about 2cm x 1,6cm x 0,5cm (respectively in their largest longitudinal x anteroposterior x transverse diameters), without causing blurring of the surrounding myoadipose planes, and the image is iso / hypodense in the non-contrast phase and has reduced enhancement, nonetheless, still in the late phase, there is an indeterminate aspect. Mesenteric angiography was also carried out and no bleeding was identified by the method.

The fact that the patient has kept an extended TAP, an evaluation of hematology was demanded. TAP collection with a 50% mixture was proposed to define factor deficiency or inhibitor presence. Episodes of bleeding

emerged on the 8th and 14th day and 4 more red blood cell transfusions were performed. The gastroenterology team introduced the use of thalidomide to stabilize the condition. Exploratory laparotomy and red cell scintigraphy were the two approaches suggested for the case.

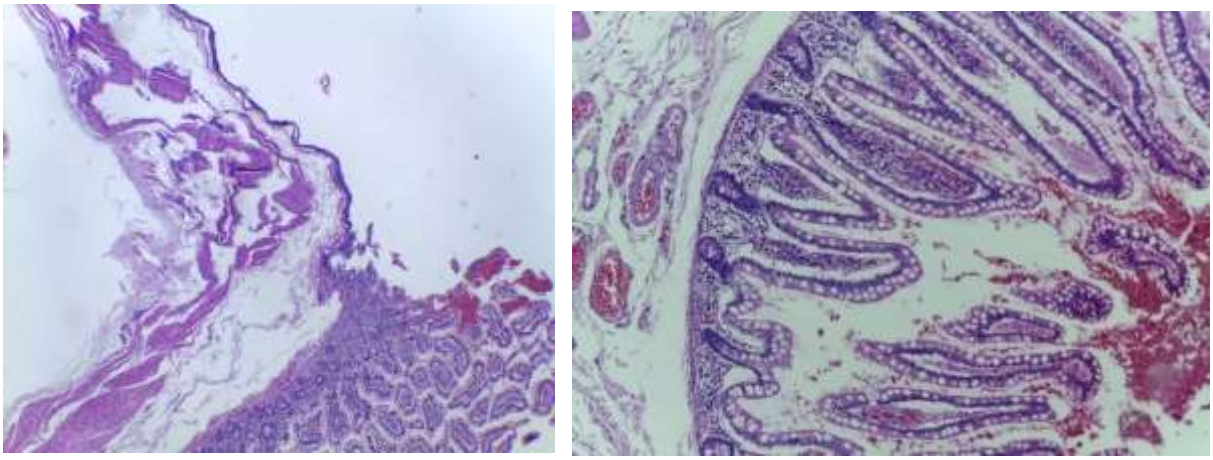
Exploratory laparotomy was indicated, as the previous measures were not successful in stopping bleeding, maintaining significant anemia and a constant need for transfusions. Scintigraphy was not indicated, as it would not be a curative test. The patient's surgical risk was resoluted, which determined low operative risk (Lee's Class 3) and the preparation for surgery started with transfusion of 2 red blood cell concentrates. On the 16th day of hospitalization, a laparotomy was performed, being identified by means of the perioperative transillumination method, an intestinal loop, a vascular lesion 15 cm away from the ileocecal valve and a bloody-looking content inside the loops of ileum and colon, resulting in ileal segment enterectomy. The histopathological analysis of the specimen determined recent superficial hemorrhage, with bright and intense blood in the light and without hemosiderin pigment. There were no signs of necrosis or thrombosis (absence of fibrin, neovascularization, inflammatory process and elements of digested blood). The mucosa was preserved, nevertheless, swollen and with congested vessels. An area of atrophy of the epithelium was evidenced, but without signs of complete reparative lesion, and the mucosa region close to the altered area is unchanged, suggesting a local mechanical trauma.

The postoperative period was conducted in the Intensive Care Unit (ICU). Changes in renal function, hyponatremia, metabolic acidosis, episodes of melena and atrial fibrillation were presented, and measures indicated for control were carried out. The patient was discharged from the ICU, returning to the infirmary, where he stayed for another 4 days, using furosemide by reason of congestion with bronchospasm and vitamin K He was discharged from the hospital, being referred to the HSCMV cardiology outpatient clinic, so that the anticoagulant drug management and the follow-up with the Geriatrics team could be determined. He also received referral to the hematologist, with the purpose of investigating coagulopathy.

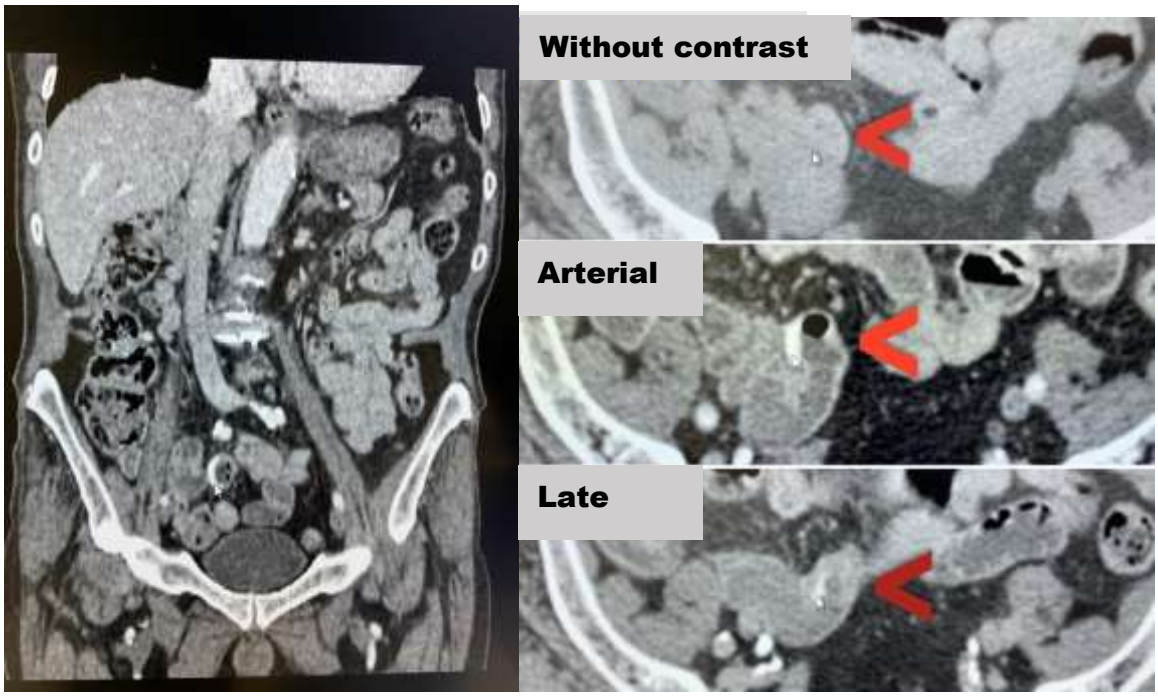
Acknowledgments

"We sincerely thank the real character of the clinical case who was another fatal victim, along with his wife, from COVID-19 (in memorian)"

IMAGES - SLIDES, ABDOMEN AND SURGERY CT



a. Atrophic epithelium, close to the region of preserved mucosa. Intestinal lumen with living blood. It shows an intense concentration of red blood cells. Note also the congested vessels.



b. Tomography images of the abdomen (without and with contrast) showing the bleeding site

c. Translucence technique surgery
Vascular injury

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ESTUDOS INTERDISCIPLINARES EM CIÊNCIAS SOCIAIS E DA SAÚDE
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Original Article

EXPOSURE TO CADMIUM AS A PUBLIC HEALTH PROBLEM AND ITS EFFECT ON RESISTANCE VESSELS

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Keywords

Cadmium exposure;
Public health;
Resistance artery.

Abstract

Objective: To elaborate a bibliographic review of cadmium exposure as a public health problem and the effect of this exposure on the vascular system and resistance vessels. Methods: This is a structured narrative review performed in three phases: 1) elaboration of guiding questions: "How is the exposure to cadmium a public health problem?" And

"What are the effects of exposure to cadmium on resistance vessels?"; 2) sampling in the literature and selection of studies; 3) Critical analysis of selected studies. Results: a review was made about the history, characteristics, levels of cadmium acetate currently used, sources of exposure, use, kinetics and distribution of cadmium in the body; as well as the effects of cadmium on the vascular system and resistance vessels. CONCLUSION: Studies show that the effects of cadmium exposure are already known to impair the cardiovascular system, as well as the function of the vascular system and resistance vessels, and constitute a public health problem. However, further studies should be performed to elucidate the mechanisms by which cadmium can participate in the pathophysiology of cardiovascular diseases.

INTRODUCTION

Cadmium metal is particularly employed as a pigment to create colors such as yellow, orange, red and brown dyes, besides being used in the composition of paints, plastics and ceramics. Cadmium is also used in the production of nickel-cadmium batteries and in the electroplating process as an anticorrosive. It can be found in electrical conductors, polyvinyl chloride (PVC), photocells, tires, car radiators, electronic components, among others.

The use of cadmium in the production of pigments, PVC stabilizers and electroplating has been reduced and, in some countries, it has even been banned. Yet, in the European Union such purposes still account for a large share of total cadmium consumption. The growing production of nickel-cadmium batteries in the world market contributes to approximately 78% of the total consumption of the metal (NCM, 2003).

Although the widespread idea that heavy metals (in particular, lead, mercury, cadmium and arsenic) are considered risk factors for health, including for cardiovascular system (Alissa & Ferns, 2011), the mechanisms by which metals produce their adverse effects are not completely clear yet.

It is noted that exposure to cadmium results in the damage of different organs and systems in the body. Depending on the dose, route and duration of exposure, cadmium may damage several organs, including kidneys, lungs, liver and testes (Friberg et al., 1986; Jarup et al., 1998). Cadmium also has teratogenic and carcinogenic activity (Degraeve, 1981; IARC, 1993). Furthermore, evidence suggests that many of the effects of cadmium in the body involve actions on the cardiovascular system, including vascular endothelium (Nolan & Shaikh, 1986, Navas-Acien et al., 2004 and 2005, Woods et al. Chen et al., 2016; Kukongviriyapanet al., 2016) .The endothelium is able to release metabolically active substances, which modulate important functions in the body such as vasomotor tone control, vascular diameter, blood flow and also to participate in the Control of inflammatory and immunological responses (Rubanyi, 1993).

In this context, considering that vascular tone of resistance arteries is the main determinant of peripheral vascular resistance, and that this resistance is important in regulating blood pressure and

blood flow distribution between and within the tissues and organs of the body, the objective of this review was to search the literature for scientific evidences related to the impact of cadmium exposure on public health, focusing on its effects on resistance vessels.

METHODOLOGY

This is a narrative review associated with the effects of cadmium exposure on the public health and, specifically, on resistance vessels. This type of literature review authorizes the incorporation of evidence for convenience, by an expertise in the subject, for the purpose of building knowledge about a certain topic of scientific relevance.

The review process was systematized into three distinct phases, the first of which was the development of guiding questions: "How is the exposure to cadmium a public health problem?" And "What are the effects of exposure to cadmium on resistance vessels? The second phase corresponded to sampling in the literature, which included the largest possible variety of identified products and ensured the variety and amplitude of results.

To that end, an electronic selection was performed in the LILACS (Latin American and Caribbean Literature), MEDLINE (National Library of Medicine, USA) and PUB MED (National Library of Medicine / National Institutes of Health) databases. The electronic search was carried out through the following combinations of Descriptors in Health Sciences (DeCS): "cadmium exposure; blood cadmium concentrations; Population exposure; Effects of cadmium; Vascular reactivity; Resistances arteries ", and was based on the adoption of the following inclusion criteria: the indexing of studies in the respective databases in Portuguese, English and Spanish. Exclusion criteria were defined as: productions without availability of the text in full or with a central theme of the study not related to the current theme.

The third phase of this review consisted of a critical analysis of the selected studies. Decision making regarding inclusion or rejection of the studies was based on reading the titles of the selected studies, followed by critical analysis of the abstracts. The studies with a central theme unrelated to the theme proposed for the review were rejected. In a second analysis, the contents altogether were verified, guided by the thematic analysis technique to identify the central ideas presented. In a second analysis, the content was verified in full, guided by the thematic analysis technique to identify the central ideas presented.

RESULTS / DISCUSSION

3.1 Characteristics of cadmium

Cadmium is a transition metal, in the periodic classification it is located in group IIB, it is silvery white, malleable, ductile, it has chemical and mechanical resistance. The oxidation states of cadmium vary based on the compounds, and may be +1, or +2. The oxidation state +1 is very rare, and most of the times it occurs in the oxidation state +2 (Russel, 2004). This metal was found out in the year 1817 by the German chemist Friendrich Stromeyer, when heating the calamite (zinc carbonate). When heating the ore in its impure state he observed a different coloration during the experiment, conjecturing if it were another metal, unknown until then. The name of the element comes from the Latin "cadmia" which means Calamite, because the cadmium is present in this ore (Russel, 2004).

Cadmium is not found in its elemental form in nature, but combined with other elements, such as oxygen, chlorine, or sulfur. It is industrially obtained as a

byproduct of electrolytic purification of copper, lead and zinc or by reduction of cadmium sulfide (CdS) (Mendham et al., 2002).The use of cadmium in the production of pigments, PVC stabilizers and galvanizing has been reduced and in some countries has even been extinguished. Nevertheless, in the European Union, such uses still account for a large portion of total cadmium consumption (NCM, 2003). The production of nickel-cadmium batteries has been gaining considerable space in the world market, contributing to about 78% of the total consumption of the metal (NCM, 2003).

3.2. Cadmium Levels

The World Health Organization assumes as the safety limit for the cadmium intake 7 μg / week / kg of body weight. This value was rooted on the critical renal concentration of cadmium from 100 to 200 μg / g dry weight, which corresponds to the urinary cadmium concentration of 5 to 10 μg / g creatinine (WHO, 1993). The main markers of exposure to cadmium are cadmium concentrations in urine and in blood. The concentration of cadmium in the 24-hour urine is used as a marker for long-term exposure (Nordberg et al., 2007). Furthermore, the blood concentration of cadmium reflects a more recent exposure higher than that of cadmium in the blood resulting from the last months (Nordberg et al., 2007) and has a biological tolerance limit of 5 μg / L of cadmium in the blood (ACGIH, 2007).

3.3. Sources of exposure and use

Natural sources of cadmium in the atmosphere are volcanic activity, erosion of sedimentary and phosphate rocks, and forest fires. Cadmium is present in a smaller amount in most soils, rocks and waters, while it is found in abundance associated with lead, zinc and some phosphate rock ores, which are a rich source of phosphate for the production of fertilizers (Cercla 1992, WHO, 1992).

Cadmium is found throughout the Earth's crust at a concentration of 0.1-0.5 ppm. It is also a natural constituent of ocean waters with mean levels between <5 and 110 ng / L and is generally concentrated near coastal areas in the form of marine phosphates (ATSDR, 2008). In 1983, about 140-1500 tons of cadmium were released into the atmosphere by volcanic eruptions (Nriagu, 1989). In the same year, Nriagu and Pacyna (1988) estimated the atmospheric contamination by anthropogenic sources in 7600 tons of cadmium.

Anthropogenic sources include the activities of mining, production, consumption and disposal of products using cadmium and sources considered "inadvertent" where cadmium is a natural constituent of the material being processed or consumed: non-ferrous metals, zinc alloys, Lead and copper, emissions from iron and steel industries, fossil fuels (FIT, 2012). The reported concentrations of cadmium in the blood of exposed workers are generally between 5 and 50 μg / L, but extreme exposures have resulted in levels between 100 and 300 μg / L (Roels et al., 1982; Hassler et al. 1983).

Anthropogenic sources are the central sources of contamination of the population with cadmium, mainly industries, responsible for the contamination of population in their surroundings areas. A classic example of cadmium contamination was widely reported: in 1910, the postwar period, after the accident on the banks of the Jintsu River in the FunchuMachi region of Japan, rice planters and fishermen were suffering from rheumatic pains and myalgias. These workers were victims of the industrial dumping of zinc and lead deposit called Kamioka and the respective zinc and lead processing plant located 50

km from the river banks. The disease, caused by cadmium, a natural contaminating element of this process, became known in the medical science as Itai-Itai. It acquired this name because the victims moaned a lot and itai-itai means the groaning of "ai" pain. It is characterized by sudden pain in the lower back, back and joints. Even with protests from the population against the contamination of rice fields, in order to meet the demand of the war industry, increased production of lead and zinc. This increased the concentration of cadmium in the effluents of the river, which resulted in a worsening of the contamination of the population (Friberg et al., 1974).

In 1996 in Itaguaí, Rio de Janeiro, Brazil, an electrolytic zinc mill was denounced for dumping more than 50 million liters of water and mud containing zinc and cadmium into the region, contaminating mangroves that contained crabs, oysters and mussels, consumed by local populations and the city of Rio de Janeiro (Gonçalves et al., 1996).

By virtue of its non-biodegradable properties, cadmium persists in the environment and bio accumulates in plants and animals including humans (Satarug et al., 2003; Clemens, 2006). Certain plants (eg tobacco, peanuts, sunflower seeds, linseed seeds) and animals (eg, oyster filters) may bioaccumulate high levels of cadmium and are referred to as hyper accumulators (Kruzynski, 2004; Whyte et al., 2009; Bendell, 2010). The cadmium content of Pacific oysters reaches 13.5 mg/kg dry weight, while the amount of cadmium observed in New Zealand coast oysters is twice as high due to contamination of this area (Copes et al. Al., 2008).

Food and smoking are the major sources of exposure for most people. High body cadmium content was related to frequent consumption of mollusks and crustaceans (Haswell-Elkins et al., 2007; Copes et al., 2008; Satarug et al., 2010) and smoking (El-Agha & Gökmen 2002, Marano et al. Al, 2012). Therefore, the largest source of human cadmium uptake is cigarette smoking (a cigarette contains approximately 1 to 2 μg, and there is a daily intake of approximately 1 to 3 μg per pack of smoked cigarettes) and for nonsmokers, food is the largest source (daily intake, approximately 30 μg, uptake of about 1 to 3 μg) (ATSDR, 2008).

Abu-Hayyeh et al. (2001) demonstrated that the cadmium content in human aortas increases in direct proportion to the years / pack of smoked cigarettes, with the selective accumulation in the middle layer. The mean cadmium concentration in the middle aorta layer of humans was 7 μmol / L. Cadmium exposure in smokers has been associated with increased risk of hypertension and cardiovascular diseases (Afridi et al., 2010) which can be also explained in the study of Colacino et al., 2014, performed with the US population through NHANES (National Health and Nutrition Survey 2003-2010). They demonstrated that smoking was a strong pro-atherosclerotic and pro-inflammatory factor.

Another form of increasing exposure, especially for children, is by colored pigments containing this metal. The concentration of cadmium has been a leading cause of recall in different children's products such as jewelry, toys, and paints, among others. In 2010, pre-adolescent companies including Claire's Stores, Walmart and Dress Barn recalled products such as necklaces, earrings and bracelets after finding that these products contained substantial levels of cadmium. In the same year, the company McDonald's recalled 12 million cups of the children's character Shrek by the same motive (Mead, 2010). Cadmium was used in these

products to produce colors such as intense red and yellow.

3.4. Cadmium kinetics and distribution in the body

As mentioned above, tobacco smoking is the primary form of non-occupational exposure to cadmium. But this is not only on account of the fact that tobacco leaves accumulate cadmium from the soil, since oily seeds, such as sunflower seed, peanut and flaxseed, also have accumulating properties of cadmium, similar to tobacco leaves. However, about 50% of the inhaled cadmium is absorbed, whereas the oral route allows the absorption of only 5% of the dose of the metal (WHO, 1992). Cadmium accumulates in many organs, mainly in the kidneys and liver, presenting half-life around 10 to 35 years in humans (WHO, 1992). Its daily renal excretion is only 0.007% of the body content of cadmium, presenting great variations between individuals (WHO, 1992).

Cadmium does not present an essential function for organisms, and consequently does not present specific mechanisms for its absorption, transport and entry into cells. In order to do so, it uses mechanisms developed for essential metals, especially iron, zinc, magnesium and calcium, such as the divalent metals carrier 1 (DMT1). As a result, the nutritional status of the individual, such as its iron content, will influence the intestinal absorption of cadmium due to the competition of iron and cadmium by the carriers. The iron deficient diet increases the expression of DMT1, which carries iron but also cadmium, increasing the absorption of cadmium (Klaassen et al., 2009). In a study of Thai people, researchers observed that women with iron depletion had cadmium content 3 to 4 times higher than that observed in women of same age and with normal iron stores (Satarug and Moore, 2004).

After absorption, cadmium (Cd2 +) gains movement where it can circulate as free ion or bind to plasma proteins such as albumin and metallothionein (MT), a low affinity cysteine-rich protein with high affinity for metals (Bressler et al., 2004; Nordberg, 2004). The binding to this protein prevents the actions of cadmium on other macromolecules, besides hindering the renal excretion of this metal (Klaassen et al., 2009). Therefore, cadmium is absorbed by the cells of the target organs (liver, kidneys and testicles) through solute transporters and channels of calcium, manganese, iron (Bressler et al., 2004; Dalton et al., 2005; Levesque et al.).

3.5. Effects of exposure to cadmium on the vascular system and resistance vessels

The vascular system functions as a complex interaction between the vascular endothelium, the vascular smooth muscle, the immune system, the nervous system, and even local chemical and metabolic factors in organs and tissues (Gibbins et al., 2003; Hill et al. , Triggle et al., 2003, Villar et al., 2006). Damage of these functions, such as that caused by the toxicity of cadmium, may contribute to a variety of pathological conditions, including atherosclerosis and hypertension (Schroeder, 1967, Navas-Acien et al., 2004, Prozialeck et al.) There are several evidences of the association between high levels of cadmium and hypertension, stroke and cardiac arrest (Navas-Acien et al., 2005; Bhatnagar, 2006; Tellez-Plaza et al., 2008).

The hypothesis that vascular endothelium is an important target in cadmium toxicity was first reported in the twentieth century, when Alsberg & Schwartze (1919) demonstrated that acute exposure to cadmium administered subcutaneously in rats caused purplish staining in the testes of these animals. In the 1950s and 1960s,

other researchers reported that cadmium caused testicular hemorrhage in a wide variety of species (Parizek & Zahor, 1956, Kar & Das, 1960, Chiquoine, 1964 and Hoey, 1966). Further studies attributed this vascular effect of cadmium to rupture of the junctions between capillary endothelial cells and testicular venules, resulting in increased testicular permeability, followed by edema, hemorrhage, and necrosis (Gunn & Gould, 1970; Gabbiani et al. Fende & Niewenhuis, 1977; Aoki & Hoffer, 1978; Priest & Cavicchia, 1983).

In vitro experiments with endothelial cells have shown that a low concentration of cadmium induces cell death and leads to increased permeability of these cells (Messner et al., 2009). Furthermore, Szuster-Ciesielska et al. (2000) reported that cadmium induces the expression of pro-atherogenic adhesion molecules in the surface of endothelial cells, such as intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM -1) facilitating the adhesion and migration of cells from the immune system to the vessel wall. Other researchers have shown that cadmium can directly inhibit the migration of endothelial cells, associating these effects with reduced production of nitric oxide by endothelial cells (Kolluruet et al., 2006).

Evidence is growing that certain toxic metals, especially cadmium and arsenic, may have important effects on angiogenesis. Prozialeck et al. (2008) published a review highlighting the possible effects of cadmium on the angiogenic process. Nai et al. (2015) have described that endothelial cells and smooth muscle cells are capable of absorbing cadmium and can transport it into the subendothelial space, initiating the proliferation of these cells and leading to thickening of the middle layer of the vessel wall.

It is worth noting the relationship between levels of cadmium and hypertension, suggested by several studies (Schroeder, 1967, Vivoli et al., 1989, Luoma et al., 1995; Satarug et al., 2003). In a clinical study, Houtman (1993) noted that patients with hypertension had higher concentrations of cadmium in the urine and, in addition, in areas contaminated with cadmium, there was a higher incidence of atherosclerosis.

Even if the association between cadmium exposure and hypertension is not fully understood in humans, the induction of hypertension through exposure to cadmium is perceived in several animal models. There are reports of induction of proximal renal tubule damage, salt retention, and increased blood volume as a possible cause of cadmium-induced hypertension (Satarug et al., 2005). Other authors associate it with glutathione depletion (Valko et al., 2005) leading to oxidative stress and lipid peroxidation as potential prohypertensive actions induced by cadmium (Yiin et al., 1999).

Supporting hypotheses for the mechanism of hypertension development following exposure to cadmium include interaction with Ca^{2+} channels (Balaraman et al., 1989) and stimulation of the sympathetic nervous system (Fadloun & Leach, 1980). Prozialeck et al. (2006) also investigated some mechanisms by which metals, such as cadmium and lead, may contribute to the development of hypertension. In the case of cadmium, considerable evidence suggests that hypertensive effects result from complex actions on the vascular endothelium and vascular smooth muscle (Almenara et al., 2013, Balaraman et al., 1989, Angeli et al., 2013, Varoni et al. 2010).

It is admitted that endothelial dysfunction contributes to the maintenance of increased vascular resistance, favoring the hypertensive process (Cannon III, 1998;

Kolluru et al., 2010; Triggle et al., 2003). In addition, evidences demonstrate that the Vascular endothelium is considered the main target of cadmium intoxication, leading to the imbalance of the bioavailability of vasodilator and vasoconstricting substances, causing an increase in vascular tone (Martinowiczet et al., 2004; Kolluru et al., 2006).

Given that, research with different experimental models revealed that exposure to cadmium promotes increased oxidative stress and endothelial dysfunction, possibly promoted by the reduction of the bioavailability of nitric oxide (NO) due to the increase of the reactive oxygen species (Donpunha et al., 2011 Siow et al., 1995; Sompamit et al., 2010). Recently, Angeli et al. (2013) and Almenara et al. (2013) confirmed these findings in the aorta artery, a vessel of conductance, where they demonstrated an increase in vascular reactivity due to the increase of reactive oxygen species and consequent reduction of NO bioavailability. On the other hand, the mechanisms involving the intoxication of cadmium on resistance vessels are poorly understood, although it is essential to know them by reason of the contribution of these vessels to the genesis and / or maintenance of arterial hypertension.

Skozynska & Martynowicz (2005), when studying mesenteric arteries of rats, observed a reduction in the serum nitric oxide concentration before cadmium poisoning at doses considered to be hypertensive (with both 50 and 200 ppm of cadmium in drinking water for three months). In the present study, these researchers described that the cadmium-poisoned rats showed a reduction in the vascular response to the e-NOS blocker, N-omega-nitro-L-arginine (L-NOARG), under basal conditions as well as after stimulation by Acetylcholine.

Taking into account that increased renin-angiotensin system activation is generally observed in hypertension and associated vascular changes, another study by Skoczyńska (1997) demonstrated a greater response to angiotensin II-produced norepinephrine in mesenteric arteries isolated from cadmium-poisoned rats (20 mg Cd / kg of body weight). It was suggested that this occurred as a result of the influence of cadmium on calcium homeostasis.

Corroborating the idea that cadmium may lead to a hypertensive effect through its influence on the renin-angiotensin system, Wróbel & Skoczyńska (2002) observed in the mesenteric arteries that the contribution of the endothelial renin-angiotensin system to the regulation of vascular resistance was higher in rats poisoned with Cadmium when compared to those poisoned with lead. The authors also suggested that the effect of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers may be slightly greater in individuals with arterial hypertension exposed to cadmium than in non-exposed patients.

In view of the above mentioned, it is possible to verify that the effects of cadmium on the population health and in the vascular system, especially on vascular endothelium, in both humans and rats, result in alterations involving several mechanisms that occur with endothelial dysfunction and increase in pressure mainly because of the increase in peripheral vascular resistance.

FINAL CONSIDERATIONS

Considering existing literature related to the toxic effects of cadmium on the cardiovascular system, it is evident that exposure to the metal is a public health problem.

Concerning the effects of cadmium on resistance arteries, it is worth noting that, despite the limited research, there is already evidence that the metal causes impairment in the function of these vessels. Therefore, it is necessary to perform new studies on the mechanisms by which cadmium impairs the vascular function of resistance arteries, whose role in maintaining vascular resistance is determinant for the hypertensive disease, among other diseases that affect the cardiovascular system.

It is expected that studies presented to date will encourage the continuity of this line of research in order to promote greater knowledge about the participation of cadmium in the pathophysiology of cardiovascular diseases, contributing to the development of new preventive, diagnostic and therapeutic strategies. Regarding prevention, it is worth emphasizing the importance of the reassessment of levels considered as safe for exposed and non-exposed persons, in order to reduce the impact of this metal on the population health.

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Original Article

ACUTE AND CHRONIC CADMIUM EFFECTS ON CONDUCTANCE VESSELS

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Abstract

This study aims to demonstrate the main effects of cadmium exposure on the vascular system emphasizing conductance vessels. For this, a narrative review was realized with two main axes: 1) Guiding question: What are the effects of acute and chronic cadmium exposure on conductance vessels in humans and experimental animals? 2) Literature review and selection of studies relevant to the theme of this study. The studies presented

in this review showed that cadmium promotes vascular changes such as the development of arterial hypertension and atherosclerosis, depending on the dose, route and time of cadmium exposure.

INTRODUCTION

Cadmium alters different organs, especially kidneys, lungs, liver, testis[1] and vascular endothelium in a harmful way.[2] By virtue of its non-biodegradable properties cadmium persists in the environment and bioaccumulates in plants and animals including humans.[3,4]

Humans and animals are exposed to cadmium by many ways, including industrial contamination, food sources and tobacco.[5] As reported by the World Health Organization (2010)[6], human exposure occurs primarily through the consumption of contaminated food, active and passive inhalation of cigarette smoke and occupational contamination, available for distribution by different ways: oral, inhalation and skin. Nevertheless, about 50% of the inhaled cadmium is absorbed, whereas the oral way allows the absorption of only 5% of the ingested dose of the metal.[7]

Studies show that the smoking population has approximately three times the blood concentration of cadmium found in the non-smoking population (1.58μg/L for smokers and 0.47μg/L for non-smokers), which makes tobacco smoke the main form of non-occupational exposure to cadmium.[8]

This exposure of cadmium in smokers has been associated with increased risk of hypertension and cardiovascular diseases[9] which can also be explained in the study by Colacino et al. (2014)[10] conducted with the US population through NHANES (National Health Survey And Nutrition 2003-2010) in which they demonstrate smoking as a strong pro-atherosclerotic and pro-inflammatory factor.

In accordance with these studies, Abu-Hayyeh et al. (2001)[11] demonstrated that the cadmium content in human aorta increases in direct proportion to the pack-years of cigarettes smoked, with the selective accumulation in the medial layer. The mean cadmium concentration in the human aortic mid layer was 7μmol/L. This cadmium concentration was sufficient to significantly reduce collagen synthesis in these cells.

One should notice that when analyzing the effects of cadmium on the vascular system, factors such as: dose, time and route of exposure must be considered,[12] since all of them influence in a different way the results provoked by this metal.

Taking into account the effects of cadmium on vasculature and damage to the cardiovascular system, the toxic effects of cadmium on conductance vessels will be highlighted in this review. We will present studies in humans and experimental animals that expressed the relationship between acute and chronic exposure to this metal with the development of cardiovascular diseases.

ACUTE AND CHRONIC EFFECTS OF CADMIUM IN HUMANS AND EXPERIMENTAL ANIMALS ON CONDUCTANCE ARTERIES

Epidemiologically, there is a great association between high concentrations of cadmium in the blood and urine with hypertension, stroke, cardiac arrest[13,14,15] and development of atherosclerosis,[16] in

addition to having teratogenic and carcinogenic activity.[17] A clinical study, carried out in a population of areas with contaminated soil and water, showed that patients with hypertension had higher concentrations of cadmium in their urine and a higher incidence of atherosclerosis.[18]

Studies by Knoflach et al. (2009)[16] evaluated histologically the aorta of Apo-Eknowout mice exposed to 100 mg/L of $CdCl_2$ for twelve weeks. It was observed that cadmium affects the integrity of endothelial cells by exposing subendothelial structures to the bloodstream, which may facilitate the influx of atherogenic serum contents and migration of inflammatory cells. This migration of inflammatory cells can occur through the increase of pro-atherogenic adhesion molecules such as ICAM-1 and VCAM1, triggering a systemic inflammatory response.

In parallel, Nai et al. (1998)[19] showed that exposure to $CdCl_2$ (400mg/L) in drinking water for 6 months caused the development of fatty streaks in those animals aorta, through the absorption of cadmium that interrupts the endothelial intercellular connections, thus facilitating their diffusion and allowing lipids and immune cells to access the intimate layer. The accumulation of smooth muscle cells in the intima, intimal invasion by macrophages and death of endothelial cells promotes a vascular inflammatory process leading to tissue remodeling, deposition of extracellular matrix and free lipids.

The induction of hypertension was observed in several experimental models of acute and chronic exposure to cadmium, suggesting that the effects result from complex actions on vascular endothelium and vascular smooth muscle.[20,21,22,23] Corroborating these results, Nai et al. (2015)[19] evidenced that endothelial cells and smooth muscle cells absorb cadmium and can transport it into the subendothelial space, initiating the proliferation of these cells, leading to thickening of the medial layer of the vessel wall. Furthermore, cadmium concentrations similar to those found in occupationally exposed populations induce increased systolic blood pressure and endothelial dysfunction in the aorta of rats treated with cadmium for 4 weeks.[23]

Vascular endothelium is considered the main target of cadmium intoxication, leading to imbalance of vasodilating and vasoconstrictive substances that participate in the control of vascular tone, resulting in endothelial dysfunction and favoring the hypertensive process. These substances produced by the endothelium were named as endothelium-derived relaxing factors (EDRFs),[25,26] which included nitric oxide (NO), prostacyclin (PGI2)[27,28,29] and Endothelium-Derived Hyperpolarizing Factors (EDHF),[30] and endothelium-derived contracting factors (EDCFs) including angiotensin II,[31] Endothelin-1,[32] superoxide anion[33] and products derived from the metabolism of arachidonic acid such as thromboxane A2 and prostaglandins.[28,34]

Tzotzes et al. (2007)[34] revealed that the endothelium-dependent vasodilator response after acute administration of cadmium (2 mg/kg) in rat aorta was not altered. In contrast, Gökalp et al. (2009)[36] demonstrated that intraperitoneal administration of 1mg/kg/day of cadmium over 15 days made the response to acetylcholine remarkably attenuated in rat aortic rings.

Angeli and collaborators (2013)[21] demonstrated that endothelial dysfunction caused by exposure to cadmium is characterized by increased free radical production, primarily superoxide anion by NADPH oxidase and increased production of vasopressor cyclooxygenase-2 prostanoids (COX-2) such as thromboxane A2 and prostaglandin E2, contributing to

the increase of free radicals and consequently to the decrease of NO bioavailability.

Studies with different experimental models have revealed that exposure to cadmium promotes an increased oxidative stress and an endothelial dysfunction, possibly promoted by the reduction of nitric oxide (NO) bioavailability due to the action of an increased reactive oxygen species.[25,37,38] Recently, Angeli et al. (2013)[21] and Almenara et al. (2013)[23] confirmed these findings in the aorta artery, where they showed an increase in vascular reactivity by the increase of reactive oxygen species (ROS) with consequent reduction in NO bioavailability.

Reduction in the production or bioavailability of NO may be one of the mechanisms that contribute to the increase of vascular resistance and to the development of hypertension in different experimental models, as well as in human.[39] The reaction of NO with ROS, mainly superoxide anion, produces toxic substances such as peroxynitrite (ONOO-), which reduces the bioavailability of NO, consequently leading to the reduction of endothelium-dependent vasodilation, thus becoming a vasoconstrictor factor.[40] In this respect, Wolf and Baynes (2007)[40] have suggested that cadmium induces oxidative stress by increasing ROS through the depletion of antioxidant enzymes leading to severe endothelial dysfunction.

The elevated blood pressure observed on exposure to cadmium[20,23] may also be related to the action of angiotensin II on vascular smooth muscle.[42] Thus, another possible factor associated with pressure elevation is the interaction of cadmium with the renin-angiotensin system which is part of a complex hormonal system and it plays an important role in regulating blood pressure and homeostasis of body fluids.[43,44,45] Angiotensin II synthesized in vascular endothelium acts on AT1 receptors on the vascular smooth muscle membrane, activating pathways mediated by G-Protein and intracellular kinases. The G-Protein-mediated pathway activates phospholipases C (PLC), A2 (PLA2), D (PLD) and lipogenases. Activation of phospholipase C (PLC) forms diacylglycerol (DAG) and inositol triphosphate (IP3), which leads to vascular smooth muscle contraction.[46,47]

Angiotensin II also changes the vascular reactivity playing an important pro-inflammatory action on the vascular wall, through the production of reactive oxygen species, inflammatory cytokines and adhesion molecules.[48,49] As a result, alterations in the renin-angiotensin system are associated with development of diseases such as atherosclerosis, hypertension and renal and cardiac insufficiency.[50,51]

Angeli et al. (2013)[21] investigated the involvement of the renin-angiotensin system in vascular reactivity in the presence of angiotensin converting enzyme inhibitor, enalapril and also the AT1 receptor antagonist, losartan, and they observed that both reduced the maximal contractile response to phenylephrine in segments of the aorta artery exposed acutely to cadmium.

Additional hypotheses for the mechanism of hypertension development following exposure to cadmium include interaction with Ca^{2++} channels and stimulation of the sympathetic nervous system.[52] Furthermore, cadmium may have an effect on angiogenesis by inhibiting endothelial cell migration, proliferation and the vascular tube formation process.[2,53] Recent studies demonstrate that these microvascular effects of cadmium on angiogenesis may involve changes in the function of the molecule of cell adhesion, VE-cadherin, which is involved in the cell-cell adhesion of the vascular endothelium as well as the intercellular formation of the

lumen.[54] Evidence suggests that in the presence of cadmium vascular quiescence predominates.[53]

As a result, it is observed that the effects of cadmium on the cardiovascular system, both in humans and animals, result in alterations involving several mechanisms that leads to a vascular dysfunction and to an increase of blood pressure, suggesting that the exposure to cadmium is a high factor risk to the population.

FINAL CONSIDERATIONS

As stated by the studies presented in this article, it was possible to observe that the acute and chronic exposure to cadmium promotes influence on endothelial function and a probable association with the development of hypertension and atherosclerosis, a process that occurs in large caliber arteries such as aorta. It is worth noticing that the effects of cadmium on the cardiovascular system, in both humans and experimental animals, result in alterations involving several mechanisms that leads to a vascular dysfunction and to an increase in blood pressure. This reinforces the hypothesis that cadmium should be considered as a risk factor in the development of cardiovascular diseases, since its exposure is involved in the development of hypertension, and increased mortality rate.

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ESTUDOS INTERDISCIPLINARES EM CIÊNCIAS SOCIAIS E DA SAÚDE
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Original Article

PILOT STUDY OF RICASA PROJECT: LATE FOLLOW-UP OF PATIENTS HOSPITALIZED WITH DISPENSED HEART FAILURE

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Keywords

Heart failure;
Hospitalization;
Adherence to Treatment;
Mortality.

Abstract

Introduction: Heart failure (HF) is a significant public health disorder, as of today a disease of high prevalence and mortality, in particular with the tendency to population aging. Moreover, it is a chronic condition with a high-priced treatment and a high rate of readmissions, largely as a result of a lack of clinical follow-up or low medication adherence. **Objective:** The current study targeted to assess the relationship between clinical characteristics and clinical follow-up with the outcome of death, in patients one year after discharge from decompensated HF. **Methods:** Prospective observational study that evaluated adult patients hospitalized for decompensated HF, included between February and

August 2017. Baseline clinical characteristics were acquired from medical records. The upshot of death and clinical follow-up, which was determined as at least one consultation with a cardiologist were surveyed by telephone contact, up to one year after hospital discharge. Chi-square test, Fisher's test and Student's t test were employed, adopting a significance level of 0.05. **Results:** Out of total 40 patients, six died in-hospital, 14 lost follow-up, and 20 patients were contacted within one year. Five of the 20 who were contacted died within a year. The mean age of the death group was 69.2 ± 14 vs 63.8 ± 14 of the non-death group (p = 0.44). The prevalence of males was 20.0% in the death group and 53.3% in the non-death group (p = 0.19). The only examined variable that was related to the mortality was clinical follow-up, which was lacking in all patients who died, whereas 60% of surviving patients maintained the post-discharge follow-up (p = 0.02). **Conclusions:** Post-discharge clinical follow-up was considerably resulting from a lower risk of death in one year in patients hospitalized for decompensated HF.

INTRODUCTION

Heart failure (HF) is viewed as a final route of the majority heart diseases and is repeatedly in consequence of an initial change in the structure and / or function of the heart. It is a clinical syndrome of fine relevance not only in the medical environment but also in the socioeconomic context, since it is a condition that, besides the impacts on morbidity and mortality, it also engenders a high cost of infrastructure to provide care to these patients, taking into account that it is a chronic disease, with pricey maintenance treatment and a high rate of readmissions.[1-2]

Decompensated HF is a potentially fatal condition, in which occurs a sudden onset or deterioration of the signs and symptoms of HF. It constitutes the main cause of hospitalization in people over 65 years of age, not merely in the USA but also the United Kingdom. It is coreferent with a high mortality, at approximately about 13% in the hospital, and about 30% in the first year. At present, intravenous loop diuretics are the mainstay of the treatment of pulmonary congestion in decompensated patients.[3] Apart from this class of drugs, after stabilizing the patient clinical monitoring of the disease with a specialist is advised who should employ the planned chronic treatment guidelines for the treatment of HF, evading additional decompensations.[4]

Furthermore, the high in-hospital mortality, the dilemma in maintaining acceptable clinical follow-up is an additional problem encountered in the management of these patients, notably in the public health service. The problem in scheduling appointments, delay in service, overcrowding of services, inadequacy of self-care, low socioeconomic status, absence of understanding about comorbidity and its risks are some of the impasses that excuse this non-medical monitoring.

Following a HF decompensation event demanding hospitalization, strict clinical follow-up is of chief relevance, mainly in the first year after discharge, a vulnerable period in which patients require regular and specialized care. Accordingly, the current study purports to evaluate the association of clinical characteristics and post-discharge clinical follow-up with the outcome of death up to one year after hospital discharge, in patients hospitalized for decompensated HF.

METHODS

This is a prospective observational study that assessed adult patients hospitalized for decompensated HF, comprised between February and August 2017, who were discharged from the hospital and followed for one year after discharge.

The inclusion criteria were patients older than 18 years of age, who were admitted with the diagnosis of acute / decompensated HF. Patients who did not have HF as their primary diagnostic hypothesis, were excluded. There was not differentiation between systolic or diastolic dysfunction, namely the normal ejection fraction was not applied as an exclusion criterion.

The data collection was conducted through the evaluation of baseline clinical characteristics in the medical record, comprising: sex, age, systemic arterial hypertension, diabetes mellitus, dyslipidemia, smoking, previous percutaneous coronary intervention, previous myocardial revascularization surgery, chronic renal failure and permanent / persistent atrial fibrillation.

After one year of hospital discharge, telephone contact was made with the patient and / or family members to question whether there was re-hospitalization or death during this period. Moreover, it was queried about the appropriate outpatient follow-up of the disease, considered as at the very least one consultation with a cardiologist. As the primary outcome measure, death was evaluated by comparing the death and non-death groups with regard to baseline clinical characteristics and post-discharge clinical follow-up.

Statistical Analysis

Through the SPSS 23.0 program, chi-square test, Fisher test and student t test were used, adopting a significance level of 0.05.

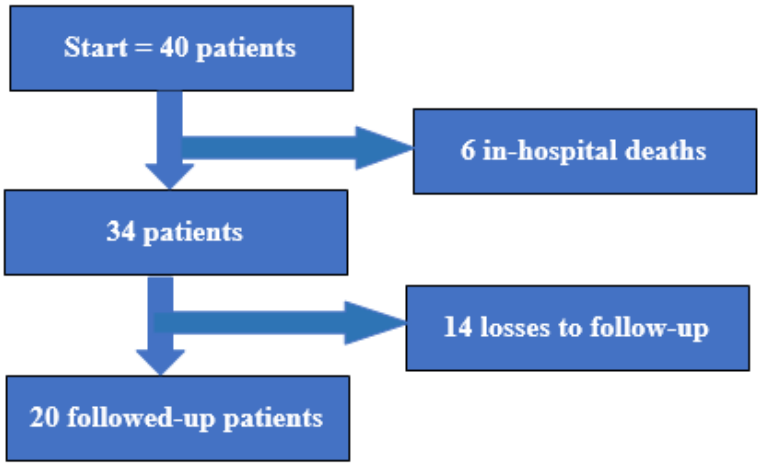
Ethical Aspects

This study was approved by the Research Ethics Committee (CEP) / EMESCAM by opinion No. 2,618,469.

RESULTS

From the 40 patients with HF included at the beginning of the follow-up, six died in hospital. Out of the 34 remaining patients, 20 were contacted with a mean post-discharge time of 12.6 ± 1.2 months and there was a loss of follow-up of 14 (Figure 1). Five deaths (25.0%) were observed in the follow-up, one of them (5.0%) in the first 30 days after discharge.

Figure 1. Study flowchart



Source: own authorship

Substantial differences in comorbidities and clinical risk factors in the death and non-death groups were not noticed. The baseline clinical characteristics observed at the time of inclusion in the study are described in Table 1, as stated in the occurrence or not of death in the clinical follow-up.

Table1. Baseline clinical characteristics and comparison between patients who died and survivors after one year of hospital discharge.

	DEATH	**NON-DEATH**	**P**
Total (n)	5 (25%)	15 (75%)	
Male, n (%)	1 (20%)	8 (53,3%)	0,19
Age (years)	69,2 ± 14	63,8 ± 14	0,44
HAS, n (%)	3 (60%)	12 (80%)	0,29
DM, n (%)	1 (20%)	10 (66,7%)	0,08
Dislipidemia, n (%)	0	4 (26,7%)	0,28
Smoking, n (%)	1 (20%)	2 (13,3%)	0,46
ICP previous, n (%)	0	0	NA
RM previous, n (%)	1 (20%)	5 (33,3%)	0,38
IRC, n (%)	1 (20%)	2 (13,3%)	0,46
FA, n (%)	1 (20%)	3 (20%)	0,47

SAH: Systemic Arterial Hypertension; DM: Diabetes Mellitus; PCI: Percutaneous Coronary Intervention; MRI: Myocardial revascularization; CRF: Chronic Renal Insufficiency; AF: Atrial Fibrillation.

With regard to the outcome, there was an association between lack of adequate clinical follow-up and death at the end of the one-year follow-up (Table 2).

Table 2. Comparison between death and non-death groups with regard to adequate post-discharge clinical follow-up.

	DEATH	NON-DEATH	p
Total, n (%)	5 (25%)	15 (75%)	
Clinical folllow-up, n (%)	0 (0%)	9 (60%)	0,02

DISCUSSION

Out of the patients hospitalized for decompensated HF, who were discharged, 25% of them died within a year, considered the vulnerable period after hospitalization as a consequence of HF. In the post-discharge follow-up, the absence of clinical follow-up evidenced to be a predictor of mortality in patients with decompensated HF. Baseline clinical characteristics, namely age, arterial hypertension or diabetes mellitus, did not reveal a statistically considerable relationship with the outcome of death.

The health system in our country presents lags, making it substantially more difficult to provide adequate services to each patient. Even though these lags are well known, it is considered that investing in the promotion of more rigorous clinical follow-up would save long-term expenses in HF. In this respect, recent scientific evidence establishes the association between clinical monitoring and reduction of unwanted clinical outcomes, suchlike death and readmission.[5,6]

Different studies that assessed post-discharge clinical follow-up warrant this understanding by displaying a reduction in readmission rates, in spite of whether the first consultation was conducted within seven days or within 30 days.[7,8] Nevertheless, it is essential to notice that early follow-up (within the first seven days) significantly reduced readmissions even in the first 30 days, which leads us to consider that the earlier the contact, the better the post-discharge prognosis. Furthermore, there was a proportional relationship between the number of consultations and the reduction in the risk of readmission.[9]

Moreover, the decrease in the readmission rate, mortality was also reduced with post-discharge clinical follow-up. A study held in China terminated that simple telephone contact via text messages via smartphone was capable of reducing the occurrence of this outcome.[5] The current study obtained mortality in the 9.9% post-discharge HF scenario,[5] lower rate when in comparison with this study (25.0%). This can be elucidated by the fact that all patients in the proposed study had some clinical follow-up, either by telephone contact or outpatient follow-up, different from this study. The same happened in a study carried out in Wales, however, in this one, the follow-up was through at least one face-to-face consultation with the cardiologist.[6] This last study was the one that most resembled the data of this research, no matter the view that used the same criterion for clinical follow-up and the same death outcome one year after hospital discharge. Another similar finding alluded to mortality in patients who were not referred for follow-up with a cardiologist, which in this study was 32%.

As a central difference, this study included only patients with systolic HF and an ejection fraction below 40%.

Individualization of treatment and follow-up based on the comorbidities and clinical characteristics of patients are crucial in this syndrome, even despite the absence of association between different clinical variables and mortality after discharge, in this study. The systolic blood pressure measured after discharge,[10] the "time at home" [11] (which can be translated as time outside any health institution) and the level of BNP or NT-proBNP, admission, can serve, for example, as a prognostic value.[12] Consequently, it is necessary to assess all these and other patient's individualities for the prognosis and promotion of due care, in the critical post-discharge period of decompensated HF.

The current study presented limitations, such as reduced sample size and great loss of follow-up of patients in one year, taking into account that the contact was made by telephone. The justification for this is by virtue of the studied population low socioeconomic and cultural level, since the major part did not possess their own telephone however, they provided telephone numbers of close relatives.

CONCLUSIONS

The absence of clinical follow-up after hospital discharge was associated with higher mortality in cases of decompensated HF. It would be important to carry out further studies in different countries and regions, with their specificities, and with a larger sample size for the purpose of corroborating these results. It is understood the need for additional studies in different countries and regions, with their particularities, and with a larger sample size, to corroborate these results. Furthermore, it is worth emphasizing the importance of making investments in health and public policies, raising awareness of the impact that clinical follow-up has on mortality and costly readmissions of patients with decompensated HF. Besides, doctors who guide these patients throughout hospitalization could as well guide them on the chronicity of their disease, non-pharmacological measures that can enhance survival, signs of decompensation and the importance of regular clinical follow-up.

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ESTUDOS INTERDISCIPLINARES EM CIÊNCIAS SOCIAIS E DA SAÚDE
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Original Article

MILD NEUROCOGNITIVE DISORDER: COMPARISON OF TWO COGNITIVE EVALUATION TESTS

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Keywords

Tracking;
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Schooling;
Mild Cognitive Impairment.

Abstract

Introduction: Mild Neurocognitive Disorder (TNCL) was aimed to conceptualize elderly individuals with no dementia, yet with mild cognitive impairment characterized by changes in memory or other cognitive functions (DSMV-2013). It displays a prevalence of 12 to 18% in people over 65 and the annual rates of progression to Alzheimer's disease from 10 to 15%. OBJECTIVES: To compare the cognitive screening instruments Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) in people of low level of education in patients with TNCL. **Methods**: patients aged 70 years or older underwent MEEM and MoCA instruments. The sample was composed of individuals with no cognitive complaints and patients with amnestic TNCL. Accuracy between tests was evaluated using the ROC curve (ACR). RESULTS: Seventeen normal patients (51.5%) were compared with sixteen patients with TNCL (48.5%). Patients with normal cognition and with TNL presented a similar distribution by sex, age, comorbidities (arterial hypertension, diabetes mellitus, dyslipidemia) and functionality / autonomy. The MMSE had a total score of 22 points ($p = 0.04$), with a ROC curve area (ARC 0.71; $p = 0.03$), with no significant change in the cognitive domains evaluated. MoCA a score of 16 ($p = 0.004$), with ROC curve area (ACR 0.78; $p = 0.005$) with difference in the visuospatial / executive domains ($p = 0.02$) and late evocation ($p = 0.01$). **Conclusions**: Both tests were good tools for screening neurocognitive disorder in elderly people with low education, with a slight MoCA superiority over MMSE.

INTRODUTION

Mild Neurocognitive Disorder (NCD) is a transient stage between normal aging and dementia, which results in mild cognitive impairment with changes in memory or other cognitive functions (1). Its standard comprises memory complaint, as indicated by the patient or a relative, and a slightly lowered score on cognitive assessment instruments (1.5 standard deviations) with regard to individuals with the same age and education or 0.5 CDR (2).

The prevalence of TNCL is 12 to 18% in people over 65 and the annual rates of progression to Alzheimer's disease are 10 to 15% (3,4).

Among the instruments used for its tracking, the most common are: the MMSE (Mini-Mental State Examination) and the MoCA (Montreal Cognitive Assessment); validated for individuals with high schooling. In a recent systematic review study, a small number of studies were encountered with tracking instruments in

elderly people with low levels of schooling (5).

This study aimed to compare the MoCA (Montreal Cognitive Assessment) instruments with the Mini Mental State Examination (MMSE) in patients with mild cognitive impairment and normal individuals, with low education.

METHODS

This is an observational, cross-sectional study of a convenience sample in a geriatric outpatient clinic at Santa Casa de Misericórdia de Vitória Hospital -ES. The elderly of both sexes agreed to participate in the study, which only occurred after reading and signing the informed consent form, with a description of its objectives. TNCL patients were in accordance with the criteria presented in the "Internatinal Working Group Mild Cognitive Impairment" (6): a) Cognitive complaint reported by the patient and / or informant; b) Report of cognitive decline in relation to the previous year; c) Change in cognition (memory or other domains) when compared to normal elderly people of the same age and education and evidenced in the clinical evaluation; d) Absence of difficulties with activities of daily living, preserved general cognitive functioning; e) Absence of dementia.

TNCL is categorized into multiple subtypes, with their own designations: amnestic; multiple altered cognitive domains, comprising memory; and single cognitive impairment, except memory (7). Patients with amnestic TNCL were included in this study merely, as it presents a greater risk of progression to Alzheimer's disease.

Patients with schooling up to 8 years old (elementary school), older than 70 years old and both sexes were included, and patients with low visual and auditory acuity and patients with severe chronic disease were excluded.

Two cognitive tracking instruments were applied, the Montreal Cognitive Assessment (MoCA), validated to evaluate elderly people with four or more years of schooling, with eight cognitive domains, with a total score of 30 points, validated in Brazil, with a cutoff point indicated 24/25, with sensitivity and specificity of 81 and 77%, respectively (8) and MINI MENTAL EXAM (MEEM) with six cognitive domains, with cut-off points of: 18/19, for illiterate and 23/24 for individuals with more than 1 year of schooling (9).

With the firm purpose of evaluating an independent and active life in the community, we used the LAWTON Scale (10). This scale is corresponding to the performance of more complex tasks, namely, cleaning the house, calling, traveling, shopping, preparing food, controlling and taking medicine and managing finances.

MoCA (11) was designed as a concise screening tool for mild cognitive impairment. This instrument evaluates different cognitive domains: executive function; visuospatial capacity; memory; attention, concentration and working memory; language; temporal and spatial orientation. The administration time is roughly 10 to 15 minutes. The maximum score is 30 (points). The test was validated for Portuguese by Memoria et al. (8).

The MMSE (12) is presumably the most used instrument worldwide, with versions in several languages, validated for the Brazilian population (13). It offers information about different cognitive parameters. It comprises questions classified into seven categories, each aimed at evaluating "functions" specific cognitive and temporal orientation (5 points), spatial orientation (5pontos), three-word record (3 points), attention and

calculation (5 points), recall of the three words (3 points), language (8 points) and visual constructive capacity (1 point). The MMSE score can vary from a minimum of zero points, which suggests the highest degree of cognitive impairment of individuals up to 30 points, which, in turn, corresponds to the best cognitive ability. The administration time takes about 10 minutes.

Variables were depicted by percentage and average (standard deviation). For statistical inference, Student's t test for independent samples or Mann Whitneye chi-square was employed, when continuous or categorical variables, respectively. The ROC curve was applied via analysis of occupation of the area of the curve (ACR), with the purpose of assessing the best accuracy between the two screening tests. Values ≤ 0.05 were considered significant, the SPSS 25.0 software was used. Project approved at CEP-EMESCAM under number 1.469.472, CAAE: 52932816.4.0000.5065.

RESULTS

Seventeen patients with normal cognition (51.5%) were compared with sixteen patients with amnestic TNCL (48.5%). Patients with normal cognition and with TNL presented a similar distribution by sex, age, comorbidities (arterial hypertension, diabetes mellitus, dyslipidemia), smoking, body mass index and functionality (LAWTON). The patients with normal cognition presented a higher level of education (F = 1.332; p 0.03).

When comparing the normal and TNCL groups, the MINI EXAME (p = 0.04) demonstrated no difference in the domains assessed, with a total average score of 22 points. MoCA (p = 0.004) revealed a difference in the visuospatial / executive domains (p = 0.02) and late evocation (p = 0.01) with a total mean score of 16 points. The MoCA test engaged a larger area of the ROC curve (078; p = 0.005) in comparison with the MINI EXAME (071; p = 0.03). The variables are delineated in TABLES 1 and 2 and FIGURE portraying the ROC curve.

DISCUSSION

The sample was paired, in order to prevent interference, by sex, age, comorbidities, Nevertheless, patients with no cognitive complaints, presented a higher level of education.

There are about 758 million illiterates in the world and around 13 million in Brazil (14).

Illiteracy and low educational level are resulting from an increased risk of mild neurocognitive disorder and dementia (15). In contrast, the rates of cognitive impairment and dementia can be overestimated in populations with low education as a consequence of a low performance in cognitive screening tests that demand some degree of literacy (16).

In a recent systematic review (2019), the authors noticed that MMSE (86%) and MoCA (27%) were the most broadly employed cognitive screening tools with low education people (5).

MoCA revealed a difference in two domains, visuospatial and late evocation, not detected in the MMSE, which assesses them as well. The majority of the studies performed, described in a recent meta-analysis, were comparing patients with dementia with TNCL. This study was related to patients without cognitive symptoms (17) without the influence of the factors: sex, age, functionality and comorbidity, formerly paired.

MoCA and MMSE presented a lower total score in patients with cognitive history, compatible with LMNT, however, with greater significance for the first test.

The cutoff point was 16 for MoCA and 22 for MMSE in patients with TNCLamnestic. Studies published in Brazil demonstrated a cutoff point of 15 for MoCA, nonetheless with low accuracy in a population with low education level, yet in patients with a lower age (18). Another study revealed a cutoff point of 20 in the MMSE (19).

With respect to the area on the ROC curve (ACR), to evaluates the accuracy of the tests, the MoCA presented (ACR 0.78; p = 0.005) with regard to the MINI EXAME (0.71; p = 0.03). Matias-Guiu et al. (2017), in a cross-sectional study comparing various cognitive screening instruments in 92 patients with TNCL with 68 healthy people with high education, noticed that the MMSE occupied 0.86 and MoCA 0.85 of the ROC curve.

This current study presented some limitations, namely the small sample size, difficulty in conducting interviews in the period preceding the consultation and willingness to participate in the control group (cognitively normal).

All things considered, both tests demonstrated good accuracy for cognitive screening with low education, with MoCA superiority over MMSE.

Table 1– Distribution of functionality, habits, age and risk factors

	NORMAIS	TNCL	ρ
Ssxo (M/F) %	41,8 / 58,8	50 / 50	0,73
Smorking*	29,4%	31,2%	0,57
Arterial Hipert.	58,8%	62,4%	0,52
Diabetes Mellitus	28,8%	37,4%	0,29
Dislipidemia	35,3%	37,5%	0,59
Katz (0-6)	0,73 ± 1,55	0,86 ± 0,29	0,80
Lawton (0-21)	16 ± 5,3	14,60 ± 3,62	0,51
IMC	25,9 ± 4,6	25,9 ± 6,3	0,99
Schooling	4,75 ±2,5	2,63 ±2,80	**0,03**
Age	80 ± 5	80± 5	0,71

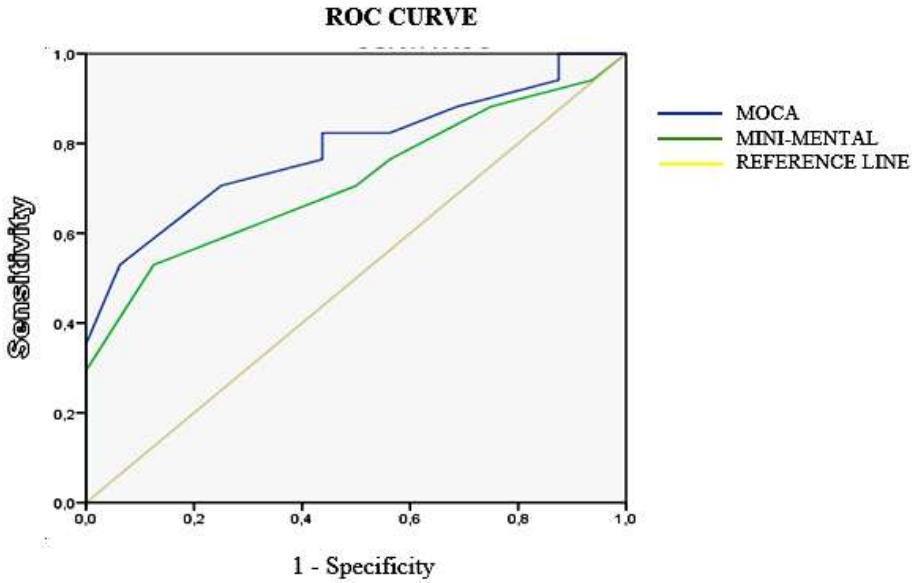
* history of smoking. T-test for independent samples (continuous variables) and chi-square for categorical variables. significant $p \leq 0.05$.

Table 2 – Cognitive evaluation of normal patients with amnestic TNCL

	NORMAL (17)	TNCL (16)	p
MINI MENTAL (30)	23,88 ± 2,80	22,06 ± 2,0	**0,04***
Register (3)	2,94 ± 0,24	2,75 ± 0,73	0,34
Calculation (5)	1,94 ± 1,79	1,56 ± 1,56	0,50
Evocation (3)	1,76 ± 1,24	1,00 ± 1,15	0,06
Language (9)	7,94 ± 1,24	7,81 ± 1,16	0, 76
MoCA (30)	19,94 ± 3,99	15,94 ± 3,47	**0,004****
Visuospatial (5)	3,29 ± 1,10	2,31 ± 1,35	**0, 02***
Appointment (3)	1,12 ± 0,78	1,69 ± 0,87	0,14
Atention(6)	3,47 ±1,62	3,25 ± 1,52	0,69
Language (3)	2,53 ± 0,71	2,00 ± 0,96	0,08
Abstraction (2)	1,53 ± 0,80	1,00 ± 0,73	0,056
Late evocation (5)	1,65 ± 1,56	0,44 ± 1,03	**0,01***
Guidance (6)	5,35 ± 0,93	5,25 ± 0,93	0,75

Teste t de studenteMann Whitney p significante ≤ 0,05*

Roc curve figure: mini mental examination and MOCA



ACR (curve area ROC): MEEM 0,71 (0,53-0,89); p 0,03 MoCA 0,78 (0,62-0,94); p = 0,005

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Original Article

COMPARATIVE STUDY INVOLVING DOLUTEGRAVIR AND EFAVIRENZ IN HIV ANTYRETROVIRAL THERAPY SCHEMES: DRUG ADHERENCE, EFFICACY AND ADVERSE EFFECTS

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Abstract

Introduction: This study has compared therapies in HIV/AIDS treatment with Dolutegravir (DTG) or Efavirenz (EFV) analyzing drug adherence, efficacy, and clinical and laboratory adverse effects. **Aim:** As since 2017, HIV treatment has included Dolutegravir integrase inhibitor (DTG), involving a significantly larger number of patients, further studies on its use in real life are needed. **Methods:** This cohort analytical study was conducted from 2017 to 2019 at an Infectious Disease Outpatient Reference Center in Vitória, ES. 100 patients were studied using DTG by means of a prospective cohort and 100 patients using EFV by retrospective analysis of medical records for a minimum of six months and a maximum of one year since the beginning of

therapy. Chi-square or Fischer tests were used to compare groups with SPSS 25 and BioEstat. **Results:** Among 200 patients, 56% were male, 43.2% white and 59.6% acquired the disease with heterosexual intercourse. The median age in the DTG group was 46 years (IQR 34-56) and in the EFV group was 38 years (IQR 30-45), with significant difference (p = 0.000). Adherence observed in the DTG Group was 89% and in the EFV Group was 86%; the efficacy in the DTG group was 85% and in the EFV group 81%, with no statistical significance of both these variables. A total of 87 adverse effects antiretroviral therapy related were recorded in 69 patients in total, the most common being neuropsychiatric events (27.6%) and lipid profile alteration (21.8%). Total cholesterol levels decreased in the DTG group, with an average of 15 mg / dl (SD ± 38; p = 0.000), with a predominance of a reduction in serum LDL levels and an increase in the EFV group with an average of 21 mg / dl (SD ± 32; p = 0.000), with a predominance of serum LDL levels. The mean increase in serum creatinine was 0.16mg / dL (SD ± 0.65; p = 0.000) in the DTG group, but without alteration of renal function. The average weight gain with the use of DTG was 1.51kg (SD ± 3.38; p = 0.009) and only 10% were in initial treatment. In the EFV group, it was 4.66kg (SD ± 6.86; p = 0.009) with more than 80% in initial treatment. Antiretroviral therapy replacement as a result of adverse effects occurred in 4.5% of patients in the DTG group, compared with 30.2% in the EFV group. **Conclusion:** The study showed that the new treatment had similar adherence, did not change efficacy during the study period, improved lipid profile, did not change the weight significantly in those who switched to DTG and resulted in less need for antiretroviral therapy replacement after adverse effects when compared to EFV.

INTRODUCTION

AIDS pandemic has turned out to be a topic of major issues, such as human rights, quality of life and drug policies[1]. Ministry of Health (MS) data reveal that the HIV / AIDS epidemic in Brazil has been increasing in number of cases and even in mortality, despite this situation substantially differs, based on the region and with specific subpopulations[2].

As reported by the 2019 UNAIDS Information Report, there are 37.9 million people with HIV / AIDS worldwide, with a rate of 1.7 million new infections. Out of these people, only 23.3 million gain access to antiretroviral therapy (ART) and 770 thousand people, adults and children, died of AIDS-related causes that year, with a decrease of more than 55% in comparison with 2004, when the peak disease mortality took place[3].

For the purpose of reaching the end of the AIDS epidemic, the United Nations (UN) has as its strategy the Goal 90/90/90, adhered by Brazil, which proposal is that 90% of people living with HIV are diagnosed by 2020 and that, among these people, 90% are under treatment and, further, that among these people under treatment, 90% have an undetectable viral load[4].

In Brazil, among people living with HIV, it is estimated that 84% are diagnosed. As stated by the 2017 MS data, 72% of the total is being treated and 91% of all people living with HIV have suppressed viral load, which suggests that Brazil has already exceeded the 90/90/90 target on this last point[5].

A growing number of antiretroviral drugs have been developed with the purpose of controlling HIV given that treatment is viewed as way to control of the epidemic, as it diminishes the risk of transmission. Dolutegravir, the latest integrase inhibitor, may have a positive effect on reaching the goal established by the UN, as it fosters better adherence to treatment, and therefore it enhances the rate of people in viral suppression.
In Brazil, HIV treatment observes the recommendations of the Clinical Protocol and Therapeutic Guidelines for the management of HIV infection in Adults (PCDT), and until 2016 the first line therapy composed of Tenofovir, Lamivudine and Efavirenz (TDF + 3TC + EFV) is advisable. [6] On the basis of the update of this protocol by the MS in 2017, the first-line therapeutic regimen became Tenofovir, Lamivudine and Dolutegravir (TDF + 3TC + DTG) [7].

By virtue of a growing concern about the adverse effects of EFV, a non-nucleoside reverse transcriptase inhibitor was occasionally replaced by other drugs, as it presented neurological and psychiatric reactions namely nightmares, dizziness, insomnia, nervousness and lack of concentration, in addition to more severe symptoms, such as depression, suicidal ideation or even psychosis[7].

Dolutegravir is an antiretroviral agent that is equally effective for both untreated patients and patients with HIV infection already being treated. This drug prognosticates few pharmacological interactions; reduced toxicity; high genetic barrier to resistance; single daily administration and reduced cost[7,8,9].

The data of 2018 reveal that, in Brazil, 76,713 people use DTG as first-line therapy and another 45,645 have switched to DTG. Simultaneously, there are more than 122 thousand Brazilians living with HIV using Dolutegravir in their antiretroviral treatment schemes, portraying 19% of the total of 572 thousand Brazilians who receive antiretroviral treatment pro bono, via SUS. It should also be noted that 87% of people who started treatment in 2018 started with DTG[1º].

On account of PCDT update, taking into account a greater number of users who will benefit from this therapy, additional clarification on Dolutegravir adherence, efficacy and adverse effects is required.

The main goal of the current study is to compare the therapies responses with Dolutegravir and Efavirenz in antiretroviral therapy regimens in the population living with HIV-AIDS monitored in a reference center of Hospital Santa Casa de Misericórdia de Vitoria (HSCMV).

This study has as objectives: a) compare the responses of therapies with Dolutegravir and Efavirenz in antiretroviral therapy regimens in the population living with HIV-AIDS monitored in a reference center of Hospital Santa Casa de Misericórdia de Vitoria (HSCMV); b) to evaluate

medication adherence, c) to analyze the efficacy by viral suppression and d) to compare adverse effects, both clinical and laboratory, between the two schemes earlier referred.

MATERIALS AND METHODS

This is a historical cohort-type analytical study, undertaken in two distinct phases, by monitoring medical records and files displayed in the appendices of this work. The study participants were divided into two groups: the first composed of ART-naïve patients who started their regimen with Dolutegravir and in patients who were on ART before, and swapped from their previous regimen to Dolutegravir (DTG Group); and the second group with patients on current or previous use of ART with Efavirenz (EFV Group).

The research was held with HIV / AIDS patients from the Outpatient Service of Infectious Diseases at HSCMV with 200 patients - 100 within each group mentioned above. Patients using ART for a minimum of six months and a maximum of one year were included.

The sample of patients in the DTG group was selected from a list with names of patients who removed this medication at the pharmacy of this service, which was updated per month in the interest of reaching the final number of participants in that first group. The sample of patients in the EFV group was selected at random by coin toss. The medical records aimed for describing therapeutic regimens that included EFV when added in the research. The difference in selection between the groups was required owing to the fact that many patients are in the process of switching to the currently recommended regimen.

Patients were identified by codes in order to protect the confidentiality of their medical record data and authorized by them after signing the Free and Informed Consent Form (ICF). This study was approved by the Research Ethics Committee of EMESCAM-CAAE: 68564417.9.0000.5065.

Data collection was conducted on the days of operation of the Outpatient Service of Infectology at HSCMV, by three researchers formerly trained and aided by the advisor, who is also part of the team of infectologists responsible for outpatient care. The information was collected from handwritten and digital medical records retrospectively for the EFV group and prospective for the DTG group.

The analyzed variables included: effectiveness, adherence and adverse events. Suppression of viral load (CV) within a period of six months to one year after the beginning of the medication was defined as efficacy, and absence of rebound (detectable CV in individuals who had reached viral suppression under treatment). Participants who did not fulfill the above criteria were portrayed as virological failure.

Adherence was evaluated in regard to the participants' report of the regular use of ART during the consultation and recorded in the medical records, apart from checking the list of medication withdrawals from the pharmacy of this service. A weak adherence was deemed in those patients who either interrupted or made irregular use of medications at a given time.

Adverse effects (AE) were evaluated by the arisen of clinical and laboratory alterations over the treatment interval recommended by the research. Clinical AEs were ranked into the following groups: neuropsychiatric, gastrointestinal, skin rash and other events. Data collection was founded on the report and perception of patients and on the

collection of laboratory data with respect to renal, liver, lipid and glycemic profiles.

The change in renal function was determined by serum creatinine> 1.3 mg / dL in patients who had previous values ≤ 1.3 mg / dL, and / or glomerular filtration rate (GFR) <60 mL / min / 1.73m² using as reference MDRD (Modification of Diet in Renal Desease) calculation, in patients who previously had values ≥ 60 mL / min / 1.73m². [11] The change in liver function was defined by transaminase values (TGP and / or TGO)> 40 U / L, which corresponds to the upper limit of normal based on the HSCMV laboratory. The change in the lipid profile was characterized by total cholesterol (TC) values> 190 mg / dL in patients who had previous values ≤ 190 mg / dL; HDL <50 mg / dL in women and <40 mg / dL in men who had previous values ≥ 50 mg / dL and ≥ 40 mg / dL respectively; LDL levels> 130 mg / dL in patients who had previous values ≤ 130 mg / dL.[12] The change in glycemic profile was defined as blood glucose values ≥ 100 mg / dL in patients who had previous values <100 mg / dL.[13]

The AE outcomes were also evaluated, and there may have been an alteration or not in the ART emplyoed by the patient.

Patients in the DTG group were in comparison to patients in the EFV group at the infectious disease clinic.

Equivalent collaborative studies are being performed in other services that are part of the Brazilian AIDS Cohort with the purpose of increasing the sample size and assessing the performance of the new protocol of the Ministry of Health in the reality of the assistance services of the Unified Health System.

The sample size calculation was held in G-Power given the comparison between the group with patients using current or previous ART with EFV, and the other group with patients using DTG, for the two main variables: CV and count of CD4 cells. A significance level of 5%, test power of 80%, an average effect size of 0.4 was contemplated. The result demands a sample size of 100 individuals in each group.

The data of participants of both assessed groups were registered in a standardized instrument and organized in spreadsheets in Excel software and arranged in SPSS version 25 and BioStat software. Data analysis was held by using descriptive statistics, for instance frequencies and percentages for categorical variables. Quantitative variables were ordered as mean standard deviation, median and interquartile range. The association between variables carried out using the Chi-square test or Fisher's exact test in the case of expected frequencies less than 5. The quantitative variables between the two groups were compared using the Student's t-test for independent samples or by the Mann-Whitney when the data did not put forward a normal probability distribution. The normality of the data was confirmed by the Kolmogorov-Smirnov test. A significance level of 5% was considered.

RESULTS

A total of 200 forms were collected, of which 100 correspond to the EFV group and 100 to the DTG group. In the service analyzed, a higher prevalence of treatment was observed in males (56%), in whites (43.2%), and through heterosexual transmission (59.6%) in relation to all patients. The prevalence of these epidemiological data was similar between the DTG and EFV groups, with no statistical significance between them (Table 1).

Table 1 - Epidemiological data from the comparative study between Dolutegravir and Efavirenz in antiretroviral therapy regimens in the treatment of HIV (n = 200).

Variable of interest	Total	Groups	
		DTG (n%)	EFV (n%)
SEX			
• Male	112 (56.0%)	55 (55%)	57 (57.0%)
• Female	88 (44.0%)	45 (45%)	43 (43%)
RACE			
• White	64 (43.2%)	41 (44.6%)	23 (41.1%)
• Brown	53 (35.8%)	31 (33.7%)	22 (39.3%)
• Black	31 (20.9%)	20 (21.7%)	11 (19.6%)
TRANSMISSION			
• Homossexual	37 (26.2%)	21 (25.0%)	16 (28.1%)
• Heterossexual	84 (59.6%)	50 (59.5%)	34 (59.6%)
• Transfusion	3 (2.1%)	2 (2.4%)	1 (1.8%)
• UDEV	2 (1.4%)	2 (2.4%)	0
• Vertical	15 (10.6%)	9 (10.7%)	6 (10.5%)

p Sex= 0.776; *p* Race= 0.789; *p* Transmission= 0.819.
Source: data collected by the authors.

The median age of patients studied in the DTG group was 46 years, with an interquartile range varying from 34 to 75 years. In the EFV group, the median age was 38 years, with an interquartile range ranging from 30 to 75 years. The DTG group was significantly older than the EFV group (p <0.001). According to data analysis, 87.5% of all patients had adherence to drug treatment, whereas in the DTG group it was 89% and in the EFV group it was 86%. The overall effectiveness observed in the study showed that 83% of patients achieved suppression of viral load. In the DTG group this number was 85% and in the EFV group it corresponded to 81%, with no significant difference between the results of both variables (Table 2).

Table 2 - Information related to age, adherence, efficacy and diagnosis related to the comparison between Dolutegravir and Efavirenz in antiretroviral therapy regimens in the treatment of HIV (n = 200).

Variable of interest	Dolutegravir	Efavirenz
AGE (p=0.000)		
• Median	46	38
• Percentile 25	34	30
• Percentile 50	56	46
ADHERENCE (p=0,521)	89 (89.0%)	86 (86.0%)
• Yes (n=175/87.5%)	11 (11.0%)	14 (14.0%)
• No (n=25/12.5%)		
EFICACY (p=0.451)	85 (85.0%)	81 (81.0%)
• Viral supression (166/83.0%		
• Virological speech (34/17.0%)		
DIAGNOSIS (p=0,0234)	18 (40.9%)	29 (67.4%)
• Clinical (n=47 (18,0%)	26 (59.1%)	14 (32.6%)
• Laboratory (87 (44,0%)	44	43
TOTAL		

Source: data collected by the authors.

A total of 87 adverse events related to HAART were counted in 69 patients, out of the total 200 studied, demonstrating that some patients had more than one event, clinical or laboratory. The maximum number of events in the same patient was four. The proportion of adverse clinical and laboratory events. The neuropsychiatric event was the most incident in total, with a value of 27.6% among all events. In the DTG group, this value was 25% against 30.2% in the EFV group. Alteration of the lipid profile was the second most incident finding, which corresponds to 21.8% of the total, being a beneficial finding seen in the group of patients who used Dolutegravir. In this group, this value was 29.5%, with a predominance of reduced serum levels of TC and LDL. In the EFV group, this value was 14%, with a predominance of increased serum levels of TC and LDL, with both variables showing statistical significance (p <0.001). The mean CT variation in the DTG group corresponds to a 15 mg / dL reduction in serum levels, while in the EFV group it corresponds to an increase of 21 mg / dL, within the period evaluated by the study. Regarding serum LDL levels, the mean of its variation in the DTG group was a reduction of 7.86 mg / dL, in contrast to the EFV group in which an increase of 14.63 mg / dl was observed. Table 3 exhibits the detailed results.

Table 3 - Information related to adverse events and laboratory changes related to the comparison between Dolutegravir and Efavirenz in antiretroviral therapy regimens in the treatment of HIV (n = 200).

Variable of interest	Dolutegravir	Efavirenz
Adverse events (p<0,001)		
• Neuropsychic (n=24/)	11(25.0%)	13 (30.2%)
• Gastrointestinal (n=14)	7 (15.9%)	7(16.3%)
• Rash/alergy (n=6)	0	6 (14.0%)
• Renal (n=7)	7 (15.9%)	0
• Hepatic (n=5)	1 (2.3%)	4 (9.3%)
• Alteration of the lipid profile (n=10)	13 (29.5%)	6 (14.0%)
• Altered fasting glucose (n=8)	5 (11.4%)	3 (7.0%)
• Others (n=4)	0	4 (9.3%)

Source: data collected by the authors.
Laboratory changes with mean and standard deviation values and p values are exhibited in Table 4.

Table 4 - Description of mean and standard deviation values of laboratory changes observed in comparison between Dolutegravir and Efavirenz in antiretroviral therapy regimens in the treatment of HIV (n = 200).

Variable of interest	Dolutegravir Mean±SD	Efavirenz Mean±SD	p Value
• Nadir	281±258	253±190	0.941
• PRE-TARV CV	54332±178896	535336±2023081	0.000
• PRE-TARV CD4	459±353	312±244	0.007
• POST TARV CD4	505±266	489±336	0.364
• Δ[1] CD4	109±179	163±208	0.153
• Δ TOTAL CHOLESTEROL	-15±38	21±32	0.000
• Δ HDL CHOLESTEROL	-3.46±11.55	-2.00±14.77	0.680
• Δ LDL CHOLESTEROL	-7.86±35.96	14.63±28.95	0.036
• Δ FAST GLUCEMIA	2.6±30.1	-0.8±15.6	1.000
• POST TARV TGO	24.00±10.92	23.43±8.78	0.912
• POST TARV TGP	29.7±23.2	27.0±17.1	0.957
• POST TARV CREATININE	1.21±0.99	1.12±1.41	0.000
• Δ CREATININE	0.16±0.65	-0.24±0.60	0.000
• POST TARV TFG[2]	72.09±18.48	107.07±35.01	0.000
• Δ TFG	-10.35±18.89	12.68±20.75	0.003
• PRE-TARV WEIGHT	69.85±14.47	61.62±10.23	0.005
• POST TARV WEIGHT	71.63±14.49	66.32±9.96	0.029
• Δ WEIGHT	1.51±3.38	4.66±6.86	0.009

[1]Δ: Pre-TARV and post TARV values variation;
[2] TFG: Glomerular Filtration Rate (calculated by MDRD).
Source: data collected by the authors.

In the outcome of adverse events when comparing Dolutegravir to Efavirenz, differences were found between the Dolutegravir and Efavirenz groups (p = 0.0039), as shown in Table 5.

Table 5 - Description of adverse events in the comparison study between Dolutegravir and Efavirenz in antiretroviral therapy regimens in the treatment of HIV (n = 200).

Variable of interest	Dolutegravir	Efavirenz
• TARV changes (n=15)	2 (4.5%)	13 (30.2%)
• No change in TARV (n=72)	42 (95.5%)	30 (69.8%)

Source: data collected by the authors.

DISCUSSION

The epidemiology observed in the study indicated a higher prevalence of treatment among males, whites and heterosexual transmission, which concurs with the profile of patients living with HIV / AIDS in Brazil in agreement with the 2018 Epidemiological Bulletin published by the Secretariat of Health Surveillance - MS.[14]

The much older age in the DTG group is a result of the fact that most patients in this group had a recent switch to this drug, with older age. It is important to mention that the majority of patients used Efavirenz eventually during the treatment, as this medication was already part of the chosen therapeutic regimen. Accordingly, the lower average age presented in the EFV group in comparison with the DTG group is warranted.

Same adherence was noticed between the groups, regardless conflicting with data in the literature that show unfavorable adherence to the use of Efavirenz as a consequence of its higher incidence of side effects.[8] This was not observed in this study, given that they are patients followed up at a reference service which emphasizes the importance of regular use of medication, which reflects the similarity between groups. The data of this research corroborate the findings of Venter et al. regarding the efficacy of both drugs, which demonstrated that the effectiveness of treatment with Dolutegravir was not inferior to the standard treatment with Efavirenz.[15] It is worth pointing that the virological failures shown in table 3 were secondary to poor adherence, with no resistance to medication being detected.

One may observe that the large amount of AEs in the DTG group, especially laboratory ones, arose on account of the greater ability of obtaining information, given that they are recent data and gathered prospectively. Conversely, some difficulty was encountered in obtaining trustworthy data in the EFV group, owing to the fact that the collection was hampered by the handwritten report of the medical records and for the reason that it was performed retrospectively. The scarcity of data in this group overestimated the proportion of laboratory AEs in the DTG group when compared. Predictably, there was an association of clinical AEs with the use of Efavirenz in this study.

About neuropsychiatric AEs, the EFV group evidenced greater quantity and severity of this type of manifestation, like: depression, sleep disturbance, nightmares and vivid dreams. The DTG group, nevertheless, further having less neuropsychiatric events, were milder, namely: headache, sleep disturbance and dizziness. Accordingly, the findings of this study corroborate those described by Kendal et al. and Curtis et al. that present mild adverse events that are not entirely concerned the medication in question. [16,17]

The alterations in the lipid profile encountered in this research were the ones described by Curtis et al., who reported that, unlike other antiretrovirals, Dolutegravir does not cause elevation of total cholesterol and LDL. [17] In the current study, it was also revealed that there was an association between the use of this drug and an improvement in lipid rates, causing a reduction in serum levels of total and LDL cholesterol.

One observed an increase in serum creatinine and a reduction in GFR with the use of Dolutegravir, a result in contrast to that observed in the EFV group. Although creatinine dosage is usually used to study glomerular function, some situations can specifically alter creatinine excretion without impacting other aspects of kidney function, like Dolutegravir, in line with studies. This happens by reason of a specific competition for the tubular excretion site of creatinine, a phenomenon analogous to what occurs with other drugs, such as Rilpivirine (RPV), Cimetidine (CMT) or Trimethoprim (TMP). Despite that, this change is not very significant: an increase of up to 0.12 mg / dL in serum creatinine. [11] In this study, an average increase in serum creatinine of 0.16 mg / dL was detected, a value close to that observed in the study by Koteff et. al.[18] Above all, both in the studies used as a reference and in the present study, no patient stopped using DTG by virtue of kidney injury. In fact, integrase inhibitors, as a class, appear to be a relevant option for patients with nephropathy.

Regarding the analysis of weight, there was a greater average gain in the EFV group [4.66 kg (SD ± 6.86)] asw against the DTG group [1.51 kg (SD ± 3.38)]. This difference is by dint of the fact that more than 80% of patients in the first group were ART-naïve, having started their treatment with schemes including Efavirenz. Thus, this weight gain generates a confusing factor given that it can be explained either by the clinical improvement related to the treatment of the disease or by the adverse effect of the drug. Nevertheless, there are no data in the literature that evidence significant weight gain with the use of Efavirenz as part of their AEs, reinforcing the hypothesis that weight gain is vindicated by the natural course of HIV treatment.[19]

With regard to DTG group, the patients presented a higher mean weight prior to the use of Dolutegravir, given that 90% of these patients were previously on treatment with another ART regimen, having switched to this medication. Even though the patients in this group had a lower average weight gain, considering that they are already on treatment, there is a considerable chance that this effect is vindicated by the use of this drug. Nonetheless, for the subgroup of patients who underwent switch to Dolutegravir, weight gain was not important, taking into account that there was a small weight increase in at least 6 months of follow-up. More current studies also disclose a small weight gain concerned the use of Dolutegravir, as in the cohort conducted by SEARCH (The Thai Red Cross AIDS Research Center) in which an average weight gain of 2 kg was observed after 48 weeks of follow-up.[2o] Thereby, more studies are required in order to compare the effect of the drug on weight gain when used in initial versus switch therapy.

This study showed the association of allergic reactions / widespread skin rash with the use of Efavirenz, a well-known manifestation of the drug and one of the biggest causes of change in ART including this medication.

By the AEs outcome analysis, one may get to the conclusion that, regardless the similar number of events between the groups, the EFV group revealed a higher incidence of change in ART, about 6 times greater than the DTG group. It may be explained by the clinical relevance of the manifestations of adverse events caused by the use of Efavirenz. The primary reasons for exchanging ART with this drug in the study were vertigo, depression, suicidal ideation, sleep disturbance and allergic reactions / disseminated skin rash. In the DTG group, the exchange of medication secondary to its use happened in only 2 patients out of 100 analyzed, both by virtue of headache, and with later resolution of the condition.

CONCLUSION

The study pointed out that treatment with Dolutegravir in our service revealed similar adherence and did not significantly alter efficacy. Moreover, it improved the patients' lipid profile and resulted in less need to change the TARV after adverse events, when compared to the use of efavirenz. it is important to emphasize that the monitoring of the glomerular filtration rate in patients using Dolutegravir starts to contemplate other alternative methods that are not only by the measurement of serum creatinine. It is perceived the need for more research to elucidate the effects that this drug generates in relation to weight and how these changes can affect the course of treatment and the disease.

Similar studies to this one have been broadly used in decision-making regarding new drugs, considering that they are carried out in a real-world environment, whose participating populations are much more representative of reality than those selected for clinical trials, these being held in controlled environments and with criteria stricter criteria for patient inclusion.

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