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EDITORIAL

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Has ethics changed or is it currently not being applied?

A ética mudou ou, atualmente, ela não é plenamente exercida?

TCBC Fernando Cordeiro

Writing on moral, ethics, and especially on medical ethics in modern times and, who knows, at any time, always brings the discussions on human conduct, its required coding between good and evil and, especially, an attempt of society to standardize the relations between people and groups.

Several thinkers and writers have left their concepts on the subject. I personally always like to avail myself of the dictionaries as reference for concepts. So, looking at the New Dictionary Aurelius, I find: ethics - "the study of assessment judgments concerning human behavior, susceptible to qualification from the point of view of good and evil, whether in respect of a given society or absolutely". One could confuse it with the concept of moral, whose definition is: "set of rules of conduct considered as valid, whether absolutely to any time or place, or to a particular group or person." The big difference is in the ethics code and its usefulness as a beacon of professional activities. But back to the topic, if medical ethics has been so often defined and coded, from the Hippocratic times to our present time, under the aegis of the current Code of Medical Ethics, 1988, why this issue still hangs over our heads ?

According to the jurist doctor, professor Genival Veloso de França, one of the great thinkers of the matter, one can no longer believe that Medical Ethics is still a corporatist instrument. Today, this code has gained space and freedom, affecting not only the doctor-patient-society relationship, but also political and social relations, which requires the doctor to take more realistic positions towards the current social life. In this sense, we can no longer imagine that that physician, in a paternalistic way, knew it all, wrote prescriptions, ordered compliance and demanded the result from the patient. Today the society questions every fact, every system and requires evidence that the conduct established will have the best result to their problems.

We increasingly hear and see reported in all the media that physicians would be willfully performing unnecessary operations, with prosthesis, orthotics and extremely costly equipment; cesarean section instead of vaginal delivery, vaginal delivery with mutilating episiotomy, for the sole purpose of financial gain. Does this happen because one does not follow the coded Medical Ethics? Does the financial interests outweigh those expected to disciples of Hippocrates?

At first glance, the two previous questions have affirmative answers, but is it the truth?

We have some problems to be solved and these begin with the demystifying of medicine itself. The medical art is not to cure, but to find possible answers backed by an investigative format. The doctor does not know what patients have, but imagines the various possibilities after a careful and methodical investigation, electing that hypothesis most likely to be the cause of the patient's problems. Nor can he/she be sure about the results that certain procedures or treatment will have on the patient-disease binomial. Various possibilities are tested and the result can be presented in a positive or negative way. Some doctors think they know everything and when the results did not benefit them, only then, they try to explain the reasons for failure. Similarly, some patients believe that the doctor has an obligation to precisely set diagnoses, drugs, procedures, especially at low cost and, when this does not happen, the responsibility rests solely with the doctor, with his greedy spirit, with the incompetence of the education system or with the controller system that does not meet its competences.

The correct and most complete information possible can settle this first conflict. To use the time to explain how to research, what is the need of certain laboratory tests and mainly explain mechanisms of action of many medications, as well as possible adverse results, does not mean a waste of time, but a doctor obligation, since the final decision will be, in most cases, in the hands of the patient. Also, to accept the demands of patients regarding results, expenses and equipment does not mean the better, easier, or more convenient alternative to the doctor. Sometimes they become the most painful, as they impose responsibilities that would not be part of the service contract and will certainly be required later.

We must not forget that medicine is an occupation and, in consequence, their professional need and are entitled to remuneration consistent with personal and family survival, with spending for medical training and also for continuing education. The form of compensation, as in any other professional activity, is expected to happen in a lawful manner, within the given social parameters.

The empathy in doctor-patient relationship, often questioned, because doctors would not have time or patience to achieve it, is not related to the qualification or to medical ethics itself, but with the human, social and individual quality.

Unfortunately, we are also a product of society we live in and in a world where advertising seems to be

the most important and easiest way to achieve social Olympus, its use in professional activity has proven increasingly deleterious to the professional image and, especially, due to its legal implications through the reversal of the liability of subjective to objective, characterizing certain acts as result ones.

And why not also remember the politics of our times? Society demands administrative responsibility of our politicians, requires lower costs and they now seek to respond to their inquisitors, finding masterful formulas to reduce costs, giving a stamp of irresponsibility to the doctor who does not fulfill his/her task without spending, forgetting the requirement of better use and especially the individual wills of citizens. So cesarean is expensive? It is not the best procedure. But can the patient require? If particular, no problem, but if public, the doctor failed in its Code of Ethics and thus the responsibility is no longer of the administrator, but of those who do not fulfill the imposed administrative rules.

Although ethics is a coding modifiable by society, I believe that there has been no recent changes or even a reduction in its weight on the day of the doctor and its compliance.

Still, we are repulsed by the Dantesque news of the not indicated implant prosthesis, operations and even consultations occurred in unfavorable conditions.

As Oscar Wilde said, "we call ethics the range of things that people do when everyone is watching. The range of things that people do when nobody is looking is called character ", that is, we will continue to find unscrupulous people, companies seeking profit above all, and governments interested in perpetuating the benefits of its participants.

We must fight on all fronts: to educate our children, to give them the moral values we want in our family environment, to require that medical schools are committed to reinforcing these values and to teach the ethical and professional concepts, to question measures that may denigrate the medical professional activity, and fundamentally to believe in the human being moral values.

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Original Article

Use of alcohol before and after bariatric surgery

Uso de bebida alcoólica em períodos pré e pós- operatório de cirurgia bariátrica

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A B S T R A C T

Objective: to assess alcohol intake in the bariatric surgery pre and postoperative periods. **Methods**: Patients were interviewed atSurgery Clinic of the Hospital das Clínicas da Universidade Federal de Pernambuco - HC/UFPE (Brazil) from July 2011 to March 2012. We analyzed socioeconomic, anthropometric and clinical variables. We used the Alcohol Use Disorders Identification Test (AUDIT C). **Results**: One hundred nineteen patients were enrolled (mean age: 41.23+11.30 years), with a predominance of the female gender (83.2%), non-Caucasian race (55%), married individuals or in a stable union (65.5%), with a high school education (40.3%)and active in the job market (37%). Weight and body mass index (BMI) were 128.77+25.28Kg and 49.09+9.26Kg/m^2,respectively in the preoperative period (class II obesity) and 87.19+19.16Kg and 33.04+6.21Kg/m^2, respectively in the postoperative period (class I obesity) ($p<0.001$). Hypertension was the most frequent disease in the pre (66.6%) and postoperative (36.5%) periods. The prevalence of alcohol use was 26.6% in the preoperative period, of which 2.2% of high risk, and 35.1% in the postoperative period, of which 1.4% of probable dependence; this difference did not achieve statistical significance ($p=0.337$). **Conclusion**: The prevalence of abusive alcohol intake and/or probable dependence was low in both the pre and postoperative periods, with little evidence of risky consumption among the patients submitted to bariatric surgery.

Key words: Obesity, Morbid. Bariatric Surgery. Alcoholic Beverage. Ethanol. Weight Loss.

INTRODUCTION

Obesity is a non-transmissible chronic disease characterized by excessive accumulation of body fat[1]. It is a multifactorial condition that involves genetic, behavioral, psychological, social, metabolic and endocrine components[2].

In its most severe form, it is called morbid obesity, where the body mass index (BMI) is above 40 kg/m^2 and it is a risk factor for developing type 2 diabetes mellitus, hypertension, congestive heart failure, dyslipidemia and atherosclerosis, arthropathies, hypoventilation, sleep apnea syndrome and other diseases that diminish patients' quality of life and self-esteem[2,3].

Nutritional counseling, the practice of regular physical activity and the use of anti-obesity drugs are the basis for weight loss. However, patients with morbid obesity are unable to maintain this weight loss and therefore do not reduce comorbidities. In this scenario, bariatric surgery has shown to be the best treatment with regard to weight loss and maintenance of long-term and comorbidities[4].

In recent years, some reports have hypothesized that individuals who underwent surgical treatment of obesity could be at increased risk for alcohol abuse after the operation. This could occur due to inability to continue past eating habits and consume large amounts of palatable foods, generating a search for reward in food like substances, such as alcohol[5-10]. Some authors also hypothesized to be a correlation between weight loss after the operation and the consumption of alcohol[5,7], but there is still no consensus in the literature.

Given the contradictory results and the lack of Brazilian studies on this subject, the objective of this study was to investigate the prevalence of alcohol consumption in bariatric surgery pre and postoperative periods and if there is difference in alcohol consumption between these periods.

METHODS

We conducted a prospective, case-series study involving 119 patients (45 preoperatively to 74 postoperatively), undergoing Roux en-Y gastric bypass at the surgical clinic of the HC/UFPE from July 2011 to March 2012. We included patients of both genders, aged over 20 years, and excluded those with severe psychiatric disorders, reoperation for complications of the previous procedure and those who underwent abdominoplasty.

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The research was conducted after approval by the Ethics in Research Committee of the UniversidadeFederal de Pernambuco, registry SISNEP FR 410 772, in obedience to the 196/96 Resolution of the National Health Council on "Research involving Human Subjects". Participation in the study was voluntary, after obtaining the consent of the patients by signing of a consent form.

Data collection was done through interviews and transcription of information from medical records. The socioeconomic variables studied were: city, age, gender, ethnicity, marital status, educational level and occupational status. The anthropometric assessment was carried from data on height and the higher weight achieved preoperatively, collected from medical records, to calculate the body mass index (BMI), classified according to the criteria of the American Society for Bariatric Surgery[11].

Wemeasured the preoperative weight and current weight in times d" 3 months, 3-6 months,6-12 months and 12-18 months postoperatively. The percentage of loss of excess weight was calculated using the equation:% loss of excess weight = (preoperative weight - current weight x100) / preoperative weight - ideal weight. The classification followed the criteria of Higa *et al.*[12], who consider appropriate the loss of 15% in three months, 35% at six months and 65% to 75% between 12 and 18 months after the procedure. The clinical data assessed were: diabetes mellitus, dyspnea, sleep apnea, dyslipidemia, gastroesophageal reflux, menstrual changes, endocrine disorders and hypertension. These were referred to by patients at the time of the interview.

For assessment of alcohol consumption, the interviewee was initially questioned whether he/she made use of alcohol and, in positive cases, the questionnaire AUDIT C[13] was applied; we further assessed the type of drink, how the patient used and its association with or without food.

We used the Pearson's Chi-square test or Fisher's exact test when the conditions for the Chi-square test were verified, and the Student t test, for independent samples.

RESULTS

Among the 119 patients studied, 79 (66.4%) were in the Metropolitan Region of Recife, with a mean age 41.23 + 11.30 years60 (50.4%) between 20 and 39 years. Females presented in greater proportion, 83.2% of patients, 55% non-white,65.5% were married or were in stable union,40.3% attended up to high school and 37% were in the active labor market. The weight in the preoperative period was 128.77 ± 25.28Kg and the BMI, 49.09 ± 9.26Kg/m^2, classified as class III obesity, and in the postoperative period, 87.19 ± 19.16Kg and BMI, 33.04 ± 6.21Kg/m^2, classified as class I obesity, with $p < 0.001$. Hypertension was the most common associated disease (Table 1).

We found that in the preoperative period 26.6% of patients consumed alcoholic beverages, and in the postoperative period, 35.1%. There was no statistical difference between groups, $p = 0.337$. The risk classification of alcohol use according to the AUDIT C showed that the majority of patients were at low risk, both before and after the bariatric procedure (Table 2).

The most widely used type of beverage before (91.6%) and after surgery (88.5%) was beer. Among the respondents, 91.6% of the preoperative group and 88.5% of the postoperative group consumed food during alcohol intake. The peanut was the most consumed food before surgery (91.6%) and the whole cheese, after (73.1%). A low percentage did not eat before drinking, and 16.6% in the preoperative period and 11.5% in the postoperative one. We have not found any significant result between drinking habits in the pre and postoperative periods and their association with the socioeconomic variables studies (Tables 3 and 4).

The percentage of excess weight loss in the times < 3 months, 3-6 months, 6-12 months and 12-18

Table 1 - Prevalence of diseases and clinical disorders pre and postoperatively.

Associated diseases, clinical disorders	Pre (N=45) N (%)	Post (N=74) N (%)
Hypertension	30 (66.6)	27 (36.5)
Dyspnoea	21 (46.6)	5 (6.8)
Menstrual Changes	16 (42.1)	8 (10.8)
GastroesophagealReflux	17 (37.7)	8 (10.8)
Sleep Apeia	13 (28.8)	1 (1.4)
Dyslipidemia	12 (26.6)	7 (9.5)
Diabetes Mellitus	11 (24.4)	3 (4.1)
Endocrine Diseases	2 (4.4)	5 (6.8)

Table 2 - Classification of AUDIT C in patients who drank alcohol.

Classification of AUDIT C	Pre (N=12)		Post (N=26)	
	N	(%)	N	(%)
Low Risk/Abstemious	9	75.0	17	65.4
Risk	2	16.7	8	30.8
Harmful/High Risk	1	8.3	-	-
Likely Dependence	-	-	1	3.8

months showed no association with alcohol consumption (Table 5).

DISCUSSION

In 2005, people drank up the equivalent of 6.1 liters of pure alcohol per person all over the world[13]. Brazil ranks fourth in alcohol consumption in the Americas, with an average of 18.5 liters of pure alcohol / year. According to the Ministry of Health[14], in 2011 16% of the Brazilian population used alcohol. Data in obese patients[9] suggest that less than 3% of patients may develop alcohol problems.

Among the socioeconomic variables, we saw a predominance of females, similar to the Brazilian studies of Prevedello*et al.*[2] and Barhouch*et al.*[3]. This is probably due to the greater concern of women with weight, health, in addition to the high prevalence of overweight in Brazilian patients, especially among those of less favorable conditions[15]. The average age and race

Table 3 - Association of the use of alcoholic beverages in the preoperative period with socioeconomic factors.

Variable	Habit of alcoholism						p value
	Yes		No		TOTAL		
	n	%	n	%	n	%	
Total Group	12	26.7	33	73.3	45	100.0	
·**Age group**							
Up to 39	9	34.6	17	65.4	26	100.0	$p^{(1)} = 0.458$
40 to 49	2	16.7	10	83.3	12	100.0	
50 or more	1	14.3	6	85.7	7	100.0	
·**Gender**							
Male	2	28.6	5	71.4	7	100.0	$p^{(1)} = 1.000$
Female	10	26.3	28	73.7	38	100.0	
·**Race**							
Caucasian	5	38.5	8	61.5	13	100.0	$p^{(1)} = 0.285$
Non-Caucasian	7	21.9	25	78.1	32	100.0	
·**Marital status**							
Single	1	33.3	2	66.7	3	100.0	$p^{(1)} = 1.000$
Married	11	26.2	31	73.8	42	100.0	
·**Schooling**							
Elementary school	5	25.0	15	75.0	20	100.0	$p^{(1)} = 0.817$
High school	4	23.5	13	76.5	17	100.0	
Higher education	3	37.5	5	62.5	8	100.0	
·**Occupation**							
Employee/Self-employed	6	37.5	10	62.5	16	100.0	$p^{(1)} = 0.339$
Unemployed	2	13.3	13	86.7	15	100.0	
Retired/Benefit	1	14.3	6	85.7	7	100.0	
Of home	3	42.9	4	57.1	7	100.0	
·**Origin**							
Recife/Surroundings	8	28.6	20	71.4	28	100.0	$p^{(1)} = 1.000$
Upstate	4	23.5	13	76.5	17	100.0	

(1) Fisher's exact Test.

Table 4 - Association of use of alcoholic beverages in the postoperative period with socioeconomic factors.

Variable	Habit of alcoholism						p value
	Yes		No		TOTAL		
	n	%	n	%	n	%	
Total Group	26	35.1	48	64.9	74	100.0	
·Age group							
Up to 39	15	44.1	19	55.9	34	100.0	$p^{(1)} = 0.288$
40 to 49	6	31.6	13	68.4	19	100.0	
50 or more	5	23.8	16	76.2	21	100.0	
·Gender							
Male	6	46.2	7	53.8	13	100.0	$p^{(2)} = 0.361$
Female	20	32.8	41	67.2	61	100.0	
·Race							
White	7	30.4	16	69.6	23	100.0	$p^{(1)} = 0.570$
White not	19	37.3	32	62.7	51	100.0	
·Marital status							
Single	10	26.3	28	73.7	38	100.0	$p^{(1)} = 0.103$
Married	16	44.4	20	55.6	36	100.0	
·Schooling							
Illiterate	2	40	3	60	5	100.0	$p^{(2)} = 0.902$
Elementary school	7	33.3	14	66.7	21	100.0	
High school	10	32.3	21	67.7	31	100.0	
Higher education	7	41.2	10	58.8	17	100.0	
·Occupation							
Employee/Self-employed	12	42.9	16	57.1	28	100.0	$p^{(2)} = 0.524$
Unemployed	7	30.4	16	69.6	23	100.0	
Retired/Benefit	3	21.4	11	78.6	14	100.0	
Of home	4	44.4	5	55.6	9	100.0	
·Origin							
Recife/ Surroundings	19	37.3	32	62.7	51	100.0	$p^{(2)} = 0.871$
Another State	4	30.8	9	69.2	13	100.0	
Upstate	3	30	7	70	10	100.0	

(1) Pearson Chi-square Test; (2) Fisher's exact Test.

differ from the findings of Costa *et al.*[16], who observed, in a group of patients in the pre and postoperative periods, an average age of 36.07 ± 10.16 years, with a predominance of Caucasians (86.53%). Herman *et al.*[17], detected a predominance of married individuals with professional activity in a bariatric population, data similar to ours. On the other hand, they reported a prevalent low level of education, differing from our results, since most of our patients had completed high school. The preoperative weight average found by Costa *et al.*[18] was 138 ± 28.8kg and BMI, 52 ± 8.6kg/m^2, while 12 months after surgery, these were 90 ± 19.5kg and 34 ± 6.6 kg/m^2,respectively, higher than our findings. Hypertension was the most common associated disease, corroborating other studies, where its prevalence was 21.97%[17] and 35.9%[19].

Ertelt*et al.*[9] observed a low preoperative alcohol consumption,7.1% of individuals having alcohol dependency and 1.4% abusing it, when assessed by the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV). In our work, with the AUDIT C we found that 2.2% of patients were high risk alcohol users preoperatively. In the postoperative period we obtained a percentage of 1.4%, with likely dependency. These are much lower results than the ones of Buffington[10], according to whom 84% of patients consumed alcohol after surgery. Data from the First Brazilian survey of alcohol consumption patterns in the Brazilian population[20] showed that the most consumed beverage in the country was beer (61%), confirming the pattern found in our patients. According to Wendling*et al.*[8], after surgery, compulsive individuals unable to consume excess food can replace it with alcohol. In our study group, there was no replacement, but the association, with food. When associated with fat or protein foods, there is significant reduction in alcohol absorption[21], this being a beneficial habit.

As for the use of alcohol and socioeconomic factors, it is evident that although there was no significant

Table 5 - Classification of the percentage of excess weight loss (% EWL) associated with the use of alcohol.

Classification of% EWL	Yes		No		Total Group		p value
	N	%	N	%	N	%	
< 3 months							
Suitable	19	100.0	30	93.8	49	96.1	p(1) = 0.523
Inappropriate	-	-	2	6.3	2	3.9	
TOTAL	19	100.0	32	100.0	51	100.0	
3-6 months							
Suitable	17	94.4	23	79.3	40	85.1	p(1) = 0.225
Inappropriate	1	5.6	6	20.7	7	14.9	
TOTAL	18	100.0	29	100.0	47	100.0	
6-12 months							
Suitable	2	20.0	8	42.1	10	34.5	p(1) = 0.414
Inappropriate	8	80.0	11	57.9	19	65.5	
TOTAL	10	100.0	19	100.0	29	100.0	
12-18 months							
Suitable	2	33.3	4	66.7	6	50.0	p(1) = 0.567
Inappropriate	4	66.7	2	33.3	6	50.0	
TOTAL	6	100.0	6	100.0	12	100.0	
End							
Suitable	11	57.9	17	53.1	28	54.9	p(2) = 0.741
Inappropriate	8	42.1	15	46.9	23	45.1	
TOTAL	19	100.0	32	100.0	51	100.0	

(1) Pearson Chi-square Test; (2) Fisher's exact Test.

association with drinking habits, those who drank were aged up to 39 years (44%), predominantly male, a fact common at this age in our region in non-operated in men. Higher percentages in this gender were seen in the Ministry of Health research[20], where 11% of men consumed alcohol very often and 28%, often.

There is evidence that the consumption of palatable foods produces in the brain effects similar to those produced after alcohol intake[22]. Substances such as sugar or fat cause an increase of endogenous opioids in the mesolimbic reward system and dopamine, although not as dramatically as alcohol and other drugs[23]. The use of alcohol is not predictive of proper weight loss[24]. The percentage ofexcess weight loss after surgery and its association with alcohol, similar to other studies[7,25], showed no positive nor negative association with weight loss.

In this sample of bariatric patients in pre and postoperative periods, there was alcohol use prevalence higher than that detected in the Brazilian population. However, we did not observehigh risk consumption / probable dependence, or consumption increase in the postoperative period.

R E S U M O

Objetivo: *avaliar a ingestão de bebidas alcoólicas nos períodos pré e pós-operatório de cirurgia bariátrica.* ***Métodos:*** *os pacientes foram entrevistados no ambulatório de Cirurgia Geral do Hospital das Clínicas/UFPE, no período de julho/2011 a março/2012. Foram analisadas variáveis socioeconômicas, antropométricas e clínicas. A avaliação do consumo de álcool nos últimos 12 meses, foi realizada pelo questionário AUDIT C (*alcohol use disorders identification test*). **Resultados:** foram estudados 119 pacientes com média de idade de 41,23+11,30 anos, com predominância do sexo feminino (83,2%), raça não branca (55%), casados ou em união estável (65,5%), com ensino médio (40.3%) e ativo ao mercado de trabalho (37%). O peso no período pré-operatório foi 128,77+25,28Kg e IMC 49,09+9,26Kg/m², classificado em obesidade classe III, e no pós-operatório foi 87,19+19,16Kg e IMC 33,04+6,21Kg/m², classificado em obesidade classe I, com p<0,001. A doença mais frequente no pré (66,6%) e pós operatório (36,5%) foi a hipertensão. No período pré-operatório 26,6% faziam uso de álcool, sendo 2,2% uso de alto risco e no pós-operatório 35,1%, sendo 1,4% provável dependência, não sendo encontrada diferença significativa entre os grupos de pré e pós-cirúrgico (p = 0,337).* ***Conclusão:*** *foi encontrada uma prevalência do uso alcoólico superior àquela detectada na população brasileira, no entanto não foi evidenciado consumo de alto risco/provável dependência, nem elevação deste consumo em período pós-operatório.*

Descritores: *Obesidade Mórbida. Cirurgia Bariátrica. Bebidas Alcoólicas. Etanol. Perda de Peso.*

REFERENCES

1. Fagundes ALN, Ribeiro DC, Naspitz L, Garbelini LEB, Vieira JKP, Silva AP, et al. Prevalência de sobrepeso e obesidade em escolares da região de Parelheiros do município de São Paulo. Rev paul pedriatr. 2008;26(3):212-7.
2. PrevedelloCF, Colpo E, Mayer ET, Copetti H. Análise do impacto da cirurgia bariátrica em uma população do centro do Estado do Rio Grande do Sul utilizando o método Baros. ArqGastroenterol. 2009;46(3):199-203.
3. Barhouch AS, Zardo M, Padoin AV, Colossi FG, Casagrande DS, Chatkin R, et al. Excess weight loss variation in late postoperative period of gastric bypass. ObesSurg. 2010;20(11):1479-83.
4. Schouten R, Wiryasaputra DC, van Dielen FM, van Gemert WG, Greve JW. Long-term results of bariatric restrictive procedures: a prospective study. Obes Surg. 2010;20(12):1617-26.
5. Heinberg LJ, Ashton K, Coughlin J. Alcohol and bariatric surgery: review and suggested recommendations for assessment and management. SurgObesRelat Dis. 2012;8(3):357-63.
6. Welch G, Wesolowski C, Zagarins S, Kuhn J, Romanelli J, Garb J, et al. Evaluation of clinical outcomes for gastric bypass surgery: results from a comprehensive follow-up study. Obes Surg. 2011;21(1):18-28.
7. Suzuki J, Haimovici F, Chang G. Alcohol use disorders after bariatric surgery. Obes Surg. 2012;22(2):201-7.
8. Wendling A, Wudyka A. Narcotic addiction following gastric bypass surgery—a case study. Obes Surg. 2011;21(5):680-3.
9. Ertelt TW, Mitchell JE, Lancaster K, Crosby RD, Steffen KJ, Marino JM. Alcohol abuse and dependence before and after bariatric surgery: a review of the literature and report of a new data set. SurgObesRelat Dis. 2008;5(4):647-50.
10. Buffington CK. Alcohol use and health risks: survey results. BT Online. 2007;4(2):21-3.
11. American Society of Bariatric Surgery. Rationale for surgery(1)1: 13 telas. Available from: URL: http://www.asbs.org.
12. Higa KD, Boone KB, Ho T, Davies OG. Laparoscopy Roux-en-Y gastric bypass for morbid obesity: technique and preliminary results of our first 400 patients. Arch Surg. 2000;135(9):1029-33; discussion 1033-4.
13. World Health Organization. Global status report on alcohol and health. Switzerland; 2011. p.286.
14. Ministério da Saúde. Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico (Vigitel); 2011.
15. Batista MCR, Franceschini SCC, Priore SE, Avaliação de indicadores antropométricos de adultos e idosos brasileiros. Nutrire Rev Soc Bras Aliment Nutr. 2002;23:67-78.
16. Costa ACC, Ivo ML, Cantero WB, Tognini JRF. Obesidade em pacientes candidatos à cirurgia bariátrica. Actapaulenferm. 2009;22(1):55-9.
17. Germano ACPL, Camelo CMBM, Batista FM, Carvalho NMA, Liberali R, Coutinho VF. Perfil nutricional dos pacientes submetidos à cirurgia bariátrica e dos critérios adotados para encaminhamento em um hospital de João Pessoa, PB. Ensaios e Ciência: CiênciasBiológicas, Agrárias e da Saúde. 2011;14(2):43-59.
18. Costa LD, Valezi AC, Matsuo T, Dichi I, Dichi JB. Repercussão da perda de peso sobre parâmetros nutricionais e metabólicos de pacientes obesos graves após um ano de gastroplastia em Y-de-Roux. Rev Col Bras Cir. 2010;37(2):96-101.
19. Anderi Júnior E, Araújo LGC, Fuhro FE, Godinho CA, Henriques AC. Experiência inicial do Serviço de Cirurgia Bariátrica da Faculdade de Medicina do ABC. ArqMed ABC. 2007;32(1):25-9.
20. Laranjeira R, Pinsky I, Zaleski M, Caetano R. I Levantamento nacional sobre os padrões de consumo de álcool na população brasileira. Brasília: Secretaria Nacional Antidrogas; 2007. p.76.
21. Maillot F, Farad S, Lamisse F. Alcohol and nutrition. Pathol Biol. 2001;49(9):683-8.
22. Del Parigi A, Chen K, Salbe AD, Reiman EM, Tataranni PA. Are we addicted to food?Obes Res. 2003;11(4):493-5.
23. Volkow ND, Wise RA. How can drug addiction help us understand obesity? Nat Neurosci. 2005;8(5):555-60.
24. Kopec-Schrader EM, Gertler R, Ramsey-Stewart G, Beumont PJ. Psychosocial outcome and long-term weight loss after gastric restrictive surgery for morbid obesity. Obes Surg. 1994;4(4):336-9.
25. Sears D, Fillmore G, Bui M, Rodriguez J. Evaluation of gastric bypass patients 1 year after surgery: changes in quality of life and obesity-related conditions. Obes Surg. 2008;18(12):1522-5.

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Assesment of the treatment of earlobe keloids with triamcinolone injections, surgical resection, and local pressure

Avaliação do tratamento de queloide do lóbulo da orelha com infiltração de triancinolona, retirada cirúrgica e compressão da cicatriz

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A B S T R A C T

Objective: To evaluate the combined treatment of ear lobe keloids. **Methods**: We studied 46 consecutive patients with 81 ear lobe keloids. Patients underwent local infiltration of triamcinolone acetonide (TCN) at concentrations of 40mg/ml (Group 1), 20 mg/ml (Group 2) and 10mg/ml (Group 3). The volume of TCN infiltrate varied according to the size of the lesion. Treatment consisted of three monthly injections before surgery, excision of keloid in the fourth month and perioperative infiltration, followed by two more leaks TCN within two months. Patients used earrings pressure on the scar after operation for four months. The pressure exerted by earrings in the ear lobe was measured electronically. Post-treatment follow-up of patients was 24 months. **Results**: TCN at concentrations of 20mg/ml and 40mg/ml were effective for the treatment of keloids, no difference between the groups (p = 0.58). However, patients in which TCN was infiltrated the 10mg/ml had poor involution of keloid and the study of this group was stopped. **Conclusion**: the combination of infiltration TCN month to 20 mg/mL (1.2mg to 2.0mg per mm^3 TCN injury), surgical excision and pressure application device is effective for treatment of keloid ear lobe.

Key words: Keloid. Triamcinolone Acetonide. Wound Healing. Surgical Procedures, Operative.

INTRODUCTION

The a wound repair process covers a wide spectrum of results, from the absence of healing to exuberant scarring. The mechanism of regulation of anomalous healing is not known; nor is the part or parts of the process in which lies the disorder that keeps the scar on inflammatory and proliferative phase. Keloids are scars that respond in an exaggerated way to a skin lesion, pushing the boundaries of the original wound and invading the normal skin, appearing about three months after trauma, and not regressing spontaneously, being a characteristic of humans. The main complaints are pain, itching of uncertain etiology and great aesthetic discomfort. The incidence of keloids in people with black skin ranges from 4.5% to 16%, approximately 15 times more than in whites. Its incidence is higher in between ten and 30 years of age[1], with no preference between genders.

Keloids are multifactorial, relating with physical, chemical, biological and endogenous agents. There seems to be a genetic predisposition, with exacerbated immune response related to emotional factors. Fibroblasts derived from keloids have an increased expression of the p63[2] gene, with increased response to the organic stimuli involved in wound healing. The beta transforming growth factor (TGF-β1) is also high in keloids[3].

Corticosteroid therapy is considered the best treatment for keloids[1,4]. Triamcinolone (TCN) in keloids has been used since 1965 due to its efficacy[6]. The mechanism by which intradermal TCN actson the injury is not fully elucidated. Its greatest effect is in the inflammatory and proliferativephase, interfering in local erythema and edema resulting from capillary dilation. There is evidence of its effect on the phagocytic activity of macrophages and modulation of the fibroblasts function in collagen synthesis.

The therapeutic objective depends on the patient'ssymptoms and aesthetic complaints caused by the keloid. Although the literature on the subject is wide, there is still no effectiveness-established treatment for keloid cure. This paper presents the authors' experience evaluating the combined approach consisted of application of TCN, surgical resection, and compression to treat earlobe keloids.

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METHODS

We studied 46 patients with 81 keloids, primary and recurrent, located in the earlobe. All keloids were caused by piercing injury for earring placement (Figure 1). Patients aged under 14 years and those with skin infections were not included.

This prospective study was approved by the Ethics Committee and Research, Department of Surgery, Faculty of Medicine and the Ethics Committee on Human Research (COEP) of UFMG, under number 133/07.

To determine the optimal dose of TCN in the treatment of keloids, the patients were divided into three groups to receive different drug concentrations: Group 1 (40mg/ml), consisting of 20 patients with 33 keloids; Group 2 (20mg/mL), consisting of 16 patients with28 keloids; and Group 3 (10mg/ml), formed by 10 patients with 20 keloids. The amount of TCN injected into the base of the lesion is proportional to the volume of the keloid. We injected 0.05ml to 0.1ml TCN per mm□ of keloid monthly for three months (Figure 2).

We recorded volumes of keloids (V) in cubic millimeters (mm□) in the preoperative phase with a digital caliper. The diameter and height of the lesions (D) were measured, and the volumetric calculation resulted from the following equation: average of diameter and height cubed, multiplied by the value of pi (3.14) and divided by six.

In the fourth month, the patients underwent excision of the keloid followed by TCN injection into the open area of the wound edges, using the same volume injected earlier. The wound was sutured with monofilament 5-0 nylon. All procedures were performed under local anesthesia with lidocaine injected into the keloid. After the suture, a pressureearring was applied (Figure 3A), coated with allergenic cotton knit on the scar (Figure 3B), and kept for four months, 18 hours a day.

The pressure exerted by the earrings, of 30mmHg, was measured in the Technological Centre Foundation - Physical Tests Sector, at the Universidade Federal de Minas Gerais, through the universal electromechanical testing machine.

To verify the effectiveness of the treatment, patients were followed for at least one year after the last dose of corticosteroids (Figure 4). To assess the best dose of TCN to be injected, we considered as therapeutic success no recurrence of the injury after removal and infiltration of corticosteroids. We compared the number of relapses in all three groups. We considered relapse when there was scar growth beyond the limits of the wound at the end of treatment, combined with complaints of itching and pain.

Two variables were considered together, as each indicates failure in the treatment of keloids. The statistical analysis took into account the patient's symptoms (pain and itching), and changes in the morphological characteristics of the lesion, such as stiffness and volume change, and the second variable took into account recurrence. We used the chi-square test with Fisher correctionfor statistical analysis.

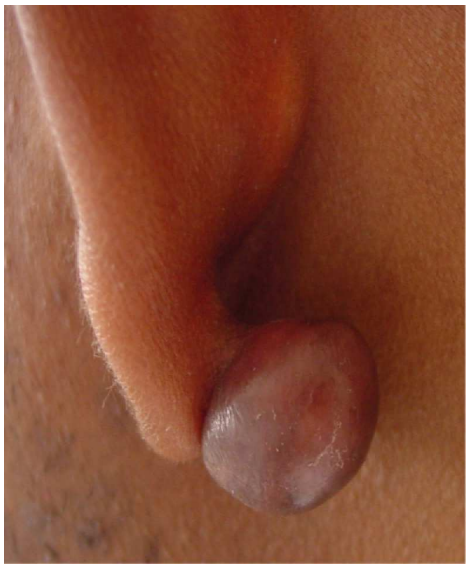

Figure 1 - *Earlobe keloid before treatment.*

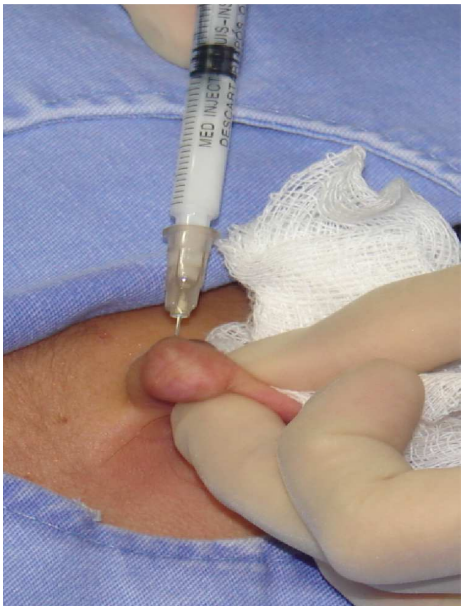

Figure 2 - *Perioperative infiltration followed by injury excision.*

RESULTS

In Group 1 (TCN to 40mg/ml) two of the 20 subjects (10%) experienced an anaphylactic reaction after the second infiltration. There was general malaise, lip swelling, flushing, dry cough, abdominal pain, symptoms that improved after intravenous administration of 1000 ml

Figure 3 - *Pressure earrings. A) Detail; B) on the spot, coated with hypoallergenic material, cotton knit.*

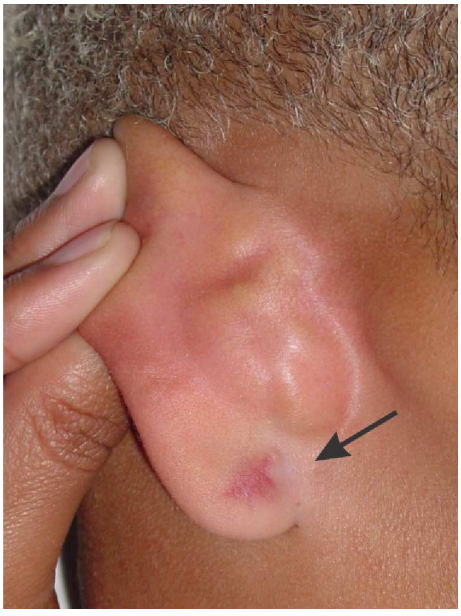

Figure 4 - *Aspect of the earlobe after treatment.*

of physiological saline. Only in this group there was a whitish deposit of TCN at the time of resection of the keloid, but with no clinical significance. There were two keloid recurrences in less than one year (6%).

In Group 2 (TCN 20 mg / ml), one patient (6.2%) had anaphylactic reactions to TCN after the third infiltration. There was wound infection in one patient, treated with cephalexin for ten days without modification of the therapeutic result, considered optimal. There was one recurrence of keloid in less than one year (4.5%).

In Group 3 (TCN to 10 mg / ml), three patients maintained itching complaint until the third dose and showed no injury improvement. In two other patients, there was lesion growth. These adverse events occurred in 50% of patients, rendering unacceptable the continuation of this TCN dose. Treatment was discontinued and all patients in this group resumed treatment as set for Group 2. These patients were not relocated in Group 2. Thus, the group 3 was not part of the final analysis and statistical work.

There was no difference in the evolution of the symptoms and scar appearance between the groups that received 20mg/ml and 40mg/ml. After the third infiltration, all patients were asymptomatic and their injuries did not progress. There was improvement in scar stiffness and size regression. There was no difference (p = 0.58) between the results obtained with patients undergoing infiltration of 40mg/ml and 20mg/mlTCN.

DISCUSSION

Even a thorough review of the literature does not allow precise analysis of the results proclaimed. Some causes of this difficulty are: lack of homogeneity description and characterization of anomalous scars; statistical methodology used; limited number of patients; insufficient follow-up; and different criteria used to define relapse.

Treatment of keloids is based on three types of potential medical intervention, and they act in the complex cascade of events leading to wound healing: manipulation of the intrinsic properties of wound synthesis process; correction of the balance between normal physiological and abnormal collagen synthesis, and in its regulatory humoral factors; modification of various immune and inflammatory responses that occur during the healing process. Therapeutic modalities include, in most cases: compression of the keloid, cryosurgery, application of silicone plates, operative excision followed or not by radiotherapy, isolated radiotherapy, laser application, and intralesional injection of corticosteroids.

Keloidcompression is based on collagenfragmentation and fibroblast degradation, the minimum effective pressure for this purpose being greater than 24mmHg, so as to exceed the capillary pressure[7]. We present a device developed by us, which was applied to the ear lobe, but of difficult usage in other parts of the body. Cryotherapy lends itself to treat minor injuries in leucodermas, by leading to keloid cold ischemia and possible volumetric reduction of the lesion[8]. This limitation has been overcome in part by applying plates of soft silicone, which improve the hydration of the lesion, eventual improvement in the color of the lesion and surrounding skin, and increased tolerance to keloidcompression[9]. Radiotherapy is used usually after surgical excision. The keloid is the benign lesion most often treated by radiotherapy[10], which was first used in 1906. The betatherapy is the most frequently used ionizing radiation mode[11]. However, it is known for its carcinogenic potential, contraindication in children, and it's side effects on scars and keloids, such as atrophy, hypopigmentation, and skin necrosis. The LASER (Light Amplification by Stimulated Emission of Radiation), has shown good results in the treatment of keloids. It acts by modulating the anomalous tissue growth, but the results

depend on the type of laser, exposure time and location of the keloid[12]. The isolated surgical removal entails risk of recurrence, ranging from 45% to 100% of the cases, and should never be used in monotherapy[13].

Among the intralesional corticosteroids, the preferred drug is triamcinolone (TCN). Although there are studies on general aspects and treatment of keloids, the best concentration and TCN dose for treatment has not yet been determined. The concentrations proposals in the literature range from 10mg/ml to 40mg/ml and the total dose, up to 120mg[5]. TCN is the only drug approved for keloid treatment by the Food and Drug Administration (FDA), USA. It's topical use, however, is ineffective to treat keloids.

The infiltration of TCN at the base of keloid is intended to act in the place of the mediators of the healing process and of the fibroblasts with greater replicative capacity. The retention of the drug in small volumes in the scar site reduces its systemic effects. In this study, the total dose infiltrated in keloids was lower than that found in the literature, and yet, therapeutic success was obtained in almost all patients.

Anaphylactic reactions using TCN are well documented. Corticosteroids are paradoxically responsible for anaphylactic type 1 reactions, mediated by IgE antibodies. The allergens may be the steroids themselves or the liquid used in the solution, usually carboxymethylcellulose[14] and succinate[15].

Compression of the keloid is an already establishedmethod to improve the quality of the scar[8]. Nevertheless, there is no publication on the pressure intensity that must be performed in the scar. In this study, we used the higher pressure bearable in all patients, without discomfort.

The development of stem cell research[16] has helped to elucidate the balance of formation and cellular remodeling activity. It is described that flags (cytokines), molecular alterations in receptor cytoplasmic membrane of fibroblasts and genetic mutations alter the healing process[17]. Growth factors are important in the modulation of various cellular activities[18]. New therapeutic strategies to enhance wound healing and promote the formation of healthy scars are currently being studied, using anti-TGF-â antibodies.

TCN infiltration at a concentration of 20mg / ml in combination with the scar removal and compression earring is effective and sufficient to treat earlobe keloids. The administration of lower doses of corticosteroids is insufficient, and higher doses are unnecessary to obtain good therapeutic results.

R E S U M O

Objetivo: *avaliar o tratamento combinado do queloide do lóbulo da orelha.* ***Métodos:*** *Foram estudados 46 pacientes consecutivos com 81 queloides de lóbulo da orelha. Os pacientes submeteram-se a infiltração local de triancinolona acetonida (TCN) nas concentrações de 40mg/ml (Grupo 1), 20mg/ml (Grupo 2) e 10mg/ml (Grupo 3). O volume de TCN infiltrado variou de acordo com o tamanho da lesão. O tratamento consistiu em três infiltrações mensais no pré-operatório, exérese do queloide no quarto mês e infiltração peroperatória, seguida de mais duas infiltrações de TCN nos dois meses seguintes. Os pacientes usaram brincos de pressão sobre a cicatriz após a operação durante quatro meses. A pressão exercida pelos brincos no lóbulo da orelha foi aferida eletronicamente. O seguimento pós-tratamento dos pacientes foi 24 meses.* ***Resultados****: A TCN nas concentrações de 20mg/ml e 40mg/ml foram eficazes para o tratamento do queloide, sem diferença entre si (p=0,58). No entanto, os pacientes nos quais a TCN foi infiltrada a 10mg/ml não tiveram involução satisfatória do queloide e o estudo desse grupo foi interrompido.* ***Conclusão:*** *A combinação de infiltração mensal de TCN a 20mg/ml (1,2mg a 2,0mg de TCN por mm³ de lesão), exérese cirúrgica e aplicação de dispositivo de pressão é eficaz para tratamento do queloide de lóbulo da orelha.*

Descritores*: Queloide. Triancinolona Acetonida. Cicatrização. Operação Cirúrgica.*

REFERENCES

1. Urioste SS, Arndt KA, Dover JS. Keloidalscars and hypertrophic scars: review and treatment strategies. SeminCutan Med Surg.1999;18(2):159-71.
2. De Felice B, Ciarmiello LF, Mondola P, Damiano S, Seru R, Argenziano C, et al. Differential p63 and p53 expression in human keloid fibroblast and hypertrophic scar fibroblasts. DNA Cell Biol.2007;26(8):541-7.
3. Bettinger DA, Yager DR, Diegelmann RF, Cohen IK. The effect of TGF-beta on keloid fibroblast proliferation and collagen synthesis. PlastReconstr Surg. 1996;98(5):827-33.
4. Ketchum LD, Robinson DW, Masters FW. Follow-up on treatment of hypertrophic scars and keloids with triamcinolone. PlastReconstr Surg.1971;48(3):256-9.
5. Griffith BH, Monroe CW, McKinney P.A follow-up study on the treatment of keloids with triamcinolone acetonide. PlastReconstr Surg.1970;46(2):145-50.
6. Babin RW, Ceilley RI. The freeze-injection method of hypertrophic scar and keloid reduction. Otolaryngol Head Neck Surg. 1979;87(6):911-4.
7. Sawada Y, Sone K.Hydration and occlusion treatment for hypertrophic scars and keloids. Br J Plast Surg.1992;45(8):599-603.

8. Shepherd JP, DawberRP.The response of keloid scars to cryosurgery. Plastic Reconstr Surg.1982;70(6):677-82.
9. Linares HA, LarsonDL, Willis-Galstaun BA. Historical notes on the use of pressure in the treatment of hypertrophic scars or keloids. Burns.1993;19(1):17-21.
10. Botwood N, Lewanski C, LowdellC. The risks of treating keloids with radiotherapy.Br J Radiol.1990;72(864):1222-4.
11. DarziMA,Chowdri NA, Kaul SK, Khan M. Evolution of various methods of treating keloids and hypertrophic scars: a 10-year follow-up study. Br J Plast Surg.1992;45(5):374-9.
12. Abergel RP, Meeker CA, Oikarinen H, Oikarinen AI, Uitto J. Retinoid modulation of connective tissue metabolism in keloid fibroblast cultures. Arch Dermatol.1985;121(5):632-5.
13. Shaffer JJ, TaylorSC, Cook-Bolden F. Keloidal scars: a review with a critical look at therapeutic options. J Am AcadDermatol.2002;46(2 Suppl Understanding):S63-97.
14. Cosman B, Wolff M. Correlation of keloid recurrence with completeness of local excision. A negative report. PlastReconstr Surg.1972;50(2):163-6.
15. Patterson DL, Yunginger JW, Dunn WF, Jones RT, Hunt LW. Anaphylaxis induced by carboxymethylcellulose component of injectable triamcinolone. Ann Allergy Asthma Immunol.1995;74(2):163-6.
16. TuanTL, NichterLS.The molecular basis of keloid and hypertrophic scar formation. Mol Med Today.1998;4(1):19-24.
17. Kim WJ. Cellular signaling in tissue regeneration. Yonsei Med J. 2000;41(6):692-703.
18. Lee TY, Chin GS, Kim WJ, Chau D, Gittes GK, Longaker MT. Expression of transforming growth factor beta 1, 2, and 3 proteins in keloids. Ann Plast Surg. 1999;43(2):179-84.

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Original Article

Submandibular gland excision

Ressecção da glândula submandibular

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A B S T R A C T

Objective: to analyze the value of fine needle aspiration and the rates of postoperative complications in patients undergoing resection of the submandibular gland. **Methods:** we analyzed the records of patients treated with resection of the gland from January 1995 to December 2008. The data collected included age, gender, findings on clinical history, surgical procedure, results of fine needle aspiration (FNA), pathological diagnosis and complications.**Results:** 117 patients were studied, aged 12-89 years (mean 48), 70 women and 47 men. Thirty-nine patients (33.3%) were affected by inflammatory diseases (28 patients with lithiasis), 70 had benign tumors, and malignant tumors, eight. Regarding FNA, the sensitivity and specificity were 85.7% and 100%, respectively. Nine patients (7.7%) had temporary paralysis of the marginal mandibular nerve and one had permanent paralysis. **Conclusion:** resection of the submandibular gland is a safe procedure, with low complication rates.

Key words: Submandibular gland. Submandibular gland diseases. Submandibular gland neoplasms. Sialadenitis. Salivary gland calculi.

INTRODUCTION

The submandibular gland is affected by various types of diseases, be them degenerative, inflammatory or neoplastic[1]. The most common clinical presentation is the edematous increase of the gland. The differentiation between a neoplastic disorder or not can be difficult[2]. Submandibular gland tumors account for about 3% of all tumors of the head and neck. Approximately 10% of tumors of the salivary glands are located in the submandibular gland, with a high rate of malignancy, though sialolithiasis and inflammatory diseases are also found[3]. The most found benign tumor is the pleomorphic adenoma. Total resection of the affected gland is the standard treatment proposed for all tumors.

The surgical transcervical lateral access is considered standard for approach the submandibular gland[4]. Although other open and endoscopic approaches have been proposed[5], the lateral transcervical remains the only one used in our Department.

The report of operative complications in the submandibular gland excision for benign lesions ranges from 0 to 14% for hematoma and infection. However, the need of reoperation is rarely reported[3,6,7]. Subjective complaints are also reported by some patients. Permanent damage to the marginal mandibular branch of the facial nerve accounts for 0 to 8%, the lingual nerve, 0 to 12%, and the hypoglossal, 0 to 1.4%[1,6-8].

The objective of this study is to analyze the value of fine needle aspiration and the rates of postoperative complications in patients undergoing resection of the submandibular gland.

METHODS

We reviewed the records of unselected cases of patients treated with resection of the submandibular gland in the Head and Neck Surgery Service at the Hospital Ana Costa and at the Irmandade da Santa Casa da Misericórdia de Santos, São Paulo – SP, Brazil, from January 1995 to December 2008. The data analyzed were age, gender, findings on clinical history, results of FNA, indication for surgery, surgical procedure, histological diagnosis and complications. Clinical examination was performed with bimanual palpation to differentiate between glandular tissue and lymph node.

The evaluated postoperative complications were hematoma, wound infection, salivary fistula and paralysis of the hypoglossal, marginal mandibular and lingual nerves. The physiological function of each involved nerve was clinically assessed before and after surgery by observing

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the movements of the facial muscles and the appearance, movement and tactile sensation of the tongue. We performed the postoperative evaluation at the time of skin suture removal, and if there were nerve changes, we carried out periodic reviews until complete resolution of paresthesia.

Ultrasonography was performed routinely as a complementary imaging study to clinical findings. The fine needle aspiration with frozen specimen was performed in patients with nodular disease of the submandibular gland to clarify the benign or malignant nature of the lesion, not being indicated for patients with stone disease and other inflammatory diseases. After resection, the submandibular gland was sent for pathological examination.

All patients were followed for a minimum of six months, with 12 months of mean follow-up for patients with benign diseases and 48 months in the case of malignancy. Patients with calculi palpable on the floor of the mouth, submitted to intraoral resection through the duct of Wharton, were not included.

RESULTS

We studied 117 patients aged 12-89 years (mean 48), 70 of them women and 47 men (1.49:1); 39 (33.3%) were affected by lithiasic inflammatory disease and 78 (66.6%) underwent resection of the gland due to benign or malignant neoplastic disease. The initial presentation of patients with neoplastic disease was the finding of an asymptomatic palpable mass, 70 patients having pleomorphic adenoma and eight, carcinoma.

Among the patients suffering from inflammatory diseases, 22 presented with a palpable asymptomatic mass, 17 complained of localized edema and pain. On physical examination, the glands had hardened. We found evidence of acute infectious processess in five cases. Ultrasonography revealed the presence of sialolithiasis in 28 patients. These findings were confirmed with the examination of the resected glands (Table 1); 59.8% of lesions analyzed were pleomorphic adenoma and 33.3%, sialoadenitis, with or without sialolithiasis. There was no bilateral glandular inflammation.

With respect to fine needle aspiration, the sensitivity and specificity for detecting malignancy was 87.5% and 100%, respectively (Table 2).

Patients with pleomorphic adenoma showed no local recurrence or disease during follow-up. One patient with carcinoma ex-adenoma underwent glandular resection and adjuvant radiotherapy with unilateral radical dissection, but died after four months of treatment due to pulmonary metastasis. The seven patients with carcinoma who underwent resection of the gland and unilateral supraomohyoid emptying were not referred to radiotherapy; none had recurrence. Patients with inflammatory diseases who underwent excision of the gland were asymptomatic in the postoperative period.

There was one case of hematoma, conducted with conservative therapy. Nine patients (7.7%) had neuropraxis of the marginal mandibular branch of the facial nerve and had good resolution in two to six months. The patient with carcinoma ex-adenoma had permanent paralysis (Table 3).

DISCUSSÃO

Each submandibular gland weighs around 10 to 15 grams and is divided anatomically into superficial and deep lobe by the posterior end of the mylohyoid muscle. The artery and facial vein, as well as the hypoglossal, lingual and marginal mandibular branch of the facial nerve, have close relationship with the gland. Damage to these structures can result in increased morbidity after operation. The submandibular gland secretes on average 71% of the daily produced saliva, consisting of serous and mucous component. Its secretion is crucial for lubricating and swallowing of the bolus, in addition to enzyme digestion, which starts in the upper digestive tract[1].

The submandibular gland is usually not noticed. When increased in size, however, it is bimanually palpable[1]. The first diagnostic evidence is a mass in the submandibular region. Inflammatory diseases often present with pain, fever, purulent secretion through the duct of Wharton and fast growth[9]. Usually the clinical differentiation between an inflammatory or neoplastic disease is not difficult. Although

Table 1 - Incidence of diseases of the submandibular gland (N = 117).

Disease	N	%
Non-neoplastic	39	33.3%
Chronic Inflammation	11	9.4%
Lithiasis	28	23.9%
Benign Neoplasias	70	59.8%
Pleomorphic Adenoma	70	59.8%
Malignant Neoplasias	8	6.8%
Mucoepidermoid Carcinoma	3	2.5%
Adenoid Cystic Carcinoma	3	2.5%
Carcinoma of acinar cells	1	0.85%
Carcinoma ex-adenoma	1	0.85%

Table 2 - Results of fine needle aspiration (FNA) of tumors of the submandibular gland (N = 78).

	Negative Histopathology	Positive Histopathology
Negative FNA	70	1
Positive FNA	0	7

Table 3 - Perioperative neural complications of submandibular gland resection.

Nerve	Damage	Inflammatory disease	Benign tumor	Malignant tumor
Hypoglossal	Paresis / paralysis	0	0	0
Lingual	Paresis / paralysis	0	0	0
Marginal Mandibular	Transient paresis	6	1	3
	Permanent paralysis	0	0	1

tumors or inflammatory processes produce increase of the gland with firm to hardened consistency, tumors tend to be more irregular, with lobed contours. In case of difficulty in the clinical diagnosis of the lesion, diagnostic resection of the gland should be performed[1].

The distribution of inflammatory and neoplastic lesions of the submandibular glands is different from the one of the parotid gland, in which the incidence of cancer is significant[4]. There is reported prevalence of neoplastic disease (66.6%) in contrast to other findings, with up to 76% of inflammatory affections[2]. The most common disease in this study was chronic inflammation in 109 of 185 patients, the incidence of reported tumor involvement being present in 14% of cases, with prevalence of malignant tumors[2]. In our sample, containing 117 patients, 39 (33.3%) were affected by lithiasic inflammatory disease and 78 (66.6%) by neoplastic disease, of which 70 had benign tumors and eight, malignancy.

Chronic inflammation and lithiasis have a higher incidence in diseases of the submandibular gland. Diagnosis can be made by plain radiography, ultrasound and sialography. Computed tomography and biopsy by fine needle aspiration should be reserved for cases of suspected neoplasia[10].

Defined as acute, subacute or chronic inflammation, sialodenitis results from of a variety of obstructive (calcullus duct obstruction) or not obstructive causes (systemic diseases, trauma and specific infective agents). In any case, the causal factor is unknown. Sialolithiasis is found in 24% of patients with sialodenitis. Compared with other salivary glands, the submandibular is more prone to calculus formation. Ninety percent of the salivary calculi have submandibular origin. Although still speculative, causal factors have been attributed to other reasons, whether physicochemical (high content of mucus, alkaline pH, high concentration of organic materials, calcium and phosphorus present in the submandibular saliva) or anatomical (duct with long and irregular course, small ductal drainage orifice and position)[1]. In the group studied, calculi were found in 28 of 39 patients with sialoadenitis (71.9%), probably due to preferred conservative therapy in patients with mildly symptomatic inflammatory diseases.

Most patients with neoplastic disease of the submandibular gland showed painless gland enlargement. The pain experienced by a small portion of patients with neoplastic disease may be due to rapid stretching of the capsule[1]. As in other studies[11,12], fine needle aspiration remains a valuable tool for the preoperative evaluation of patients with suspected malignancy. In this series, fine needle aspiration was performed in 78 patients with suspected cancer, with a sensitivity of 85.7% and specificity of 100%. Tumors have been reported involving the gland, with a high rate of adenoid cystic carcinoma[13].

The submandibular gland is closely related to the marginal mandibular branch of the facial nerve, lingual and hypoglossal nerves. These nerves do not pass through the gland, such as with the parotid. This means that small iatrogenic paralysis can occur due to dissection. In this series, the genial branch was affected in 8.5% of cases, only 0.85% permanently (one case of advanced carcinoma ex-adenoma). Hypoglossal or lingual nerve palsy has been observed by other authors[10].

In conclusion, the major diseases of the submandibular gland that justify surgical treatment are pleomorphic adenoma and sialodenitis with sialolithiasis. The excision of the submandibular glands has low morbidity, with few complications.

R E S U M O

Objetivo: *analisar o valor da punção aspirativa por agulha fina e os índices de complicações pós-operatórias em pacientes submetidos à ressecção da glândula submandibular.* ***Métodos:*** *foram analisados os prontuários de pacientes tratados com a ressecção da glândula, de janeiro de 1995 a dezembro de 2008. Os dados coletados foram: idade, sexo, achados na história clínica, procedimento cirúrgico, resultados da punção por aspiração com agulha fina (PAAF), diagnóstico anatomopatológico e complicações.* ***Resultados:*** *foram estudados 117 pacientes, com idade variando de 12 a 89 anos (média, 48 anos), sendo 70 mulheres e 47 homens. Trinta e nove pacientes (33,3%) foram acometidos por doenças inflamatórias (28 pacientes com litíase), 70 tiveram tumores benignos e oito tumores malignos. A respeito da PAAF, a sensibilidade e especificidade foram de 85,7% e 100%, respectivamente. Nove pacientes (7,7%) tiveram paralisia temporária do nervo mandibular marginal e um apresentou paralisia definitiva.* ***Conclusão:*** *a ressecção da glândula submandibular é um procedimento seguro, com baixa taxa de complicações.*

Descritores: *Glândula Submandibular. Doenças da Glândula Submandibular. Neoplasias da Glândula Submandibular. Sialadenite. Cálculos das glândulas salivares.*

REFERENCES

1. Goh YH, Sethi DS. Submandibular gland excision: a five-year review. J Laryngol Otol. 1998;112(3):269-73.
2. Gallina E, Gallo O, Boccuzzi S, Paradiso P. Analysis of 185 submandibular gland excisions. ActaOtorhinolaryngol Belg. 1990;44(1):7-10.
3. Preuss SF, Klussmann JP, Wittekindt C, Drebber U, Beutner D, Guntinas-Lichius O. Submandibular gland excision: 15 years of experience. J Oral Maxillofac Surg. 2007;65(5):953-7.
4. Springborg LK, Møller MN. Submandibular gland excision: long-term clinical outcome in 139 patients operated in a single institution. Eur Arch Otorhinolaryngol. 2013;270(4):1441-6.
5. Beahm DD, Peleaz L, Nuss DW, Schaitkin B, Sedlmayr JC, Rivera-Serrano CM, et al. Surgical approaches to the submandibular gland: a review of literature. Int J Surg. 2009;7(6):503-9.
6. Winkel R, Overgaard TI, Balle VH, Charabi S. Surgical results of submandibular gland excision. UgeskrLaeger. 2000;162(40):5354-7.
7. McGurk M, Makdissi J, Brown JE. Intra-oral removal of stones from the hilum of the submandibular gland: report of technique and morbidity. Int J Oral Maxillofac Surg. 2004;33(7):683-6.
8. Kukuckova B, Svec M. Surgical management of submandibulary gland diseases: ten years of experience. BratislLekListy. 2011;112(5):264-8.
9. Colella G, Garau V, Albanese G. Submandibular sialadenectomy. Our experience. Minerva Stomatol. 1991;40(12):821-3.
10. Lacosta JL, Zabaleta M, Sánchez Galán L. Surgical pathology of submandibular gland. Experience in La Rioja community. An Otorrinolaringollbero Am. 1998;25(6):577-88.
11. Shaha AR, Webber C, DiMaio T, Jaffe BM. Needle aspiration biopsy in salivary gland lesions. Am J Surg. 1990;160(4):373-6.
12. Jayaram G, Verma AK, Sood N, Khurana N. Fine needle aspiration cytology of salivary gland lesions. J Oral Pathol Med. 1994;23(6):256-61.
13. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. Head Neck Surg. 1986;8(3):177-84.

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Original Article

Temporary abdominal closure with zipper-mesh device for management of intra-abdominal sepsis

Fechamento abdominal temporário com dispositivo tela-zíper para tratamento da sepse intra-abdominal

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A B S T R A C T

Objective: to present our experience with scheduled reoperations in 15 patients with intra-abdominal sepsis. **Methods:** we have applied a more effective technique consisting of temporary abdominal closure with a nylon mesh sheet containing a zipper. We performed reoperations in the operating room under general anesthesia at an average interval of 84 hours. The revision consisted of debridement of necrotic material and vigorous lavage of the involved peritoneal area. The mean age of patients was 38.7 years (range, 15 to 72 years); 11 patients were male, and four were female. **Results:** forty percent of infections were due to necrotizing pancreatitis. Sixty percent were due to perforation of the intestinal viscus secondary to inflammation, vascular occlusion or trauma. We performed a total of 48 reoperations, an average of 3.2 surgeries per patient. The mesh-zipper device was left in place for an average of 13 days. An intestinal ostomy was present adjacent to the zipper in four patients and did not present a problem for patient management. Mortality was 26.6%. No fistulas resulted from this technique. When intra-abdominal disease was under control, the mesh-zipper device was removed, and the fascia was closed in all patients. In three patients, the wound was closed primarily, and in 12 it was allowed to close by secondary intent. Two patients developed hernia; one was incisional and one was in the drain incision. **Conclusion:** the planned reoperation for manual lavage and debridement of the abdomen through a nylon mesh-zipper combination was rapid, simple, and well-tolerated. It permitted effective management of severe septic peritonitis, easy wound care and primary closure of the abdominal wall.

Key words: Abdominal Abscess. Abdominal Wall/surgery. Peritonitis. Sepsis/complications

INTRODUCTION

Despite significant technological progress in surgery, the treatment of intra-abdominal sepsis (IAS) remains challenging. IAS can be classified into complicated and uncomplicated cases. Complicated IAS occurs when infection spreads from the primary affected viscus to the peritoneal cavity and triggers a systemic inflammatory response, which is associated with a mortality of up to 30-35%[1]. An early and efficient source of control combined with effective antibiotic therapy and modern intensive care and sepsis treatment is definitive for the outcome and prog-nosis of secondary peritonitis[1,2]. Surgery may have disappointing results when sepsis becomes clinically manifest through signs of multiple organ failure. Severe abdominal sepsis carries unacceptable mortality in surgical patients due to persisting intra-abdominal sepsis, recurrent sepsis, wound necrosis and dehiscence[2]. Several surgical strategies have been developed to reduce mortality caused by intra-abdominal sepsis. A prospective randomized controlled study of radical peritoneal debridement and standard surgical management did not confirm the value of the peritoneal radical debridement[3]. Postoperative peritoneal lavage requires close surveillance of the fluid and electrolyte balance, and there is also a tendency for fistulas to develop at the drain sites[4]. Leaving the abdominal incision completely open allows for complete drainage of the purulent exudation from the peritoneal cavity and has markedly reduced mortality[5]. Leaving the abdomen open without creating a temporary closure does not reduce intraperitoneal abscess, and nursing care becomes difficult in the postoperative period, as there may be loss of fluids, electrolytes, and heat and the development of enteric fistulas; for these reasons, this method has been abandoned[6]. Performing scheduled laparotomies every three to four days until the peritoneal cavity is clean is an attractive treatment approach, though this method suffers the disadvantages of frequent evisceration, requirement for respirators, and severe patient discomfort[5,7-10].

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However, there are two current indications for having an open abdomen in cases of complicated IAS. The first corresponds to cases with no possibility of closing the abdomen due to edema of the abdominal viscera, and the second occurs when the complete eradication of the infectious focus is not possible[11-14]. There are several techniques that can be used to assist in temporary abdominal closure when scheduled reoperation is chosen for the treatment of cases of complicated IAS. Surgical treatment based on a zipper-mesh combination that provides access to the abdominal cavity can be used as an alternative method to improve mortality rates in patients with severe intra-abdominal sepsis[15,16].

This study describes the experience in 15 patients and also provides a literature review regarding the in-hospital mortality and morbidity of temporary abdominal closure with the zipper-mesh device.

METHODS

The authors reviewed the records of 15 patients who underwent planned relaparotomy for complicated IAS between 1985 and 1990 and included only those who used the zipper-mesh device for temporary closure of the abdomen. Six cases of IAS were caused by pancreatitis, three were caused by large bowel perforation, three were caused by postoperative anastomotic leakage and there was one case each caused by appendicitis, rectal perforation, and mesenteric thrombosis. All cases were treated at the Hospital das Clínicas, Universidade de São Paulo.

All patients who underwent scheduled relaparotomy for complicated IAS and also had a zipper-mesh device for abdominal access were included in the study. However, patients who died after the placement of the zipper-mesh device and prior to relaparotomy were excluded.

At the time of surgery, the presenting problem was addressed using standard surgical techniques. Six patients underwent debridement of necrotic tissues; for the repair of intestinal perforations, three patients underwent repair by excision with anastomosis and four underwent repair with ostomy; and two patients had a distal pancreatectomy with splenectomy.

The authors used a 25-centimeter (cm) nylon zipper with jagged ribbons that can be separated completely. The mesh was built with nylon line measuring 0.2286 millimeters (mm) in diameter with a pore size of 0.6180mm. A ribbon zipper without a cursor was tailored to four centimeters from the edge of the rectangular patch of mesh, which was sized 30 x 8 cm. The other tape was stitched with the cursor at the edge of a rectangular screen that was sized 30 x 5 cm (Figure 1). Thus, one side of the mesh passed over the jagged edges to protect the intestinal loops during movement of the cursor to the zipper (Figure 2).

The mesh was trimmed to fit the wound circumferentially and may have been secured to the abdominal wall fascia with a running nylon suture. Sterile gauze was placed over the mesh, and the patient was transferred to the surgical intensive care unit. Planned relaparotomies were performed every 48-120 hours (mean time 84 hours) for repeated lavage and debridement. Early on, a concerted effort was made to lyse all adhesions that formed between episodes of lavage and to debride any tissue that had become necrotic. At the end of the lavage, the mesh was re-zipped, and sterile gauze was replaced over the mesh. Planned relaparotomies were discontinued when the abdomen was judged to be clean and when the infection had subsided. All surgical manipulations were performed in the operating room.

On the day of the first surgery, the APACHE II score was calculated for each patient[17]. All patients were treated with broad-spectrum antibiotics, and microbiologic specimens were taken for aerobic and anaerobic cultures.

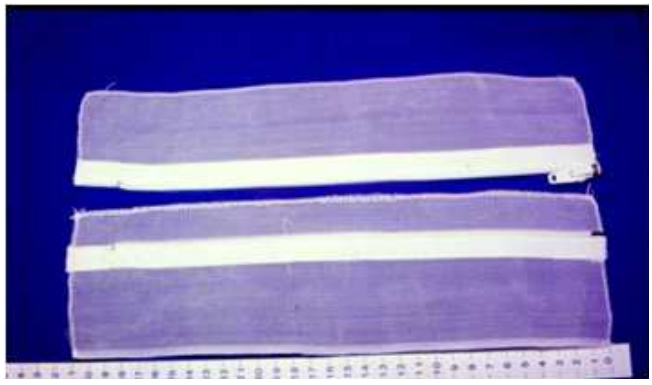

Figure 1 - *Device constructed with nylon mesh-zipper. Note that the device consists of two separate, independent segments.*

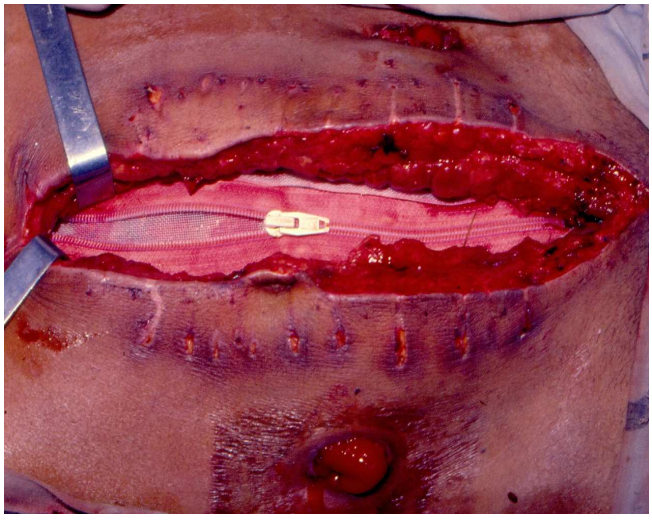

Figure 2 - *One side of the mesh passes over the jagged edges to protect the intestinal loops during movement of the cursor to the zipper.*

A review of the literature was performed to identify all reports of temporary abdominal closure techniques with a mesh-zipper device between January 1936 and December 2010 that mentioned the indication for the open abdomen, the closure rate, and the mortality and morbidity. The Medline database was searched using the following keywords: open abdomen; laparostomy; mesh; zipper; temporary abdominal closure; fascial. Only studies published in English were included in this review. Reports of temporary abdominal wall closure that used a zipper sewn directly into the fascia were excluded.

RESULTS

The patients consisted of 11 men and four women, with a mean age of 35 years (range 15-72). The patients remained in the hospital for an average of 29.9 days (nine to 61 days). The APACHE II score ranged from three to 24 and had a mean of 13.3 (Table 1). The pathogens detected from the infection of the abdominal cavity were gram-positive and gram-negative bacteria, as well as anaerobes. The number of bacterial species isolated for each patient ranged from one to eight. The most common bacteria isolated were *S. aureus (*46.6% of patients), *E. coli* (46.6% of patients) and *P. mirabilis, P. aeruginosa, S. faecalis* (33.3% of patients).

The number of relaparotomies ranged from two to seven (mean 3.2). The mean use duration of the zipper-mesh device was 13 days (ranged from six to 27 days). One patient experienced displacement of the mesh and required re-exploration. Another patient suffered from acute myocardial infarct and died before the mesh could be removed. One patient had the mesh replaced four times to reduce the retraction of the fascial edges. Finally, one patient who had undergone cholecystectomy developed a biliary fistula. The fistula was naturally exteriorized through the skin wound and closed spontaneously. The abdominal wall was closed primarily with running absorbable stitches. The skin was closed in three patients.

Four patients (2.6%) died within 30 days of the first surgery. The first patient had upper intestinal bleeding 23 days after the resolution of the intra-abdominal infection. The second had an acute myocardial infection. The third had pneumonia, and the fourth had endocarditis.

At the end of treatment, all patients underwent closure of the abdominal wall (Figure 3). None of the patients developed intestinal fistulas or abscesses following treatment, and none died directly from treatment. Two patients developed incisional hernia, and they successfully underwent surgery. Four patients had surgery to close the ostomies. One patient died two days after the intestinal closure due to intra-abdominal hemorrhage.

After the literature review, 12 articles were selected[16,18-28] (Table 2).

DISCUSSION

Persistent or recurrent intra-abdominal sepsis continues to have high mortality rates in patients with complicated IAS[13,15]. The most frequent cause of death in these patients is the persistence of septic foci or incomplete drainage of these foci, which leads to the development or worsening of established multiple organ failures[13-15].

Table 1 - Patient data.

Case	Age/ Gender	Indication	APACHE-II	Number of abdominal operations	Days of mesh-zipper use	Length of hospital stay (days)	Outcome
1	28 / F	Fecal peritonitis	14	3	14	24	Alive
2	15 / F	Fecal peritonitis	14	3	11	27	Alive
3	36 / M	Fecal peritonitis	24	3	12	32	Died
4	23 / M	Necrotizing pancreatitis	20	4	12	44	Alive
5	72 / M	Fecal peritonitis	16	2	8	9	Died
6	75 / F	Fecal peritonitis	12	3	8	21	Alive
7	49 / M	Necrotizing pancreatitis	15	3	8	9	Died
8	28 / M	Necrotizing pancreatitis	6	2	6	25	Alive
9	40 / M	Fecal peritonitis	7	5	26	44	Alive
10	28 / M	Necrotizing pancreatitis	7	3	12	30	Alive
11	20 / M	Fecal peritonitis	20	4	26	61	Alive
12	50 / M	Fecal peritonitis	3	2	7	17	Alive
13	33 / F	Necrotizing pancreatitis	11	7	27	55	Alive
14	26 / M	Fecal peritonitis	10	2	7	20	Alive
15	58 / M	Necrotizing pancreatitis	21	2	11	27	Died

The principles of prevention and treatment of persistent or recurrent intra-abdominal sepsis include debridement of dead tissue, drainage of septic foci and prevention of reaccumulation[9,15,16]. Initial radical debridement has not been reproduced with good results[3], and multiple operations are frequently required.

Considering that diffuse secondary peritonitis constitutes a major abscess that can be treated by broad drainage, an open abdomen technique has been suggested by some authors. However, the open abdomen is not recommended due to high rates of complications and difficulty in the management of patients. The temporary closure of the abdomen facilitates patient care, allows access to the abdominal cavity for relaparotomy and ultimately allows for permanent closure of the abdomen[5,9-11].

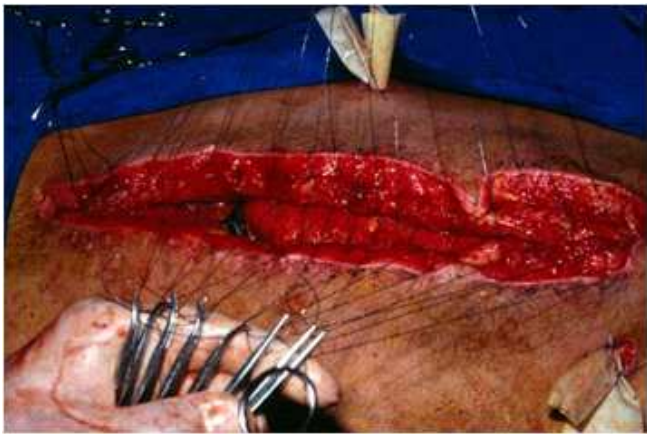

Figure 3 - *Primary closure of the abdominal wall.*

While the use of an open mesh abdomen technique alone decreases the problems associated with evisceration and ventilation, it is insufficient to prevent the reaccumulation of septic foci in the intestinal loop areas and deeper recesses of the abdomen. This issue can be resolved by the adoption of daily manual exploration and lavage of the abdominal cavity through a zipper inserted in a marlex mesh abdominal closure[16].

In 1936, the first reference to a zipper in the abdominal wall was described in the treatment of inoperable carcinoma of the stomach by direct electrical coagulation. The physician performed a gastrostomy by suturing the gastric wall to the skin to facilitate access to the gastric injury. Due to leakage of gastric juice and to prevent dermatitis and facilitate access to the tumor, the stomach was occluded by a zipper sewed onto the skin[29].

The use of a zipper in the abdominal wall was forgotten until 1982, when Leguit described a fast and secure method for abdominal reoperation using a conventional nylon zipper in two patients with intestinal vascular disease. A conventional 10-cm zipper was stitched onto the surface of a marlex mesh with a running suture and sterilized with ethylene oxide. A small longitudinal slit was made in the marlex mesh, just outside the midline of the zipper, to allow entry to the abdomen in a trapdoor-like fashion and to avoid damage to the bowel by the zipper[18]. The zipper could be sutured to the edges of the transverse incision, as done by Stone in 1985, for drainage of pancreatic abscesses. Access to the abdominal cavity is easy via the zipper and can prevent evisceration[30]. For more sufficient prevention of IAH, a zipper has been combined with mesh for temporary abdominal closure in cases of complicated IAS

Table 2 - Complications observed.

Author – Year [Ref]	Number patients	Indication	Average days with zipper	Average reoperations per patient	Intestinal fistula %	Intra-abdominal abscess %	Primary abdominal closure %	Mortality %
Hedderich, 1986[16]	10	Peritonitis	11	Daily in ICU**	20	40	0	20
Leguit, 1982[18]	2	SMAO*	6	2	0	0	100	0
Garcia-Sabrido, 1988[19]	15	Pancreatitis	-	Daily in ICU	0	0	0	26.6
Walsh, 1988[20]	34	Peritonitis	18.4	Daily in ICU	-	-	-	35
Bose, 1991[21]	5	Peritonitis	-	-	-	1	-	60
Cuesta, 1991[22]	24	Pancreatitis and Peritonitis	-	6,8	12.5	-	25	25
Hakkiluoto, 1992[23]	21	Peritonitis	-	Daily in ICU	0	0	10	52.3
Singh, 1993[24]	2	Peritonitis	-	-	0	0	-	50
Ercan, 1993[25]	14	Peritonitis	-	-	-	-	-	28.5
Hubens, 1994[26]	23	Peritonitis	-	-	-	-	35	39
Roeyen, 1996[27]	7	Peritonitis	-	1.9	0	0	100	0
Mimatsu, 2006[28]	5	SMAO	4.4	Daily in ICU	0	-	40	0
This series	15	Pancreatitis and Peritonitis	13	3.2	0	6.6	100	26.6

Ref = reference
**SMAO = superior mesenteric arterial occlusion*
***ICU = intensive care unit*

due to intestinal perforation or anastomosis dehiscence; this approach was proposed by Hedderich *et al.*[16] in the USA and by Teichmann *et al.*, in Germany[31]. Although this device allows easy access to the abdominal cavity, mandatory exploration prior to wound closure or healing appears disadvantageous[32].

The indications for zip closure treatment remain debatable. The mortality varies between 7% and 67%, which likely results from varying methods of patient selection[10,16,20,31]. Van Goor *et al.*[10] defined the indication for zip closure as diffuse suppurative peritonitis caused by colonic perforation or anastomotic dehiscence in which the abdominal cavity remains grossly contaminated after the initial laparotomy. Garcia-Sabrido *et al.*[19] recommend zipper laparotomy when there is uncertain control or incomplete drainage of septic foci, when a compromised anastomosis must be observed, or when bowel viability is uncertain in cases of mesenteric ischemia. According to Walsh *et al.*[20], it is likely that the approach was used too early in some patients and too late in others. The author limited the use of the open abdomen technique to a defined subgroup of patients with diffuse, non-localizing peritonitis. These patients usually had one re-exploration or necrotizing pancreatitis accompanied by infection, and patients with discrete abscesses or regional peritonitis were excluded[20]. We advocate this criterion in our study.

In a series of 10 cases, Hedderich *et al.*[16] reported a survival rate of 80%. Among patients undergoing the zipper technique, none developed fistulas. The daily explorations were well tolerated by patients with only mild doses of anesthetics. Despite daily laparotomy, paralytic ileus was not a problem. However, all patients developed abdominal wall hernias. Another series[8] of eight patients reported no deaths. All patients had the abdomen closed without a fascia defect, and none developed an incisional hernia. According to the author, stomas pose no special problems, and the design of the fastener is such that loops of bowel cannot become trapped in its closure mechanism. The mortality rate of 26.6% observed in this series was similar to that expected in patients with APACHE II scores of 13. A Spanish study[19] of 15 patients with severe intra-abdominal sepsis and APACHE II scores of greater than 15, among whom the mean APACHE II score was 25, reported a mortality rate of 26.5% as opposed to the 45% mortality expected by Knaus *et al.*[17]. A Dutch study[9] of 24 consecutive patients reported effective control of intra-abdominal infection, as a residual abscess was found in only one patient. Moreover, cultures from the abdominal cavities of 21 patients grew less than 10^3 cfu/ml in 62%, 76%, and 95% of patients after two, three, and four relaparotomies, respectively. In this series, no patient developed intra-peritoneal abscess or intestinal fistula during reoperation or after permanent closure of the abdominal wall. However, bowel perforation and fistulas were common complications, and we encountered these particularly after more than four relaparotomies, which suggests that multiple planned relaparotomies have risks.

All papers on temporary abdominal closure techniques with a mesh-zipper device that mentioned the indication for the open abdomen, the closure rate, and the mortality and morbidity were reviewed (Table 2). The search identified 29 articles describing the mesh-zipper device. After reading the abstracts, the authors excluded 17 articles because they did not meet the inclusion criteria. There were no randomized controlled trials or other comparative studies. The 12 included articles described case series with 162 patients[16,18-28]. In this series, the mesh-zipper device stayed in place for 13 days. The average number of surgeries per patient was 3.2. No patients developed intestinal fistula, but 6.6% of patients developed intra-abdominal abscess. Definitive closure of the abdomen was possible in 100% of patients, and mortality was 26.6%. Among papers from the literature review, the mesh-zipper device remained in place for an average of ten days (range 4.4 to 18.4), and patients underwent an average of seven reoperations (ranging from 1.9 to 18). The incidence of intestinal fistula was 16%, and 20% developed intra-abdominal abscess. Primary wound closure occurred in an average of 52% of patients (ranging from 0 to 100%), and the average mortality was 28% (ranging from 0 to 60%). These results differed from our series with regards to the incidence of intra-abdominal abscess, intestinal fistula and definitive closure of the abdominal wall. The low incidence of intra-abdominal abscess is likely because the reoperations were performed in the operating room, which allowed for rapid control of an infectious focus that is not possible at the bedside. The reoperations were performed at shorter intervals, and the gradual approximation of the incision edges explains the absence of intestinal fistula and the achievement of permanent closure in 100% of our patients.

Temporary abdominal closure with the mesh-zipper device allowed easy access to the abdominal cavity, and the planned reoperation was effective in cleaning the peritoneal surface and prevented the formation of residual abscesses. There were no deaths due to intra-abdominal sepsis in our series. All patients had primary closure of the abdominal wall. There were no intestinal fistulas. Planned relaparotomies using the zip mesh closure are not always harmless. The patients must be properly selected, and the closure device must be used at the correct time. These two issues remain unclear in the literature.

The zipper-mesh device is a good alternative for temporary abdominal closure in patients with severe intra-abdominal sepsis.

R E S U M O

Objetivo: *apresentar nossa experiência com reoperações agendadas em 15 pacientes com sepse intra-abdominal.* ***Métodos:*** *foi empregada uma técnica mais eficaz que consiste em fechamento abdominal temporário com uma folha de malha de nylon contendo um zíper. Realizamos as reoperações no centro cirúrgico, sob anestesia geral, com um intervalo médio de 84 horas. A revisão consistiu de desbridamento de material necrosado e lavagem vigorosa da área peritoneal envolvida. A média de idade dos pacientes foi 38,7 anos; 11 pacientes eram do sexo masculino e quatro do sexo feminino.* ***Resultados:*** *Quarenta por cento das infecções foram devido à pancreatite necrosante. Sessenta por cento foram ocasionadas por perfuração intestinal secundária à inflamação, oclusão vascular ou trauma. Foram realizadas 48 reoperações, média de 3,2 operações por paciente. O dispositivo tela-zíper foi deixado no local por uma média de 13 dias. Um estoma intestinal estava presente ao lado do zíper em quatro pacientes e não ocasionou complicação para o paciente. A mortalidade foi 26,6%. Nenhuma fístula resultou dessa técnica. Quando a doença intra-abdominal estava sob controle, o dispositivo de fecho do tipo de rede foi removido, e a fáscia foi fechada em todos os pacientes. Em três pacientes, a ferida foi fechada primariamente, em 12 permitiu-se fechar por intenção secundária. Dois pacientes desenvolveram hérnia: uma incisional e outra na incisão de drenagem.* ***Conclusão:*** *A nova operação prevista para lavagem manual e desbridamento do abdômen através de uma combinação de tela-zíper em nylon foi rápida, simples e bem tolerada, permitindo uma gestão eficaz da peritonite séptica grave, fácil tratamento das feridas e fechamento primário da parede abdominal.*

Descritores: *Abscesso Intra-Abdominal. Parede Abdominal/cirurgia. Peritonite. Sepse/complicações.*

REFERENCES

1. Loganathan A, Gunn J. The surgical treatment of intra-abdominal sepsis. Surgery. 2012;30(12):662-6.
2. Strobel O, Werner J, Büchler MW. Surgical therapy of peritonitis. Chirurg. 2011;82(3):242-8.
3. Polk HC Jr, Fry DE. Radical peritoneal debridement for established peritonitis. The results of a prospective randomized clinical trial. Ann Surg. 1980;192 (3):350-5.
4. Stephen M, Loewenthal J. Continuing peritoneal lavages in high-risk peritonitis. Surgery. 1979;85(6):603-6.
5. Steinberg D. On leaving the peritoneal cavity open in acute generalized suppurative peritonitis. Am J Surg. 1979;137(2):216-20.
6. Schein M, Saadia R, Decker GG. The open management of the septic abdomen. Surg Gynecol Obstet. 1986;163(6):587-92.
7. Charleux H, Mongredien P, Anfroy JP, Normand P, Fichelle A. Non-closure of the abdominal wall in the surgery of peritonitis. Chirurgie. 1980;106(1):63-5.
8. Hannon RJ, Hood JM, Curry RC. Temporary abdominal closure: a new product. Br J Surg. 1992;79(8):820-1.
9. Wittmann DH, Aprahamian C, Bergstein JM. Etappenlavage: advanced diffuse peritonitis managed by planned multiple laparotomies utilizing zippers, slide fastener, and Velcro analogue for temporary abdominal closure. World J Surg. 1990;14(2):218-26.
10. van Goor H, Hulsebos RG, Bleichrodt RP. Complications of plannedre laparotomy in patients with severe general peritonitis.Eur J Surg. 1997;163(1):61-6.
11. Open Abdomen Advisory Panel, Campbell A, Chang M, Fabian T, Franz M, Kaplan M, et al. Management of the open abdomen: from initial operation to definitive closure. Am Surg. 2009;75(11 Suppl):S1-22.
12. Leppäniemi AK. Laparostomy: why and when? Crit Care. 2010;14(2):216.
13. Robledo FA, Luque-de-León E, Suárez R, Sánches P, de-la-Fuente M, Vargas A, et al. Open versus closed management of the abdomen in the surgical treatment of severe secondary peritonitis: a randomized clinical trial. Surg Infect. 2007;8(1):63-72.
14. Waibel BH, Rotondo MF. Damage control for intra-abdominal sepsis. Surg Clin North Am. 2012;92(2):243-57, viii.
15. Ordoñez CA, PuyanaJC. Management of peritonitis in the critically ill patient. Surg Clin North Am. 2006;86(6):1323-49.
16. Hedderich GS, Wexler MJ, McLean AP, Meakins JL. The septic abdomen: open management with Marlex mesh with a zipper. Surgery. 1986;99(4):399-408.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.
18. Leguit P Jr. Zip-closure of the abdomen. NethJ Surg. 1982;34(1):40-1.
19. Garcia-Sabrido JL, Tallado JM, Christou NV, Polo JR, Valdecantos E. Treatment of severe intra-abdominal sepsis and/or necrotic foci by an 'open-abdomen' approach. Zipper and zipper-mesh techniques. Arch Surg. 1988;123(2):152-6.
20. Walsh GL, Chiasson P, Hedderich G, Wexler MJ, Meakins JL. The open abdomen. The Marlex mesh and zipper technique: a method of managing intraperitoneal infection. Surg Clin North Am. 1988;68(1):25-40.
21. Bose SM, Kalra M, Sandhu NP. Open management of septic abdomen by Marlex mesh zipper. Aust N Z J Surg. 1991;61(5):385-8.
22. Cuesta MA, Doblas M, Castañeda L, Bengoechea E. Sequential abdominal reexploration with the zipper technique. World J Surg. 1991;15(1):74-80.
23. Hakkiluoto A, Hannukainen J. Open management with mesh and zipper of patients with intra-abdominal abscesses or diffuse peritonitis. Eur J Surg. 1992;158(8):403-5.
24. Singh K, Chhina RS. Role of zipper in the management of abdominal sepsis. Indian J Gastroenterol. 1993;12(1):1-4.
25. Ercan F, Korkmaz A, Aras N. The zipper-mesh method for treating delayed generalized peritonitis. Surg Today. 1993;23(3):205-14.
26. Hubens G, Lafaire C, De Praeter M, Ysebaert D, Vaneerdeweg W, Heytens L, et al. Staged peritoneal lavages with the aid of a Zipper system in the treatment of diffuse peritonitis. Acta Chir Belg. 1994;94(3):176-9.
27. Roeyen G, Hubens G, Vaneerdeweg W, Mahieu L, Eyskens E. Scheduled relaparotomies using a zipper system for the treatment of diffuse generalized peritonitis in children. Acta Chir Belg. 1996;96(5):201-5.
28. Mimatsu K, Oida T, Kanou H, Miyake H, Amano S. Open abdomen management after massive bowel resection for superior mesenteric arterial occlusion. Surg Today. 2006;36(3):241-4.
29. Strauss AA. A new method and end results in the treatment of carcinoma of the stomach and rectum by surgical diathermy (electrical coagulation). JAMA. 1936;106(4):285-6.

30. Stone HH. Strom PR, Mullins RJ. Pancreatic abscess management by subtotal resection and packing. World J Surg. 1984;8(3):340-5.
31. Teichmann W, Wittmann DH, Andreone PA. Scheduled reoperations (etappen lavage) for diffuse peritonitis. Arch Surg. 1986;121(2):147-52.
32. Schachtrupp A, Fackeldey V, Klinge U, Hoer J, Tittel A, Toens C, et al. Temporary closure of the abdominal wall (laparostomy). Hernia. 2002;6(4):155-62.

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Original Article

Resection of liver metastasis from neuroendocrine tumors: evaluation of results and prognostic factors

Ressecção de metástases hepáticas de tumores neuroendócrinos: avaliação dos resultados e fatores prognósticos

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A B S T R A C T

Objectives: to determine the prognostic factors that may impact on morbidity and mortality and survival of patients undergoing surgical treatment of liver metastases from neuroendocrine tumors. **Methods**: We studied 22 patients undergoing liver resection for metastases from neuroendocrine tumors between 1997 and 2007. Epidemiological and clinical data were correlated with morbidity and mortality and overall and disease-free survivals. **Results**: twelve patients were male and ten female, with a mean age of 48.5 years. Bilobar disease was present in 17 patients (77.3%). In ten patients (45.5%) the primary tumor originated in the pancreas, terminal ileum in eight, duodenum in two, rectum in one and jejunum in one. Complete surgical resection (R0) was achieved in 59.1% of patients. Eight patients (36.3%) developed complications in the immediate postoperative period, one of them dying from septicemia. All patients undergoing re-hepatectomy and/or two-stage hepatectomy had complications in the postoperative period. The overall survival at one and five years was 77.3% and 44.2%. The disease-free survival at five years was 13.6%. The primary pancreatic neuroendocrine tumor ($p = 0.006$) was associated with reduced overall survival. Patients with number of metastatic nodules < 10 ($p = 0.03$) and asymptomatic at diagnosis ($p = 0.015$) had higher disease-free survival. **Conclusion**: liver metastases originating from pancreatic neuroendocrine tumors proved to be a negative prognostic factor. Symptomatic patients with multiple metastatic nodules showed a significant reduction in disease-free survival.

Key words: Neuroendocrine Tumors. Hepatectomy. Survival Analysis. Neoplasm Metastasis.

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous and unusual group of neoplasms, with variable natural history, slow-growing and often indolent evolution. They are characterized by the ability to synthesize, store and secrete hormonal substances and vasoactive amines, which are directly related to clinical manifestations[1]. The exact incidence of neuroendocrine tumors is variable between different studies, involving 1-7 cases / 100,000 individuals[2], representing 0.49% of all cancers[3]. Over the past 30 years there has been an increased incidence of this tumors at a rate of 6% per year, possibly due to improvement in diagnostic methods and greater awareness of the disease by doctors[3,4].

Although neuroendocrine tumors are generally indolent, slow-growing compared to carcinomas, metastases can occur, making the prognosis poor. Neuroendocrine tumors series show that 17% to 27% haveregional disease, and 17% to 74%, distant metastatic involvement [1]. The liver is the organ which is most affected by distant metastases and it is estimated that 75% of patients with small bowel TNE and 30% to 85% of those with TNE of pancreatic origin develop liver metastases, of whom 80% die within five years[3,5] . The liver is often the only organ affected by distant metastases[6]. The TNE five-year survival in the presence of liver metastases ranges from 13% to 35%[5,7-9] , and from 77% to 99% in the absence of hepatic involvement[2].

There is no consensus on how best to treat patients with NET liver metastases despite several attempts of systematization[10,11]. Due to the rarity and clinical and biological heterogeneity of such neoplasms, there is a paucity of published randomized studies. Surgical resection is the only potentially curative therapy. While in patients with untreated liver metastases survival is 20% to 40% in five years[3,12], in patients undergoing resection of the metastases this rate reaches 50% and 90%[13]. Furthermore, the alleviation of symptoms is achieved in 90% of cases.

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Due to the heterogeneity of results, it is important to evaluate the possible prognostic factors for survival in an attempt to predict the evolution and treatment planning.

This study aims to determine the prognostic factors that may impact mortality, morbidity and survival of patients undergoing surgical treatment of liver metastases from neuroendocrine tumors.

METHODS

We conducted a retrospective study with patients with liver metastases from neuroendocrine tumors who underwent surgical resection with curative intent. Data were prospectively collected in the period between January 1997 and December 2007. Twenty-two patients were eligible, according to the following inclusion criteria: patients with liver metastases originating from neuroendocrine tumor, histologically confirmed, submitted to hepatic resection with curative intent; availability of material in appropriate conditions for histological evaluation in the Department of Pathology.

Demographics, primary tumor characteristics and metastases, as well as surgical and pathological findings were used to define the following parameters for prognosis analysis: age; gender; symptoms; extent of hepatectomy; Full (R0) or incomplete (R1) liver resection; need for perioperative blood transfusion; presence of immediate postoperative complications; presence of extrahepatic disease; clinical presentation of liver metastases (synchronous X metachronous); distribution of metastases (bilobar X unilobar); number and size of liver metastases; location of the tumor; histological grade; tumor staging; number of operations; morbidity and mortality; and recurrence.

Patient characteristics, tumor tissue and surgical procedures were evaluated and correlated with: morbidity and mortality, overall survival and disease-free survival.

The size, number, location and extent of liver metastases were defined by computed tomography and/or magnetic resonance imaging of the abdomen, isotopic mapping with labeled octreotide (octreoscam). Careful palpation of the liver and intraoperative ultrasonography were performed in all patients for the evaluation of metastases not detected by preoperative imaging studies, and for defining surgical strategy. The surgical reports were reviewed to determine the location, extent of liver involvement and type of liver resection performed.

Patients were considered to have synchronous disease when the identification of liver metastasis and primary tumor was simultaneous or when detected up to six months after diagnosis of the primary tumor. Metachronous disease was defined if the metastasis became apparent after a period of six months after the detection of the primary tumor.

The classifications of the location and type of liver resection were based on Brisbane classification[14]. Liver resection was ranked as major when three or more segments were resected - right hepatectomy (segments 5, 6, 7 and 8); left hepatectomy (segments 2, 3 and 4); trisegmentectomy right (segments 4, 5, 6, 7 and 8); left trisegmentectomy (segments 2, 3, 4, 5 and 8). Segmentectomies, enucleations, wedge resections were classified as minor liver resection. The primary tumor was resected simultaneously to metastases in 11 patients.

Patients with negative margins and no evidence of macroscopic residual disease were considered to have undergone complete resection (R0); resection margins coincident with the section area or microscopic residual disease were classified as R1.

Liver resection was performed in two stages in patients with bilobar metastases not amenable to resection in only one surgical procedure. In these we performed in the first procedure, the resection of liver nodules of one of the sides associated with ligation of the portal vein of the contralateral lobe for the purpose of causing hypertrophy of the remaining liver, allowing the removal of all liver metastases. This technique was used in two patients.

Re-hepatectomy was performed in patients evolving with hepatic recurrence for whom the preoperative evaluation proved possible thecomplete resection of secondary lesions. Four patients have undergone this type of resection.

Patients who developed non-resectable recurrences and those with disease progression were treated with somatostatin analogues, hepatic artery chemoembolization, chemotherapy or radiation therapy.

Complications were considered all events that required any medical intervention or prolonged hospital stay. Postoperative complications were classified as immediate when occurred until the 30th day after surgery.

Survival was calculated from the first liver resection. Overall survival (OS) was defined as period of time in months elapsed between the date of the first liver resection and the date of death or last follow-up. Disease-free survival (DFS) was defined as the period of time in months elapsed between the date of first liver resection and date of diagnosis of recurrence or last follow-up.

We used the distribution of absolute and relative frequencies to describe categorical variables. We applied central tendency and dispersion in the analysis of numerical variables. We used the chi-square test for the correlation between categorical variables. In cases where the expected values in the contingency table were smaller than 5 by more than 20% of barriers and / or less than 1, the Fisher's exact test was performed. We used the Kaplan-Meier technique for the analyses of global and disease-free survival and the significance was evaluated by the log-rank test. We considered statistical significance when $p < 0.05$.

RESULTS

Twelve patients were males and ten females. The mean age was 48.5 years, ranging from 32 to 69. In six patients (27.3%) the diagnosis was incidental, the other 16 patients (72.7%) being symptomatic at diagnosis. Liver metastases were diagnosed synchronously with the primary tumor in 17 cases (77.3%). In 17 patients (77.3%) metastases were distributed in a bilobar fashion in the liver parenchyma, and unilobar in five (22.7%). Eleven patients had less than ten nodes. The liver parenchyma presented involvement greater or equal to 50% in eight (36.4%) patients, and less than 50%, in 14 (63.6%).

The primary tumor was resected simultaneously to metastases in 11 patients. Although resection with curative intent have been designed in all 22 patients, in only 13 (59.1%) was achieved radical or R0 resection; for the other nine (40.9%) the procedure was R1. Among the 22 patients, 20 underwent single-time liver resections, those being: 13 minor liver resections; two left side sectionectomies; two right hepatectomies; two left hepatectomies; and one right posterior sectionectomy. In two patients we opted for the realization of two-stage hepatic resection: in one patient, on the first time we performed a segmentectomy of segment 7, enucleations in segments 4, 5 and 8, and ligation of the left branch of the portal vein; on the second time, a left trisegmentectomy was performed. The other patient was submitted to segmentectomy of segment 3, with enucleation in segment 4 and ligation of the right branch of the portal vein; on the second time we carried outa right hepatectomy.

Four patients developed hepatic recurrence and underwent re-hepatectomy; one of them had two more recurrences in the liver, which were resected. Three minor liver resections were performed, one left trisegmentectomy, one right hepatectomy and one left hepatectomy.

The mean duration of surgical procedures was 337 minutes, ranging from 65 to 840. The mean hospital stay was 7.2 days (2-17). Eight patients (36.4%) received blood transfusion, with an average of 360ml per transfusion.

Ten patients (45.5%) had the primary neuroendocrine tumor located in the pancreas, eight (36.4%) in the terminal ileum, two (9.1%) in the duodenum; one in (4.5%) in the rectum and one (4.5%) in the jejunum. The average size of the resected metastatic lesions was 48,3mm, with a median of 42.5mm, ranging from 6 to 150 mm. The average number of resected metastatic nodules was 3.4, ranging between one and 11. Eleven patients (50%) had involvement of lymph nodes regional to the primary tumor.

Eight patients (36.3%) developed postoperative complications, two with pneumonia, one urinary tract infection, one septicemia, one liver failure, one intraperitoneal abscess, one pleural effusion and one cardiac arrhythmia. The patient with peri-hepatic abscess needed percutaneous drainage, all the others having been treated medically. All patients undergoing liver resection in two stages or re-hepatectomy had postoperative complications. One patient (4.5%) submitted to re-hepatectomy developed sepsis and died in the postoperative period.

The mean follow-up was 37 months (12-107). Among the thirteen patients who underwent complete resection, six (46.15%) had recurrences in the liver, two showed bone relapse, and one, in bone and central nervous system. At the end of the study, five patients (22.7%) were alive without neoplastic disease; eight were alive with disease (35.4%) and nine had died (40.9%).

On statistical analysis of patients who developed complications in the immediate postoperative period, the only factor correlated with the occurrence of complications was the performance of more than one hepatectomy (two stages or re-hepatectomy) ($p = 0.028$). The other variables showed no significant statistical correlation with the occurrence of postoperative complications.

Overall survival was 77.3% at three years and 44.2% at five years. The disease-free survival at five years was 13.6%. No variable related to patient characteristics or treatment had any influence on overall survival (Table 1). Among the variables related to the tumor, the location of the primary tumor showed a statistically significant difference in the overall survival curve; the five-year survival for patients with the primary tumor originating in the pancreas was 15%, and 91.7% for patients who had the primary tumor originating in the digestive tract ($p = 0.006$) (Figure 1).

Among the variables related to patient characteristics, the number of liver metastases was statistically significant; patients with less than ten metastatic nodules showed 9.1% disease-free survival versus 0% for patients with greater than or equal to ten metastatic nodules ($p = 0.03$). The presence of symptoms at diagnosis was also statistically significant, since patients without symptoms to diagnosis showed 18.8% of disease-free survival versus 0% for symptomatic patients ($p = 0.015$) (Table 2). No variable relative to treatment or tumor characteristics had a significant impact on disease-free survival.

DISCUSSION

Neuroendocrine tumors, although considered slow growing tumors and mildly aggressive, tend to develop distant metastatic disease with relative frequency, and the liver is the most affected organ. The development of liver metastasis results in a significant reduction in survival and quality of life of patients. There is some doubt in the management of patients with liver metastases from neuroendocrine tumors: what is the goal of treatment (curative or palliative)? When should treatment be start? How to treat best?[15]

The goals of treatment when there is metastatic disease are improved quality of life by relieving symptoms

Table 1 - Overall survival rates (SR) in five years by the Kaplan-Meier method.

Variable	Category	n	SR(%/5 anos)	p(Log rank)
Presentation of metastases	Syncronous	17	38.2	0.565
	Metachronous	5	80	
Age	< 50 years	13	67.7	0.069
	> 50 years	9	0	
Symptoms	Asynptomatic	6	66.7	0.598
	Syntomatic	16	32.5	
Distribution of metastases	Unilobar	5	40	0.75
	Bilobar	17	45.9	
Number of metastases	< 10	11	49.1	0.394
	> 10	11	36.4	
Gender	Female	10	23.3	0.138
	Male	12	62.5	
Treatment intent	R0	13	38.50	0.610
	R1	9	46.70	
Relapse	Yes	6	42.90	0.9
	No	16	43.80	
Re-hepatectomy	Yes	4	25	0.444
	No	18	72.2	
Postoperative complication	Yes	10	20	0.219
	No	12	75	
Prior resection of primary	Yes	7	85.7	0.2
	No	15	29.3	
Blood transfusion	Yes	8	42.9	0.876
	No	14	43.8	
Primary Location	Pancreas	10	15	0.006
	TGI	12	91.70	
Regional lymph node disease	Yes	11	81.80	0.15

and increased survival. Surgical resection is the only potentially curative treatment.

Other forms of treatment have been employed with intra-arterial chemoembolization and systemic treatment, with results poorer than resection[13]. Due to the indolent behavior and less aggressive evolution when compared with other metastatic diseases to the liver, patients with liver metastases deemed unresectable have undergone liver transplantation. The result of the transplant for this group of patients was very heterogeneous, with five-year survival ranging from 14 to 90%, being much better for patients with non-pancreatic tumor metastasis[3]. For patients with restricted but unresectable liver disease, transplantation appears to be the best therapeutic alternative[16].

In our study, complete surgical resection (R0) of liver metastases was achieved in 13 patients (59.1%), although the operation with curative intent has been intended in all patients. Our data are consistent with the literature, which describes a complete resection rate ranging between 20% and 54%[13,17-19]. This high percentage of incomplete resection is due to the low sensitivity of preoperative diagnostic methods[20], the thorough examination of the cavity, with detailed palpation of the liver and the use of intraoperative ultrasonography being of great importance.

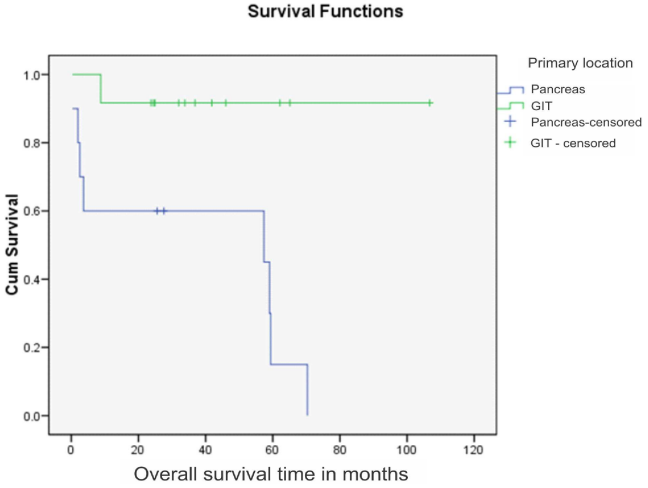

Figure 1 - *Overall survival curve according to the location of the primary tumor.*

Legend: Cum: cumulative; GIT: Gastrointestinal Tract.

Table 2 - Disease-free survival rates (DFS) in five years by the Kaplan-Meier method.

Variable	Category	n	DFS(%/5 years)	p(Log rank)
Presentation of metastasis	Synchronous	17	17.6	0.155
	Metachronous	5	0	
Age	< 50 years	13	19.2	0.162
	e" 50 years	9	11.1	
Symptoms	Asymptomatic	6	18.8	0.015
	Symptomatic	16	0	
Distribution of metastases	Unilobar	5	0	0.121
	Bilobar	17	17.6	
Number of metastases	< 10	11	9.1	0.03
	e" 10	11	0	
Gender	Female	10	0	0.966
	Male	12	25	
Re-hepatectomia	Yes	4	0	0.796
	No	18	27.8	
Blood transfusion	Yes	8	0	0.319
	No	14	21.4	
Postoperative complication	Yes	10	0	0.676
	No	12	33.3	
Prior resection of primary	Yes	7	14.3	0.621
	No	15	0	
Primary location	Pancreas	10	0	0.052
	TGI	12	41.7	
Regional lymph node disease	Yes	11	36.4	0.347
	No	11	9.1	

Because of the rarity of these neoplasms, most studies are retrospective and composed of small case series, ranging between 13 and 47 patients, especially when only analyzing patients who underwent surgical treatment of metastases[17,20-22].

In our study, the overall five-year survival after liver resection was 44.2% over a mean follow-up of 37 months. Although superior to historical controls of patients who did not receive surgical treatment[23-25], our results were relatively lower than those of more recent studies[13,24-26]. These overall survival rates can be explained by the characteristics of our study population, comprised of 45.5% of patients with primary tumor originating in the pancreas; bilobar involvement of hepatic parenchyma in 77.3% of cases; average size of metastases 48,3mm; synchronicity between the primary tumor and liver metastasis in 77.3% of patients; and half of patients with over ten metastatic nodules.

In our study, liver metastases originating from pancreatic neuroendocrine tumors showed significant differences in overall survival. Patients with pancreatic primary tumor showed an overall five-year survival of 15%, this being 91.7% for those with primary tumors originating in the digestive tract. Neuroendocrine tumors of the pancreas and cecum are those with the highest percentage of non-localized disease, 71.9% and 81.5%, respectively[2]. The pancreatic neuroendocrine tumors develop liver metastases from 30% to 85% of cases[27]. Several studies have demonstrated adverse movement in neuroendocrine tumors originating in the pancreas[3,17,28-3].

Patients with liver metastases from TNE have high recurrence rate[28,30-32] and less than 15% are cured[6,13]. In this study, relapse occurred in 46.1% of patients who underwent complete resection of liver metastases. Disease-free survival was 13.6%. A multi-institutional study of 339 patients undergoing liver resection for TNE metastases reports AN overall survival of 74% and 51% in five and ten years, respectively. However, despite the good results in terms of survival, the authors reported 94% of recurrence[33].

The number of metastatic lymph nodes showed significant influence on disease-free survival; patients with a number higher than or equal to ten metastatic nodules had lower disease-free survival. The presence of symptoms at diagnosis also had a significant influence on disease-free survival, and symptomatic patients had lower disease-free survival.

In the past, liver resections were considered highly complex operations. Nevertheless, with the development of surgical and anesthetic techniques and perioperative management, these operations have become safer, especially if performed in specialized centers. In our study, eight patients (36.3%) had complications within 30 days

after surgery and, of these, one was fatal. In the analysis of predictive factors for the occurrence of postoperative complications, the highlights were the performance of multiple hepatectomies and other procedures associated with the liver resections. Likewise, SØreide et al.[34] demonstrated that patients submitted to aggressive surgical treatment, including the re-hepatectomy and operations in two stages, had gain in overall survival, but displayed high complications (33%) and mortality (9%).

The sample size of several published studies is invariably small. The rarity of neuroendocrine tumors enables few institutions to collect large series, making it difficult for a single center to have sufficient numbers of patients to allow the conduction of studies on the clinical course of the disease for long periods.

Despite the great heterogeneity of presentation and clinical behavior of TNE, it is clear that surgical treatment plays an important role in addressing these patients. It is worth noting that, in symptomatic patients with multiple nodules, surgical treatment in isolation is not able to provide cure. In this situation, and also in those patients with TNE metastases of pancreatic origin, of known worse prognosis, other forms of treatment deserve to be studied. Efforts should be taken to the selection of patients seeking surgical treatment and new therapeutic approaches.

In conclusion, liver metastases originating from pancreatic neuroendocrine tumors proved to be a negative prognostic factor. Symptomatic patients with multiple metastatic nodules showed a significant reduction in disease-free survival.

RESUMO

Objetivos: *determinar fatores prognósticos com possível impacto na morbimortalidade e sobrevida de pacientes submetidos ao tratamento cirúrgico das metástases hepáticas de tumores neuroendócrinos.* ***Métodos:*** *foram estudados 22 pacientes submetidos à ressecção hepática por metástases de tumores neuroendócrinos entre 1997 e 2007. Dados epidemiológicos e clínicos foram correlacionados com morbimortalidade e sobrevidas global e livre de doença.* ***Resultados:*** *doze pacientes eram do sexo masculino e dez do feminino com média de idade de 48,5 anos. Doença bilobar esteve presente em 17 pacientes (77,3%). Em dez pacientes (45,5%) o tumor primário se originou no pâncreas, em oito no íleo terminal, em dois no duodeno, em um no reto e em um no jejuno. Ressecção cirúrgica completa (R0) foi alcançada em 59,1% dos pacientes. Oito pacientes (36,3%) evoluíram com complicações no pós-operatório imediato, com um paciente evoluindo ao óbito por septicemia. Todos os pacientes submetidos à re-hepatectomia e/ou hepatectomia em dois tempos evoluíram com complicações no período pós-operatório. A sobrevida global em um e cinco anos foi 77,3% e 44,2%. A sobrevida livre de doença em cinco anos foi 13,6%. O tumor neuroendócrino primário do pâncreas (p=0,006) foi associado à redução na sobrevida global. Os pacientes com número de nódulos metastáticos <10 (p=0,03) e os assintomáticos ao diagnóstico (p=0,015), apresentaram maior sobrevida livre de doença.* ***Conclusão:*** *metástases hepáticas oriundas de tumores neuroendócrinos pancreáticos demonstraram ser um fator prognóstico negativo. Pacientes sintomáticos e com múltiplos nódulos metastáticos apresentam redução significativa na sobrevida livre de doença.*

Descritores: *Tumores Neuroendócrinos. Hepatectomia. Análise de Sobrevida. Metástase Neoplásica.*

REFERENCES

1. Rothenstein J, Cleary SP, Pond GR, Dale D, Gallinger S, Moore MJ, et al. Neuroendocrine tumors of the gastrointestinal tract: a decade of experience at the Princess Margaret Hospital. Am J Clin Oncol. 2008;31(1):64-70.
2. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97(4):934-59.
3. Frilling A, Sotiropoulos GC, Li J, Kornasiewicz O, Plöckinger U. Multimodal management of neuroendocrine liver metastases. HPB. 2010;12(6):361-79.
4. Gustafsson BI, Kidd M, Modlin IM. Neuroendocrine tumors of the diffuse neuroendocrine system. Curr Opin Oncol. 2008;20(1):1-12.
5. Yao KA, Talamonti MS, Nemcek A, Angelos P, Chrisman H, Skarda J, et al. Indications and results of liver resection and hepatic chemoembolization for metastatic gastrointestinal neuroendocrine tumors. Surgery. 2001;130(4):677-82; discussion 682-5.
6. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. Gastroenterology. 2005;128(6):1717-51.
7. Gulec SA, Mountcastle TS, Frey D, Cundiff JD, Mathews E, Anthony L, et al. Cytoreductive surgery in patients with advanced-stage carcinoid tumors. Am Surg. 2002;68(8):667-71; discussion 671-2.
8. Norton JA. Endocrine tumours of the gastrointestinal tract. Surgical treatment of neuroendocrine metastases. Best Pract Res Clin Gastroenterol. 2005;19(4):577-83.
9. Osborne DA, Zervos EE, Strosberg J, Boe BA, Malafa M, Rosemurgy AS, et al. Improved outcome with cytoreduction versus embolization for symptomatic hepatic metastases of carcinoid and neuroendocrine tumors. Ann Surg Oncol. 2006;13(4):572-81. Erratum in: Ann Surg Oncol. 2006;13(8):1162.
10. Steinmüller T, Kianmanesh R, Falconi M, Scarpa A, Taal B, Kwekkeboom DJ, et al. Consensus guidelines for the management of patients with liver metastases from digestive (neuro)endocrine tumors: foregut, midgut, hindgut, and unknown primary. Neuroendocrinology. 2008;87(1):47-62.
11. Kwekkeboom DJ, Krenning EP, Lebtahi R, Komminoth P, Kos-Kudla B, de Herder WW, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: peptide receptor radionuclide therapy with radiolabeled somatostatin analogs. Neuroendocrinology. 2009;90(2):220-6.
12. Chen H, Hardacre JM, Uzar A, Cameron JL, Choti MA. Isolated liver metastases from neuroendocrine tumor: does resection prolong survival? J Am Coll Surg. 1997;187(1):88-92; discussion 92-3.
13. Chamberlain RS, Canes D, Brown KT, Saltz L, Jarnagin W, Fong Y, et al. Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg. 2000;190(4):432-45.

14. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. J Hepatobiliary Pancreat Surg. 2005;12(5):351-5.
15. Madoff DC, Gupta S, Ahrar K, Murthy R, Yao JC. Update on the management of neuroendocrine hepatic metastases. J Vasc Interv Radiol. 2006;17(8):1235-49.
16. Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R, et al. Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol. 2014;15(1):e8-21.
17. Nave H, Mössinger E, Feist H, Lang H, Raab H. Surgery as primary treatment in patients with liver metastases from carcinoid tumors: a retrospective, unicentric study over 13 years. Surgery. 2001;129(2):170-5.
18. Niederhuber JE, Fojo T. Treatment of metastatic disease in patients with neuroendocrine tumors. Surg Oncol Clin N Am. 2006;15(3):511-33.
19. Landry CS, Scoggins CR, McMasters KM, Martin RC 2nd. Management of hepatic metastasis of gastrointestinal carcinoid tumors. J Surg Oncol. 2008;97(3):253-8.
20. Elias D, Lasser P, Ducreux M, Duvillard P, Ouellet JF, Dromain C, et al. Liver resection (and associated extrahepatic resections) for metastatic well-differentiated endocrine tumors: a 15-years single center prospective study. Surgery. 2003;133(4):375-82.
21. Jaeck D, Oussoultzoglou E, Bachellier P, Lemarque P, Weber JC, Nakano H, et al. Hepatic metastases of gastroenteropancreatic neuroendocrine tumors: safe hepatic surgery. World J Surg. 2001;25(6):689-92.
22. Musunuru S, Chen H, Rajpal S, Stephani N, McDermott JC, Holen K, et al. Metastatic neuroendocrine hepatic tumors: resection improves survival. Arch Surg. 2006;141(10):1000-4; discussion 1005.
23. Dousset B, Saint-Marc O, Pitre J, Soubrane O, Houssin D, Chapuis Y. Metastatic endocrine tumors: medical treatment, surgical resection, or liver transplantation. World J Surg. 1996;20(7):908-14; discussion 914-5.
24. Norton JA, Warren RS, Kelly MG, Zuraek MB, Jensen RT. Aggressive surgery for metastatic liver neuroendocrine tumors. Surgery. 2003;134(6):1057-63; discussion 1063-5.
25. Touzios JG, Kiely JM, Pitt SC, Rilling WS, Quebbeman EJ, Wilson SD, et al. Neuroendocrine hepatic metastases: does aggressive management improve survival? Ann Surg. 2005;241(5):776-83; discussion 783-5.
26. Frilling A, Li J, Malamutmann E, Schmid KW, Bockisch A, Broelsch CE. Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. Br J Surg. 2009;96(2):175-84.
27. Oberg K, Eriksson B. Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol. 2005;19(5):753-81.
28. Panzuto F, Nasoni S, Falconi M, Corleto VD, Capurso G, Cassetta S, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. Endocr Relat Cancer. 2005;12(4):1083-92.
29. Bettini R, Boninsegna L, Mantovani W, Capelli P, Bassi C, Pederzoli P, et al. Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. Ann Oncol. 2008;19(5):903-8.
30. Cho CS, Labow DM, Tang L, Klimstra DS, Loeffler AG, Leverson GE, et al. Histologic grade is correlated with outcome after resection of hepatic neuroendocrine neoplasms. Cancer. 2008;113(1):126-34.
31. AmFersi Garza AM, Ahmad A, Bilchik AJ. Survival benefit of extensive hepatic cytoreduction for symptomatic metastases from neuroendocrine tumors. Ann Surg Oncol. 2006;13(Suppl 2):14.
32. Hibi T, Sano T, Sakamoto Y, Takahashi Y, Uemura N, Ojima H, et al. Surgery for hepatic neuroendocrine tumors: a single institutional experience in Japan. Jpn J Clin Oncol. 2007;37(2):102-7.
33. Mayo SC, de Jong MC, Pulitano C, Clary BM, Reddy SK, Gamblin TC, et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. Ann Surg Oncol. 2010;17(12):3129-36.
34. SØreide O, Berstad T, Bakka A, Schumpf E, Hanssen LE, Engh V, et al. Surgical treatment as a principle in patients with advance abdominal carcinoid tumors. Surgery. 1992;111(1):48-54.

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Original Article

Comparative study of the different degrees of risk of gastrointestinal stromal tumor

Estudo comparativo dos diferentes graus de risco no tumor estromal gastrointestinal

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A B S T R A C T

Objective: To evaluate the applicability of the main categories of risk and morphological factors in the prognosis of gastrointestinal stromal tumors. **Methods**: we retrospectively studied fifty-four cases of GIST, assessing the main prognostic factors of this neoplasis: risk levels, topography, size, mitotic index, necrosis, histological subtype and immunophenotype. We also verified their association and the reduction of overall survival. **Results**: Univariate analysis showed that tumors with mitoses number greater than 5 per 50CGA (high-power fields), the presence of necrosis and a high risk for both the systems proposed by Fletcher and Miettinen had a significant association with reduced survival (p = 0.00001, 0.0056, 0.03 and 0.009, respectively). The remaining analyzed factors (size, histological subtype, topography and immunophenotype) had no such association. Multivariate analysis (Jacard index) showed that the Miettinen degree of risk was the one that best correlated with prognosis. **Conclusion**: the risk criteria of Fletcher and Miettinen are important in assessing the prognosis of patients with gastrointestinal stromal tumors, especially the latter, which adds to the mitotic index and the presence of tumor necrosis.

Key words: Gastrointestinal Stromal Tumors. Risk Factors. Digestive System Neoplasms. Prognosis. Mitotic Index.

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract[1], their incidence being estimated at 14 to 20 cases per million population[2]; they are more frequent in male patients older than 50 years old[3]. The pathogenesis is related to mutational changes in two tyrosine kinase receptors: KIT and PDGFR-alpha (platelet-derived growth factor receptor alpha) on the surface of the interstitial cells of Cajal, the former being the most common (85% of cases)[4,5]. Gastrointestinal stromal tumors can develop in any topography, from the esophagus to the rectum. However, they are more common in the stomach (50% to 60%), followed by small intestine (20% to 30%), colon (10%), rectum or esophagus (5%)[6]. Macroscopically, the tumor lesions often have a nodular form, transmural involvement and submucosal growth, with ulceration of the mucosa or not. In light microscopy, histology reveals three types: the most common spindle (70%), epidermoid (20%) and the mixed type (10%), when there is combination of epithelioid and spindle ones[7].

The diagnosis of stromal neoplasms is based on immunohistochemical study with CD117 marker, expressed in most such neoplasias[1]. Noteworthy are also other markers: DOG 1, nestin, theta protein kinase C and carbonic anhydrase II[8]. The differential diagnosis includes: desmoid tumor, inflammatory myofibroblastomas, leiomyoma, inflammatory fibroid polyp, neuroma, neurossarcoma, sarcomatoid mesothelioma and metastatic melanoma[7,9,10]

GIST prognosis is still matter of discussion. Currently there are different classifications[7,11-15] aimed to stratify tumors into groups, linking them to a higher or lower risk of tumor recurrence and/or distant metastasis[8,12]. Of all the classifications mentioned above, the two most commonly used are the one of Fletcher *et al.*[7] and Miettinen*et al.*[11]. The first classification established two factors as prognostic parameters, one macroscopic and the other microscopic. This combination resulted in a system that ranked the stromal tumors in different degrees of risk. The second,

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based on a larger number of cases, whose diagnosis was supported both by immunohistochemical and genetic studies, and especially with a prolonged follow-up. In addition to the criteria used in Fletcher *et al.*[7] classification, a third was added to Miettinen *et al.*[11] classification, the location of the tumor, allowing greater stratification of risk groups and the establishment of a percentage related to the chances of development of recurrence and / or metastasis.

The aim of this study was to evaluate the applicability of the main risk categories (Fletcher and Miettinen) and morphological factors in the prognosis of gastrointestinal stromal tumor.

METHODS

We retrospectively studied a cohort of 54 cases of gastrointestinal stromal tumors with positive immunohistochemistry for the expression of anti-CD117 antibody, completely excised with no evidence of disseminated disease and not associated with other malignancies. These came from the files of the Pathology Services of the Hospital Univeristário Gaffrée e Guinle (HUGG/UNIRIO) and Hospital Univeristário Clementino Fraga Filho (HUCFF/UFRJ). We obtained data on age, gender and clinical outcomes of patients from medical records and requests from pathological examinations. The study evaluated the data of patients alive and without recurrence, of patients who died from the disease, and of live patients with recurrent disease. Thetime with disease evolution was counted from the date of surgery until the last contact of the patient, recorded in the medical record. The project was approved by the Ethics in Research Committee of HUCFF under number 079/05.

Morphological data and risk degrees

The topography and tumor size were obtained from requests from pathological examinations. The mitotic index was assessed in 50CGA (high-power fields), using an Olympus BX40 microscope with a 40X objective and 10x eyepiece[7]. The mitotic count was performed by two pathologists. The histological subtype was determined by the predominant presentation form at microscopy (spindle, epithelioid, mixed); the presence of necrosis was evaluated in areas distant from those corresponding to the ulceration of the overlying mucosa, when present[7]. When assessing degrees of risk, we employed the ones proposed by Fletcher et al.[7] (Table 1) and Miettinen et al.[11] (Table 2).

Immunohistochemistry

The following antibodies were used: anti-CD117 (Dako, Carpinteria, California / USA) diluted 1:100; anti-protein S-100 (Dako, Carpenteria, California / USA) diluted 1:1,000; and anti-smooth muscle actin (Dako, Carpinteria, California / USA) diluted 1: 250. Subsequently, sections were incubated with Universal LSAB ™2 kit / HRP Rabbit / Mouse - K0675 (Dako, Carpinteria, California / USA). The positivity for anti-protein S-100 antibody and muscle-specific anti-actin defined the immunophenotype of neoplasms,

Table 1 - Fletcher risk degrees.

Risk degree	Macroscopic size (cm)	Mitotic index (50 CGA)
Very low	<2	<5
Low	2-5	<5
Intermediary	<5 5-10	6-10 <5
High	> 5> 10any size	> 5any index> 10

Fletcher *et al.*[7]

Table 2 - Mettinen Risk Degrees.

Tumor parameters	Risk of disease progression				
Index Mitotic	Size	Stomach	Duodenum	Ileum/ jejunum	Rectum
< 5 per50CGA	< 2 cm	No(0)	None (0)	No(0)	No(0)
	2 > to < 5 cm	Very low (1.9 percent)	Low(4.3%) and	Low(8.3 percent)	Low(8.5 percent)
	5 > to < 10 cm	Low(3.6 percent)	Moderate(24)	Datainsufficient	DataInsufficient
	> 10 cm	Moderate(10% off)	High(52% off)	High(34% off)	High(57)
> 5 per50 CGA	< 2 cm	None (0)	High(61)	Datainsufficient	High(54% off)
	2 > to < 5 cm	Moderate(16% off)	High(73)	High(50% off)	High(52% off)
	5 > to < 10 cm	High(55% off)	High(85 percent)	Datainsufficient	DataInsufficient
	> 10 cm	High(86)	High(90 percent)	High(86)	High(71)

Miettinen *et al.*[11]

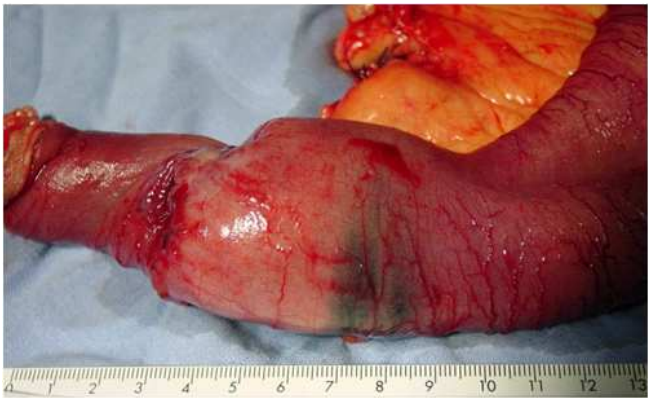

Figure 1 - *Gastrointestinal stromal tumor of the jejunum, with serosal bulging.*

classifying them respectively as muscular, neural, double or null (no expression)[7].

Statistical analysis

All factors were submitted to analysis of the direct and univariate frequencies with the chi-square test. The statistical significance was set at $p < 0.05$. The criteria that showed statistical significance in the univariate analysis were submitted to the Jaccard similarity index.

RESULTS

The study group consisted of 54 patients, 30 (59.5%) of them women and 24, men (40.5%) with a mean age of 57.34 ± 13.71, ranging from 24 to 83. Regarding the topography of neoplasms, tumors were located: one (1.8%) in the esophagus, 27 (50%) in the stomach, 20 (37.1%) in the small intestine (Figure 1) and six (11.1%) in the large intestine.

The size of the tumors ranged from 2.0 to 33 cm (median 8) with 12 measuring up to 5 cm (included) along the longest axis (22.3%) and 42 were greater than 5 cm (77.7%). As for the mitotic index, 36 cases had less than five mitosis per 50 CGA (66.8%) and the others (18), more than five (33.2%). The histological subtype of 32 tumors (59.3%) were spindle, of nine (16.6%), epithelioidand of 13, (24.1%) mixed. Necrosis was absent in 33 cases (61.2%) and present in 21 (38.8%). The immunophenotype was as follows: 26 (48.1%) tumors showed muscle differentiation, 11 (20.4%) neural, seven (13.3%), double differentiation (nerve and muscle) and 10 (18.2%), none.

Regarding the degree of risk, according to Fletcher *et al.*[7] tumors were thus classified: Ten (18.6%) of low-risk, 17 (31.4%) of intermediate risk, 27 (50%) of high-risk and none of very low risk; and according to Miettinen *et al.*[11], three (5.4%) had no risk, four (7.4%) of very low risk, ten (18.6%) of low-risk, 14 (26%) of intermediate risk and 23 (42.6%) of high risk.

As for the status of the patients, 33(61.2%) were alive without disease (good prognosis) and 21 (38.8%), alive with disease and / or died due to the neoplasia, and the follow-up period ranged from one to 248 months, with a median of 53 months. Among the parameters studied and tested in the univariate analysis, those who showed an adverse effect on overall survival was the mitoses number greater than five mitosis per 50 CGA ($p = 0.00001$). In multivariate analysis, employing the Jaccard Index, we found that the Miettinen degree of risk showed better association with reduced overall survival.

DISCUSSION

The characterization of the biological behavior of GIST is essential for signaling of patients who are outpatients, those who have the indication of treatment with imatinibmesylate. In this series, the gender distribution was different from the ones in the literature, there was a predominance of females (59.5%), while literature indicates a homogeneous distribution or a slight predominance of males[11,16-18] and, by contrast, the average age of patients (57 years) was similar to that found in other series[2,17].

In this sample, the preferred location in the stomach, followed by small intestine, large intestine and esophagus was also observed by other authors[2,11]. Although we found no statistically significant difference between the different organs involved ($p=0.08$), some studies[11,19,20] have shown that the GIST location directly influences the prognosis and those located in the stomach had more favorable course than those found in other topographies. Statistically, we found that the colonic topography directly influenced prognosis, since five out ofthe six tumors had unfavorable follow-up (metastasis/death), which was also found in another study[3].

The importance of tumor size in GIST prognosis has undergone major changes since the publication of Miettinen *et al.*[11], and came to corroborate evidence that linked the neoplastic diameter with tumor topography, ie, gastric tumors showed worse prognosis when their size was greater than 10cm, while cancer of the small intestine showed poor prognosis when greater than 5cm[19,20]. However, in general, gastrointestinal stromal tumors with more than five centimeters are related to a worse prognosis. In this series there was no demonstration of prognosis associated with tumor size, a fact possibly influenced by the number of cases. Independently of this demonstration, some data needs to be emphasized, because the average size of the tumors of patients with worse prognosis was higher than in patients with good prognosis. Also, of the 21 tumors with recurrence, 17 were larger than 5cm, from which it can be inferred that size is an important prognostic criteria.

The mitotic index (MI) of more than 5 per 50 CGA was also a variable associated with prognosis, as observed

by other authors[7,11,15,17,18,20]. The evaluation of this variable is present in the two main risk levels[7,11] used to characterize GIST prognosis. The risk degree of Fletcher *et al.*[7], has three MI subdivisions (< 5,6-10 and > 5), while for Miettinen *et al.*[11], there is a binary division (< 5 and > 5). These forms of division diminish the discriminatory power ofMI, a fact described after analysis of 929 tumors and observation of differences in patient survival when the stratification was done in four segments (< 5, 5-10, 10-30 and > 30)[21]. In addition, the correct interpretation of true mitosis is another problem since the material fixation time may impair its identification[18].

The histological subtype in our study was not related to patients' prognosis. However, it is noteworthy that among the 12 epithelioid and mixed neoplasms, ten had unfavorable follow-up. The poor survival of patients with tumors of the mixed or epithelioid patterns has also been reported, but this finding only held for the mixed pattern in multivariate analysis[22,23]. Another study suggests that the spindle histological pattern is associated with longer patients survival[20]. In view of these conflicting results, we believe that this point still needs further study.

The presence of necrosis was associated with poor prognosis, which was also found in other studies[18,20]. It is believed that necrosis is directly related to severe proliferative activity of the tumor, ie, the most aggressive would present necrosis areas.

As for the studied immunohistochemical markers, there was no correlation of the neoplasia immunophenotype with patients' prognosis, as evidenced in another series[2]. Nonetheless, neoplasms with muscle differentiation showed greater disease-free intervals[17]. However, the authors point out that these results need to be evaluated carefully, since the tumors with muscle differentiation had a less aggressive biological course.

Regarding the two GIST prognostic characterization systems, there was evidence of association with prognosis in both Fletcher *et al.*[7] and Miettinen *et al.*[11] classification, which was also found by other authors[14,18,24,25]. However, in this series we found a better risk statistical correlation with the Miettinen *et al.*[11] classification. This can be explained by the introduction of a third criterion (location), the study of more than 2,000 cases, with long follow-up of patients and mainly the greater stratification of the risk categories, allowing a reclassification of the neoplasias[25]. This can be observed in our study, with the appearance of three tumors with no risk, four tumors with very low risk, and also reduction in both neoplasias at intermediate risk (from 17 to 14) and high risk (from 27 to 23).

Although the relationship between prognosis and the two classifications, there are still tumors that do not follow this natural history, ie there are neoplasms classified as low risk that progress to metastasis / death, and other categorized as high risk, whose patients present favorable follow-up (alive without recurrence)[7]. The foregoing can be explained due to various conflicting situations in the two proposed systems. Fletcher *et al.*[7] fails to point out the mitosis counting method, the size measuring mode, the definition of what is a high-power field, and also does not define the risk degree to neoplasias with exactly five mitosis per 50 CGA[25]. In Miettinen *et al.*[11], certain subgroups have few documented neoplasias, such as duodenal tumors less than 2cm and lesions with mitotic index greater than five per 50 CGA, which prevents their categorization[8]. In addition, there is no classification for GIST in the esophagus or colon, whose biological behavior can be misinterpreted[25].

We conclude that both the systems proposed by Fletcher *et al.*[7] and Mettinnen*et al.*[11] in cases of GIST showed correlation with prognosis, although in this series the latter has proved to be superior. However, we understand that such systems need to be reviewed, either through a new form of the current division criteria (number of mitosis per CGA and tumor size) or by including other morphological variables, such as necrosis and less frequent location sites. However, we understand that we still need more studies involving more cases, especially in those places where GISTs are less common.

R E S U M O

***Objetivo**: avaliar a aplicabilidade das principais categorias de risco e de fatores morfológicos no prognóstico tumor estromal gastrointestinal. **Métodos**: cinquenta e quatro casos de GIST foram estudados retrospectivamente considerando-se os principais fatores prognósticos da neoplasia: graus de risco, topografia, tamanho, índice mitótico, necrose, subtipo histológico e imunofenótipo. Foi também verificada a sua associação e a redução da sobrevida global dos pacientes. **Resultados**: a análise univariada mostrou que os tumores com número de mitoses maior que 5/50CGA (campos de grande aumento), a presença de necrose, de alto risco tanto para os sistemas propostos por Fletcher, quanto para Miettinen tiveram associação significativa com redução da sobrevida (p=0,00001, 0,0056, 0,03 e 0,009, respectivamente). Enquanto que os demais fatores analisados (tamanho, subtipo histológico, topografia e imunofenótipo) não tiveram tal associação. A análise multivariada (índice de Jacard) demonstrou que o grau de risco de Miettinen foi aquele que melhor se relacionou com o prognóstico. **Conclusão:** os critérios de risco de Fletcher e de Miettinen são importantes na avaliação do prognóstico de pacientes com tumor estromal gastrointestinal, principalmente este último, que se soma ao índice mitótico e a necrose tumoral.*

***Descritores**: Tumores do Estroma Gastrointestinal; Fatores de Risco; Neoplasias do Sistema Digestório. Prognóstico. Índice Mitótico.*

REFERENCES

1. Miettinen M, Lasota J. Histopathology of gastrointestinal stromal tumor. J Surg Oncol. 2011;104(8):865-73.
2. Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, et al. Gastrointestinal stromal tumors: the incidence,prevalence, clinical course, and prognostication in the preimatinibmesylate era—a population-based study in western Sweden. Cancer.2005;103(4):821-9.
3. Gold JS, van der Zwan SM, Gönen M, Maki RG, Singer S, Brennan MF, et al. Outcome of metastatic GIST in the era before tyrosine kinase inhibitors. Ann Surg Oncol. 2007;14(1):134-42. Erratum in: Ann Surg Oncol. 2007;14(10):3027.
4. Kitamura Y, Hirota S, Nishida T. Gastrointestinal stromal tumors (GIST): a model for molecule-based diagnosis and treatment of solid tumors. Cancer Sci. 2003;94(4):315-20. Erratum in: Cancer Sci. 2003;94(10):930.
5. Rubin BP. Gastrointestinal stromal tumours: an update. Histopathology. 2006;48(1):83-96.
6. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors:an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol. 2005;100(1):162-8.
7. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002;33(5):459-65.
8. Wong NA. Gastrointestinal stromal tumours—an update for histopathologists. Histopathology. 2011;59(5):807-21.
9. Shidham VB, Chivukula M, Gupta D, Rao RN, Komorowski R. Immunohistochemical comparison of gastrointestinal stromal tumor and solitary fibrous tumor. Arch Pathol Lab Med. 2002;126(10):1189-92.
10. Plaat BE, Hollema H, Molenaar WM, Torn Broers GH, Pijpe J, Mastik MF, et al. Soft tissue leiomyosarcomas and malignant gastrointestinal stromal tumors: differences in clinical outcome and expression of multidrug resistance proteins. J Clin Oncol. 2000;18(18):3211-20.
11. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med. 2006;130(10):1466-78.
12. Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol. 2012;13(3):265-74.
13. Huang H, Liu YX, Zhan ZL, Liang H, Wang P, Ren XB. Different sites and prognoses of gastrointestinal stromal tumors of the stomach: report of 187 cases.World J Surg. 2010;34(7):1523-33.
14. Goh BK, Chow PK, Yap WM, Kesavan SM, Song IC, Paul PG, et al. Which is the optimal risk stratification system for surgically treated localized primary GIST? Comparison of three contemporary prognostic criteria in 171 tumors and a proposal for a modified Armed Forces Institute of Pathology risk criteria. Ann Surg Oncol. 2008;15(8):2153-63.
15. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008;39(10):1411-9.
16. Nakamura N, Yamamoto H, Yao T, Oda Y, Nishiyama K, Imamura M, et al. Prognostic significance of expressions of cell-cycle regulatory proteins in gastrointestinal stromal tumor and the relevance of the risk grade. Hum Pathol. 2005;36(7):828-37.
17. Belev B, Brèiæ I, Prejac J, Golubiæ ZA, Vrbanec D, Bo•ikov J, et al. Role of Ki-67 as a prognostic factor in gastrointestinal stromal tumors. World J Gastroenterol. 2013;19(4):523-7.
18. Artigiani Neto R, Logullo AF, Stávale JN, Lourenço LG. Ki-67 expression score correlates to survival rate in gastrointestinal stromal tumors (GIST). Acta Cir Bras. 2012;27(5):315-21.
19. Cao H, Zhang Y, Wang M, Shen DP, Sheng ZY, Ni XZ, et al. Prognostic analysis of patients with gastrointestinal stromal tumors: a single unit experience with surgical treatment of primary disease. Chin Med J. 2010;123(2):131-6.
20. Hou YY, Lu SH, Zhou Y, Qi WD, Shi Y, Tan YS,et al. Stage and histological grade of gastrointestinal stromal tumors based on a new approach are strongly associated with clinical behaviors. Mod Pathol. 2009;22(4):556-69.
21. Dei Tos AP, Wagner AJ, Modena P, Comandone A, Leyvraz S. Epithelioid soft tissue tumors. Semin Oncol. 2009;36(4):347-57.
22. Singer S, Rubin BP, Lux ML, Chen CJ, Demetri GD, Fletcher CD, et al.Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. J ClinOncol.2002;20(18):3898-905.
23. Koay MH, Goh YW, Iacopetta B, Grieu F, Segal A, Sterrett GF, et al. Gastrointestinal stromal tumours (GISTs): a clinicopathological and molecular study of 66 cases. Pathology. 2005;37(1):22-31.
24. Eisenberg BL, Pipas JM. Gastrointestinal stromal tumor—background, pathology, treatment. Hematol Oncol Clin North Am. 2012;26(6):1239-59.
25. Patel S. Navigating risk stratification systems for the management of patients with GIST. Ann Surg Oncol. 2011;18(6):1698-704.

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Endovascular treatment of popliteal artery aneurysm. Early and midterm results

Tratamento endovascular de aneurisma de artéria poplítea: resultados em curto e médio prazo

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A B S T R A C T

Objective: to evaluate the efficacy of endovascular repair of popliteal artery aneurysms on maintaining patency of the stent in the short and medium term. **Methods**: this was a retrospective, descriptive and analytical study, conducted at the Integrated Vascular Surgery Service at the Hospital da Beneficência Portuguesa de São Paulo. We followed-up 15 patients with popliteal aneurysm, totaling 18 limbs, treated with stent from May 2008 to December 2012. **Results**: the mean follow-up was 14.8 months. During this period, 61.1% of the stents were patent. The average aneurysm diameter was 2.5cm, ranging from 1.1 to 4.5cm. The average length was 5cm, ranging from 1.5 to 10 cm. In eight cases (47.1%), the lesion crossed the joint line, and in four of these occlusion of the prosthesis occurred. In 66.7% of cases, treatment was elective and only 33.3% were symptomatic patients treated on an emergency basis. The stents used were Viabahn (Gore) in 12 cases (66.7%), Fluency (Bard) in three cases (16.7%), Multilayer (Cardiatis) in two cases (11.1%) and Hemobahn (Gore) in one case (5.6%). In three cases, there was early occlusion (16.6%). During follow-up, 88.2% of patients maintained antiplatelet therapy. There was no leakage at ultrasound (endoleak). No fracture was observed in the stents. **Conclusion**: the results of this study are similar to other published series. Probably, with the development of new devices that support the mechanical characteristics found on the thighs, there will be improved performance and prognosis of endovascular restoration.

Key words: Endovascular Procedures. Popliteal Artery. Aneurysm. Peripheral Vascular Disease.

INTRODUCTION

The popliteal artery aneurysm (PAA) is the most common peripheral aneurysm, accounting for 70% of all aneurysms. Its highest incidence occurs in males. It is bilateral in 50% of cases, and is associated with abdominal aortic aneurysms in 60%. The pathogenesis is multifactorial[1-3]. Popliteal aneurysms are often asymptomatic and the diagnosis is usually made by physical examination, when palpating a wide arterial pulse in the popliteal fossa region, and possibly by imaging examination performed for other purposes. Although there is a risk of rupture, it is rare. Symptomatic patients have complaints resulting from acute ischemia, caused by thrombosis of the aneurysm, or chronic ischemia by distal embolization. Both presentations are related to a significant risk of limb loss[1-3].

Complementary tests used to confirm the diagnosis are eco-color-Doppler, angiography and CT angiography. Despite the controversy on surgical indication, it is reserved for aneurysms more than 2cm in diameter or smaller sizes, when there is a mural thrombus, which is considered a significant risk factor for thrombosis or microemboli[2,4].

Conventional surgical treatment is the exclusion of the aneurysm and in-bridge graft limb revascularization or partial or total resection of the aneurysm sac and interposition of a bypass graft. Despite the well-established conventional surgical treatment, the development of endovascular techniques has brought a new alternative to correct this disease.

The first report of endovascular popliteal artery aneurysm was from Marin *et al* in 1994[5]. This treatment modality has gained importance in recent years due to the several advantages over open surgery, such as: less surgical time, shorter hospital stay, less blood loss, less morbidity, and possibility of treatment at the same time when the aneurysm is bilateral. However, since this is an innovative therapy, the findings on mid and long term evolution are still controversial[6-10].

The objective of this study was to evaluate the efficacy of the endovascular repair of popliteal artery aneurysm on short and mid term stent patency.

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METHODS

This was a retrospective, descriptive and analytical study, conducted at the Integrated Vascular Surgery Service at the Hospital da Beneficência Portuguesa de São Paulo. We revised the medical records of 15 patients treated by endovascular technique diagnosed with popliteal aneurysm from May 2008 to December 2012. In total, 18 limbs were operated, since the aneurysm was bilateral in three patients. The study group consisted of 12 men (77.7%) and three women (23.3%), with mean age of 67.1 years.

We analyzed the following variables: presence of ischemia, elective or emergency surgery, affected limb, examination conducted for diagnosis, aneurysm relation to the knee joint line, diameter and length of the aneurysm, patency of distal arteries, type of stent used, mode of antiplatelet therapy in the postoperative period and the patency in the follow-up period.

The procedure was performed under spinal anesthesia or local anesthesia with sedation. Postoperatively, patients were kept in the intensive care unit for 12 to 24 hours.

Three types of stents were considered suitable for endovascular treatment of popliteal artery aneurysms: Hemobahn® (Gore), then replaced by Viabahn®, Fluency® (Bard) and Multilayer® (Cardiatis).

The reevaluation of the patients was made in one month, three months, six months and one year after year the procedure. After the first year, the follow-up was every six months. To assess the patency of the prostheses, we used both sonographic criteria and clinical evaluation, defined by palpation of distal pulses and maintenance of the ankle-brachial index (ABI). In this case, where there was substantial change in clinical examination, palpation loss of distal pulses or decrease in ABI, the patient underwent examination with echo-color-Doppler.

After the procedure, dual antiplatelet therapy was initiated. The antiplatelet model was 75mg clopidogrel associated with acetylsalicylic acid (ASA) 100mg, once a day, both oral drugs, during the first month. From the 30th day on, the ASA was maintained indefinitely and clopidogrel was discontinued.

We defined a 0.05 significance level (5%). All confidence intervals were built with 95% statistical confidence. We decided to use non-parametric tests due to the small sample (less than 25 subjects). In the characterization of the qualitative variables with more than two response levels, we used the equality test of two proportions. To compare the amount of patent distal arteries for evolution result, we used the Mann-Whitney test. To evaluate the result of the relationship and / or association of the evolution with antiplatelet therapy, compared with joint line and urgency, we used the chi-square test for independence.

RESULTS

The mean follow-up was 14.8 months. As a diagnostic examination, angiotomography was used in 55.6%, followed by the echo-color-Doppler in 27.8% and arteriography in 16.7%. The average aneurysms diameter was 2.5cm, ranging from 1.1 to 4.5. The average length found was 5cm, ranging from 1.5 to 10. In eight cases (47.1%), the lesion crossed the joint line. In 12 cases (66.7%) treatment was elective; six (33.3%) patients had ischemia and were treated on an emergency basis. One of the three patients with bilateral aneurysm had the two sides operated in the same surgery. In eight cases we found the three distal arteries patent; in seven cases, two; in one case, only one artery was patent; and two cases presented with occlusion of all arteries; these patients underwent emergency procedure and received thrombolysis during surgery.

The stents used were Viabahn® (Gore) in 12 cases (66.7%), Fluency® (Bard) in three (16.7%), Multilayer® (Cardiatis) in two (11.1%) and Hemobahn® (Gore) in one case (5.6%).

In the follow-up period, 88.2% of patients maintained antiplatelet therapy according to the aforementioned. There were no intraoperative complications.

Early occlusions (30 days) were found in three cases (16.6%). One patient developed acute arterial obstruction on the first day after surgery and was treated successfully with thrombolysis. This patient had been submitted to an elective procedure and received a Viabahn® (Gore) stent. The other two cases occurred in patients operated on an emergency basis: the first, undergoing treatment with Multilayer® stent, presented with occlusion in the 12th day after surgery, with moderate intensity symptoms. There was a satisfactory clinical improvement, with disappearance of symptoms at rest and residual mild intermittent claudication, for which he was treated medically; the second showed thrombosis of the Hemobahn® prosthesis and ischemia of moderate to severe intensity on day 30 postoperatively, undergoing a successful femoropopliteal bridge with polytetrafluoroethylene prosthesis.

There were four late obstructions, identified clinically and confirmed by echo-color-Doppler. A patient who had two patent distal arteries at the elective treatment, whose aneurysm did not cross the joint line and used the Viabahn® stent, evolved with obstruction of the endoprosthesis three months after the procedure. He had not used the double antiplatelet therapy as directed. The other obstruction occurred five months after the procedure on a patient who also had two patent arteries at the elective treatment, received the Viabahn® endoprosthesis, but the aneurysm crossed the joint line. There was another obstruction, six months after the procedure, on one patient submitted to elective surgery,

whose aneurysm did not cross the joint line, had three patent arteries and received Viabahn®. Another occlusion was identified 12 months after the elective procedure. He had three patent distal arteries, the aneurysm crossed the joint line, he did not use double antiplatelet therapy and had received Viabahn®.

All patients who developed late occlusion of the endoprosthesis were treated clinically, ie without the need for surgical approach, since they evolved with moderate to mild ischemia.

There was one arteriovenous fistula between the fibular vessels, identified 12 months after the procedure on a routine reassessment. The fistula was corrected by endovascular approach, with good results. We did not find any leakage (endoleak) on follow-up ultrasound. No fracture was observed in the stents. The patency assessed at the end of the 24 months period was 61.1% (Figure 1). There were two deaths, one early and one late.

Statistical analysis showed no significant association in the variables studied, especially with regard to stents' patency.

DISCUSSION

The popliteal artery aneurysm is the most common peripheral aneurysms. Unlike the abdominal aortic aneurysm, for which the main concern is the failure, the popliteal artery aneurysms is distinguished by the risk of thrombosis, with significant risk of limb loss[11,12].

While some patients experience intermittent embolization of distal arteries, causing chronic ischemia, others evolve with acute arterial obstruction, with imminent risk of limb loss. These complications justify the broader indication of surgical correction, even for small aneurysms that present thrombi[12].

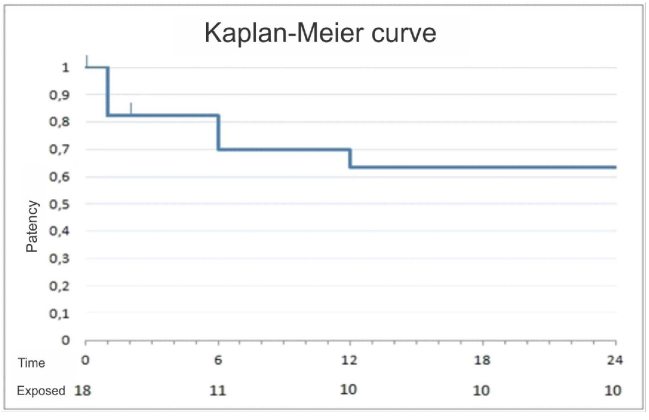

Figure 1 - *Kaplan-Meier curve for stent patency.*

Source: Medical records of patients of the Integrated Vascular Surgery, Hospital da Beneficência Portuguesa de São Paulo, São Paulo State, Brazil.

The classical treatment of popliteal artery aneurysm is the exclusion of the aneurysm with interposition of autologous or synthetic graft or bypass[13,14]. The results of several series show satisfactory results. However, the operation time is an important factor for the success of surgical treatment, and the patients operated on acute ischemia have a worse prognosis due to the involvement of distal vessels[15,16].

Although the popliteal artery can be surgically treated by posterior approach, this makes it difficult to use the internal saphenous vein as an autologous replacement. Therefore, medial approach by the Szilagyi technique is more common. However, this incision is susceptible to complications related to healing, especially when the lesion crosses the joint line and there is need of section of the muscles that attach to the medial aspect of the knee structures. Sometimes, prolonged healing and pain delays patient recovery[2,3].

As in other vascular diseases, the endovascular technique is an alternative that has been experienced in the correction of popliteal artery aneurysms. The first endovascular treatment was performed by Marin *et al.*[5], In 1994. Since then, this technique has become a feasible option for the treatment of this disease. With the growing experience and advances in the endovascular technique, this procedure is no longer exceptional and went on to compete with conventional surgery for the preference of surgeons[6-9].

Among the advantages of the endovascular treatment of the popliteal artery aneurysm, there are the following: minimally invasive procedure, requiring only small incisions or catheterization by the Seldinger technique; reduced operative time; less postoperative morbidity; and early mobilization, thus shortening hospital stay[5,7,15].

Despite the promising scenario, there are still many concerns about problems observed in the short and long term. These problems are the result of the variables that were considered in this study.

Considering the pathophysiology of silent microembolization quoted above, the evaluation of the distal arterial territory is deemed an important topic for the durability of the endovascular repair, because the greater the presence of patent distal arteries, the lower the chance of stent occlusion[17]. Garg *et al.*[18] reported that patients with only one patent distal artery had a higher incidence of thrombosis than those with two or more patent vessels. In our study we observed that in eight cases three patent arteries were found and in seven cases, there were two patent arteries. In one case, a single artery was patent and, in two cases, all three arteries were occluded, addressed in urgency. Statistical analysis did not show significance of the success of the procedure in relation to these findings.

The femoropopliteal axis is a region subject to continuous stress and twisting forces that can compromise the performance and durability of stents. These

characteristics may determine kinking of the graft and stent fracture, and consequently its closure. Tiellui *et al.*[19] studied 64 cases of endovascular repair of popliteal artery aneurysm and identified 13 (16.7%) cases of fracture. They observed that most of these fractures were related to the treatment of aneurysms crossing the joint line. Other possible complicating factors are the placement of multiple stents and the treatment of younger patients, since they are subject to more intense mobility, emphasizing the role of physical and mechanical stress. In our study, we did not identify any cases of stent fracture; however, there was no active search protocol by radiographs of the treated region. In eight cases the correction exceeded the joint line, of which four (50%) developed stent graft occlusion during follow-up. However, due to our modest sample, this finding was not statistically significant. Nevertheless, this finding corroborates the impression that the extension of the aneurysm beyond the joint line is a problem that must be considered when opting for the endovascular technique[6,19].

In our study, there was no leakage (endoleak). In a retrospective study, Midy *et al.*[6] found six endoleaks (10.5%) in 57 aneurysms corrected by endovascular approach in 50 patients, one being of type I, two type II and three type III. All patients were instructed on the use of dual antiplatelet therapy at the time of hospital discharge. Despite repeated requests, the guidance was not met in 11.8% of patients for several reasons. With the work of Tielliu *et al.*[19], it became evident that the antiplatelet therapy is of fundamental importance in the upper behavior of stents with respect to patency. Particularly in our study, there was no statistically significant difference between patients who adhered properly or not, to antiplatelet therapy.

There was no amputation, regardless of patients being operated in elective mode or in emergency situations. Lowell *et al.*[12] mention an amputation rate of 8.7%, more frequent in patients operated on during acute arterial obstruction. Although one cannot say from the obtained data, it is believed that shortening the time between diagnosis and treatment should influence the results of patency associated with intraoperative fibrinolysis, important to restore patency of the distal bed. Our study observed three cases in need of intra-arterial fibrinolysis by catheter, since these patients developed acute arterial occlusion, two in urgency and in the immediate postoperative period. One of these patients died during the early follow-up. Despite fasciotomies performed and the clinical support measures adopted, the patient developed severe metabolic changes, probably determined by reperfusion syndrome. The death occurred two months after the procedure due to an abdominal focus of sepsis, unrelated to the procedure.

In our study there were three early occlusions, but without leading to limb loss. It is possible that these occurrences are related to technical failures of the endovascular procedures, which are influenced by the material and the indication. It is important to monitor these patients for early identification of failure and rapprochement. One patient underwent successfully fibrinolysis in the first postoperative day, and the other underwent a femoropopliteal bypass. The third patient recovered successfully, although the occlusion involved the distal arteries. In this specific case, the patient was discharged two days after the procedure, with all distal pulses present and returned with occlusion one week later. The use of Multilayer® (a stent of greater rigidity) across the joint line may have affected this outcome. Tielliu *et al.*[7] reported 12 patients (21%) who developed occlusion, and none of them required femoropopliteal bypass or amputation, five of them occluded within the first month of follow-up. According to the authors, these early occlusions occurred before it was established a strict protocol of dual antiplatelet therapy[7], which may have influenced results.

In our study, 61.1% of the grafts were patent in two years, results comparable to those found in the literature, with 65% of patent prostheses[7]. Among the studies that describe conventional surgery[12,15], patency in five years ranges from 82 to 92%, with even better results in elective patients.

The failure to show in this study the importance of some variables recognized for their impact on the results is due to the small number of cases, which did not allow a more detailed statistical analysis. We believe that the incorporation of the endovascular technique is important and should be encouraged, taking care of proper patients' selection, the correct choice of material to be used, and the use of antiplatelet therapy. However, conventional surgery must not be abandoned and certainly will still be the best choice for many patients. It can be said that this treatment produces satisfactory results, despite the published studies accusing a lower patency rate when compared with conventional treatment.

The results of this study are similar to other published series. There is no denying the allure of endovascular treatment, particularly with regard to more comfortable postoperative recovery. However, the placement of a stent in that location is a challenging measure, both from a technical point of view and from a careful evaluation of the results in the medium and long term. For this, it is necessary to follow a strict protocol for the early identification of complications and to monitor the attitudes of patients, especially in relation to the accuracy of antiplatelet therapy.

It is believed that with the development of new devices that support the mechanical characteristics found on the popliteal region, there will be improvement in the performance and outcome of endovascular restoration in the near future.

R E S U M O

Objetivo: *avaliar a eficácia da correção endovascular do aneurisma de artéria poplítea quanto à manutenção da perviedade da endoprótese, em curto e médio prazo.* ***Métodos:*** *trata-se de estudo retrospectivo, descritivo e analítico, realizado no Serviço de Cirurgia Vascular Integrada do Hospital Beneficência Portuguesa de São Paulo. Foram acompanhados 15 pacientes com aneurisma de poplítea totalizando 18 membros tratados com endoprótese, no período de maio de 2008 a dezembro 2012.* ***Resultados:*** *o tempo médio de seguimento foi 14,8 meses. Nesse período, 61,1% das endopróteses estavam pérvias. A média de diâmetro dos aneurismas foi 2,5cm, variando de 1,1 a 4,5cm. A extensão média encontrada foi 5cm, variando de 1,5 a 10cm. Em oito casos (47,1%), a lesão cruzava a linha articular e, em quatro destes, ocorreu oclusão da prótese. Em 66,7% dos casos, o tratamento foi eletivo e apenas 33,3% eram pacientes sintomáticos, tratados em caráter de urgência. As endopróteses usadas foram a Viabahn (Gore) em 12 casos (66,7%), Fluency (Bard) em três casos (16,7%), Multilayer (Cardiatis) em dois casos (11,1%) e Hemobahn (Gore) em apenas um caso (5,6%). Em três casos, ocorreu oclusão precoce (16,6%). Durante o seguimento, 88,2% dos pacientes mantiveram a antiagregação plaquetária. No seguimento ultrassonográfico não foi observado nenhum vazamento (endoleak). Não foi verificada nenhuma fratura nos Stents.* ***Conclusão:*** *Os resultados obtidos nesse estudo são semelhantes aos de outras séries publicadas. Provavelmente com o desenvolvimento de novos dispositivos que suportem as particularidades mecânicas encontradas na região poplítea, haverá como melhorar o desempenho e prognóstico da restauração endovascular.*

Descritores*: Procedimentos Endovasculares. Artéria Poplítea. Aneurisma. Doenças Vasculares Periféricas.*

REFERENCES

1. Dawson I, Sie RB, van Bockel JH. Atherosclerotic popliteal aneurysm. Br J Surg. 1997;84(3):293-9.
2. Brito CJ, Schulze GC, Loureiro E. Aneurismas de membros inferiores. In: Brito CJ, editor. Cirurgia Vascular, cirurgia endovascular e angiologia. 2ª Ed. Rio de Janeiro: Revinter; 2008. p.609-27.
3. Szilagyi DE, Schwartz RL, Reddy DJ. Popliteal arterial aneurysms. Their natural history and management. Arch Surg. 1981;116(5):724-8.
4. Harder Y, Notter H, Nussbaumer P, Leiser A, Canova C, Furrer M. Popliteal aneurysm: diagnostic workup and results of surgical treatment. World J Surg. 2003;27(7):788-92.
5. Marin ML, Veith FJ, Panetta TF, Cynamon J, Bakal CW, Suggs WD, et al. Transfemoral endoluminal stented graft repair of a popliteal artery aneurysm. J Vasc Surg. 1994;19(4):754-7.
6. Midy D, Berard X, Ferdani M, Alric P, Brizzi V, Ducasse E, et al. A retrospective multicenter study of endovascular treatment of popliteal artery aneurysm. J Vasc Surg. 2010;51(4):850-6.
7. Tielliu IF, Verhoeven EL, Zeebregts CJ, Prins TR, Span MM, van den Dungen JJ. Endovascular treatment of popliteal artery aneurysms: results of a prospective cohort study. J Vasc Surg. 2005;41(4):561-7.
8. Thomazinho F, Silvestre JMS, Sardinha WE, Motta F, Perozin IS, Morais Filho D. Tratamento endovascular de aneurisma de artéria poplítea. J vasc bras. 2008;7(1):38-43.
9. Moore RD, Hill AB. Open versus endovascular repair of popliteal artery aneurysm. J Vasc Surg. 2010;51(1):271-6.
10. Mohan IV, Bray PJ, Harris JP, May J, Stephen MS, Bray AE, et al. Endovascular poplíteal aneurysm repair: are the results comparable to open surgery? Eur J Vasc Endovasc Surg. 2006;32(2):149-54.
11. Dawson I, Sie R, van Baalen JM, van Bockel JH. Asymptomatic popliteal aneurysm: elective operation versus conservative follow-up. Br J Surg. 1994;81(10):1504-7.
12. Lowell RC, Gloviczki P, Hallett JW Jr, Naessens JM, Maus TP, Cherry KJ Jr, et al. Popliteal artery aneurysms: the risk of nonoperative management. Ann Vasc Surg. 1994;8(1):14-23.
13. Edwards WS. Exclusion and saphenous vein bypass of popliteal aneurysms. Surg Gynecol Obstet. 1969;128(4):829-30.
14. Sarcina A, Bellosta R, Luzzani L, Agrifoglio G. Surgical treatment of popliteal artery aneurysm: a 20 year experience. J Cardiovasc Surg. 1997;38(4):347-54.
15. Aulivola B, Hamdan AD, Hile CN, Sheahan MG, Skillman JJ, Campbell DR, et al. Popliteal artery aneurysms: a comparison of outcomes in elective versus emergent repair. J Vasc Surg. 2004;39(6):1171-7.
16. Kauffman P, Puech-Leão P. Tratamento cirúrgico do aneurisma da artéria poplítea: experiência de 32 anos. J vasc bras. 2002;1(1):5-14.
17. Borowicz MR, Robison JG, Elliott BM, Brothers TE, Robinson CK. Occlusive disease associated with popliteal aneurysms: impact on long term graft patency. J Cardiovasc Surg. 1998;39(2):137-40.
18. Garg K, Rockman CB, Kim BJ, Jacobowitz GR, Maldonado TS, Adelman MA, et al. Outcome of endovascular repair of popliteal artery aneurysm using the Viabahn endoprothesis. J Vasc Surg. 2012;55(6):1647-53.
19. Tielliu IF, Verhoeven EL, Prins TR, Post WJ, Hulsebos RG, van den Dungen JJ. Treatment of popliteal artery aneurysms with the Hemobahn stent-graft. J Endovasc Ther. 2003;10(1):111-6.

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Preliminary study of coconut water for graft tissues preservation in transplantation

Estudo preliminar da água de coco para preservação de enxertos teciduais em transplante

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A B S T R A C T

Objective: to verify the effectiveness of coconut water in preserving tissues for transplant. **Methods:** Fifty male Wistar rats were randomly distributed in five groups, according to the following preservation solutions for tissue grafts: Group 1: Lactated Ringer; Group 2: Belzer solution; Group 3: mature coconut water; Group 4: green coconut water; Group 5: modified coconut water. In Group 5, the green coconut water has been modified like the Belzer solution. From each animal we harvasted the spleen, ovaries and skin of the back segment. These tissues were preserved for six hours in one of the solutions. Then, the grafts were reimplanted. The recovery of the function of the implanted tissues was assessed 90 days after surgery, by splenic scintigraphy and blood exame. The implanted tissues were collected for histopathological examination. **Results:** The serum levels did not differ among groups, except for the animals in Group 5, which showed higher levels of IgG than Group 1, and differences in relation to FSH between groups 1 and 2 ($p < 0.001$), 4 and 2 ($p = 0.03$) and 5 and 2 ($p = 0.01$). The splenic scintigraphy was not different between groups. The ovarian tissue was better preserved in mature coconut water ($p < 0.007$). **Conclusion:**the coconut water-based solutions preserves spleen, ovary, and rat skin for six hours, maintaining their normal function.

Key words: Coconut, Organ preservation solutions, Autogenous transplantation, Ovary, Spleen, Skin.

INTRODUCTION

Methods to preserve organs and tissues for transplantation are associated with the suppression of metabolism by hypothermia. The blood is replaced by a preservation solution to become tolerant to the organ hypothermia. The composition of preservation solutions is critical to organ tolerance stored in hipotermia[1-4]. The introduction of the solution of the University of Wisconsin, or Belzer solution, at the end of the 1980s, was a major breakthrough in organ preservation [2].

Studies with gametes of various animal species have shown that coconut water (endosperm of Cocosnucifera L.) can be successfully used in the preservation of pre-antral follicles of sheep and goats, and semen of sheep, pigs and humans. This solution was also tested as a means for storage and maturation of immature oocytes from bovine ovaries and as culture medium for mouse and bovine embryos [3].

The objective of this study was to verify the effectiveness of coconut water in the preservation of tissue grafts, aiming atautografting, considering the high cost of the preservation solutions in use.

METHODS

This study was conducted in accordance with the recommendations of the International Standards for Animal Protection and the Brazilian Code of Animal Experimentation (1988), "Ethical Principles in Animal Experimentation", according to the Federal Law 11.794, of October 8th, 2008 and was aproved by the Ethics Committee on Animal Experimentation at UFMG under No 220/2009 and the Department of Education, Research and Extension of the Clinics Hospitalof the Faculty of Medicine, UFMG, memorandum 054/11.

Fifty three-month-old Wistar rats weighing between 200g and 250g were placed in appropriate cages, five animals per cage, at room temperature between 20°C and 28°C (mean 25°C), natural humidity and light-darknesscycles of 12h, with natural ventilation by

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mechanical exhaustion. The animals had free access to water and standard laboratory rodent chow (Labina®, Purina, Brazil) during the pre- and postoperative.

After 15 days of adaptation, the rats were randomized into five groups of ten animals each, following the guidance of statistical significance. The randomization was done by the distribution of animals in separate cages, without regard to any characteristic. All animals were from litters of the same race and origin, gathered in one group with similar ages and weights. The groups were determined by the preservation solution used: Group 1- Ringer lactate; Group 2- Belzer solution (ViaSpan, Bristol-Myers Squibb Pharmaceutical, Dublin.); Group 3- Mature coconut water; Group 4- green coconut water; and Group 5- modified coconut water.

Coconuts were obtained in the local market on the day of use; they were whole, with eight to 12 months of age. Parts of the mesocarp and endocarp were removed to expose the endosperm without injure it. After antisepsis of its surface with povidone-iodine containing 1% active iodine, (polvidona 10%, Rioquímica, Sao Josédo Rio Preto, Sao Paulo), the endosperm was cut with sterile scalpel blade and the coconut water was aspirated with a 14G x 22 peripheral catheter" (BB Braun®, Melsungten, Germany) and a 20ml plastic hypodermic syringe (BD Plastipak®, Curitiba, PR, Brazil) and transferred to a metal tank. The sterility of the coconut water extracted was confirmed by sampling with inoculation into Petri dishes with bacterial culture medium.

The modified coconut water solution was prepared in the Analytical Pharmaceutical Development Center at UFMG, based on the electrolyte composition of the green coconut water. Changes were made in its electrolyte composition to make it similar to the Belzer solution[1]. During the procedure, due to the precipitation of magnesium phosphate salt, it was necessary to reduce the solution pH to 7 by addition of hydrochloric acid. The final concentration of the modified solution is shown in relation to other preservation solutions and to mature and green coconut water, whose electrolyte compositions were measured by sampling and used in this study (Table 1).

The weight of the animals was checked immediately before surgery. The day of the operation was considered the first day of the experiment. Under general

Table 1 - Electrolyte composition and other components of tissue preservation solutions and green, mature and modified coconut waters (mg/L)[4].

	RL	ER	rER	UW	Celsior	LPD	HTK	CV	CM	M
pH	7,4	7,2	–	7,4	7,3	7,4	7,1	6,9	6,9	7,0
pH	7.4	7.2	-	7.4	7.3	7.4	7.1	6.9	6.9	7.0
Na*	234	180	2070	540	180	3024	27	252.08	466.67	540
K*	7.2	2070	180	2250	27	72	16.2	933.33	3000	2250
Mg^{2+}	-	-	-	90	23.4	-	-	66.26	237.2	90
Cl^{-}	196.2	270	270	-	74.7	1854	-	-	-	2569
Cálcio	5.4	-	-	-	0.26	-	-	-	-	-
SO_4^{2-}	-	-	90	-	-	-	-	<1	<1	90
PO_4^{3-}	-	1035	1035	450	-	660.6	0	238.7	1324.58	450
HCO_3^{-}	-	180	180	-	-	-	-	-	-	-
Glucose	-	0.35	.35	-	-	-	-	NM	583.33	NM
Lactobionate	-	-	-	180	80	-	-	-	-	-
Glutathione	-	-	-	5.4	3	-	-	-	-	-
Raffinose	-	-	-	54	-	-	-	-	-	-
Carbohydrate hydroxyethyl	-	-	0.5	-	-	-	-	-	-	-
Adenosine	-	-	-	9	-	-	-	-	-	-
Histidine	-	-	-	-	30	-	324	-	-	-
Tryptophan	-	-	-	-	-	-	3.6	-	-	-
ketoglutarate	-	-	-	-	-	-	1.8	-	-	-
Mannitol	-	-	-	-	60	-	54	-	-	-
Glutamate	-	-	-	-	2	-	-	-	-	-
Lactate	50.4	-	-	-	-	-	-	-	-	-
Osmolality (mOsm/L)	272	400	380	320	360	285	310	>300	>300	NM

ER-Euro Solution-Collins, rER-Euro-Collins Solution with little potassium, UW-Wisconsin/Belzersolution, LPD – low potassium dextran Solution/ Toronto, RL-Ringer lactate, HTK-Histidine-tryptophan solution-ketoglutarate, CV-green coconut water, CM-mature coconut water, M – modified coconut water, In^{+} -K^{+} sodium – potassium, Mg^{2+} -magnesium, Cl^{-} Chlorine-, SO_4^{-2}-sulfate, PO_4^{-3}-Phosphate, HCO_3^{-}bicarbonate, NM – not measurable by Hidrocepe lab kit, mOsmol/L – miliosmoles per litre.

anesthesia with intramuscular infusion of 10% ketamine hydrochloride (Agener Union, Embu, São Paulo a 60mg/kg) associated with2% xylazine(Agener Union, Embu, São Paulo - 8mg/kg). We performed trichotomy of the abdominal wall and dorsal interscapular region, followed by antisepsis of the abdominal wall and back, with polyvinylpyrrolidone solution containing 1% active iodine, (polvidona 10%, Rioquímica, São José do Rio Preto, São Paulo).

Through a laparotomy from the xiphoid process to the pelvic region, the spleen and both ovaries were removed after ligation and section of their vasculars pedicles. The spleen was cut into four segments, with a scalpel blade. These organs and tissues were immediately immersed in the preservation solution corresponding to each group and kept at 4°C for six hours. After closing the abdomen, a total skin segment of the animal's back was removed and immersed in the same preservation solution that already contained the spleen and ovaries. The donor site wound edges were approximated with 4-0 nylon sutures.

During six hours, with the organs kept in the preservation solution, the rats were kept in separate cages without food or water, but with free movement. After this period, the rats were anesthetized again, according to the technique described. We then withdrew the abdominal suture, opening the cavity. The four splenic fragments were sutured side by side on the greater omentum, with 4-0 nylon[5]. All procedures were performed under sterile conditions[6]. Both ovaries were fixed with 4-0 nylon stitches in the right pelvic fat[7]. The abdominal cavity was closed in two layers with continuous suture using 3-0 silk suture. After the abdominal operation, the cutaneous wound of the back was opened and the skin flap taken from the preservation solution was fixed on the superficial fascia of the wound bed using 4-0 nylon[8].

Within three months of follow-up, five animals were evaluated daily. At the end of each follow-up period, all rats were weighed and prepared for the study of grafts functionality. The animals were anesthetized again according to the aforementioned technique.

The phagocytic activity of autogenous splenic grafts was qualitatively and quantitatively assessed by scintigraphy, using as contrast the radiopharmaceutical phytate sodium labeled with technetium-99m (99Tcm-sodium phytate) 90 days after the operation. Then, after the collection of blood and death of animals, we removed three fragments of the liver left lobe and the splenic grafts to measure their radiation in a gamma counter. We calculated the radiation emitted by the splenic implants from the average measurements of the three tissue specimens. This abstraction represents the amount of colloid phagocytosed by the phagocytic mononuclear tissues of liver and spleen.

We collected Blood samples from the abdominal vena cava for measurement of red blood cells, hemoglobin, hematocrit, white blood cells, IgM, IgG, FSH and estradiol. The removal of blood caused the rat to died of hypovolemia.

After blood collection, we harvested the splenic fragments of the omentum, ovaries implanted in the pelvis and skin graft. The macroscopic appearance of the tissues was assessed and they were then immersed in a 4% formaldehyde solution. Samples were collected for histological processing and stained with hematoxylin and eosin for examination by optical microscopy, by a single pathologist, who was unaware of the group to which the tissue belonged. The analysis was qualitative for the splenic tissue, ovarian one and skin, the values varying from one to 5, according to the presentation of the tissue structures of these organs in comparison with the morphological structures of histologically normal skin, spleen and ovaries.

Tests used were: parametric ANOVA, non-parametric Kruskal-Wallis, the multiple comparison Tukey test, the non-parametric test for multiple comparisons, the Levene variance homogeneity test. The samples and the power of the test were obtained through the PASS software version 11. Differences were considered significant when corresponding to $p < 0.05$.

RESULTS

The animals remained healthy, gaining weight during the postoperative period until their death on the 90th day of autogenous implants. Behavioral changes were not noticed.

There was no difference in the radiotracer uptake by splenic grafts of the five groups. Serum dosages of leukocytes, erythrocytes, hemoglobin, hematocrit, IgM and estradiol showed no difference among groups regarding the tested parameters.

The group whose tissues were preserved in modified coconut solution displayed higher levels of IgG compared with the group whose preservation was in Ringer lactate ($p = 0.03$).

The animals whose tissues were preserved in Ringer's lactate showed lower values of FSH that the group with conservation in Belzer, $p < 0.001$. The group whose conservation occurred in coconut solution showed lower FSH levels than the group with conservation in Belzer solution, p-value = 0.03. In the group whose tissues were stored in modified coconut solution FSH levels were lower than the group with conservation in Belzer solution, p-value = 0.01.

The splenic fragments reduced their size and were attached to the liver edge. Ovarian fragments were located in the pelvic fat, also reduced in size.

Skin implants evolved with areas of necrosis during the first seven days. Then granulated wound areas formed and subsequently, hardly visible scars. The microscopic study of cutaneous implants found no difference between the preservation solutions studied. Microscopic

evaluation of the splenic implants also found no difference between the preservation solutions studied.

At microscopic analysis of the ovarian tissue, we found the preservation in mature coconut water to be more effective than the modified coconut water (p = 0.01) and Belzer (p = 0.007) (Figure 1).

DISCUSSION

The choice of tissues included in this study was due to their ease of mobilization and for being part of lines of research initiated in 1983[9-12].

The scintigraphic images recorded the radiotracer uptake by splenic implants with difficulty due to the overlapping of liver image[13]. However, the emission of radiation dosages by implanted spleen fragments left no doubt that 12 weeks were sufficient for their phagocytic functional recovery[13,14]. There was no difference between the conservation of liquids studied in relation to the evaluation of the function of the splenic implants by scintigraphy, which is a more sensitive method to indicate uptake by spleen cells than the blood tests[14].

The higher IgG levels observed in conservation with modifiedcoconut solution than the conservation with Ringer solution can mean a better splenic preservation with that solution, perhaps because of its chemical composition.

In other studies, the coconut water solution was as effective as the Braun-Collins solution in the preservation of preantral follicles in goats at 4°C and higher temperatures. In addition, it proved to be effective in the preservation of sperm, oocyte maturation and embryo

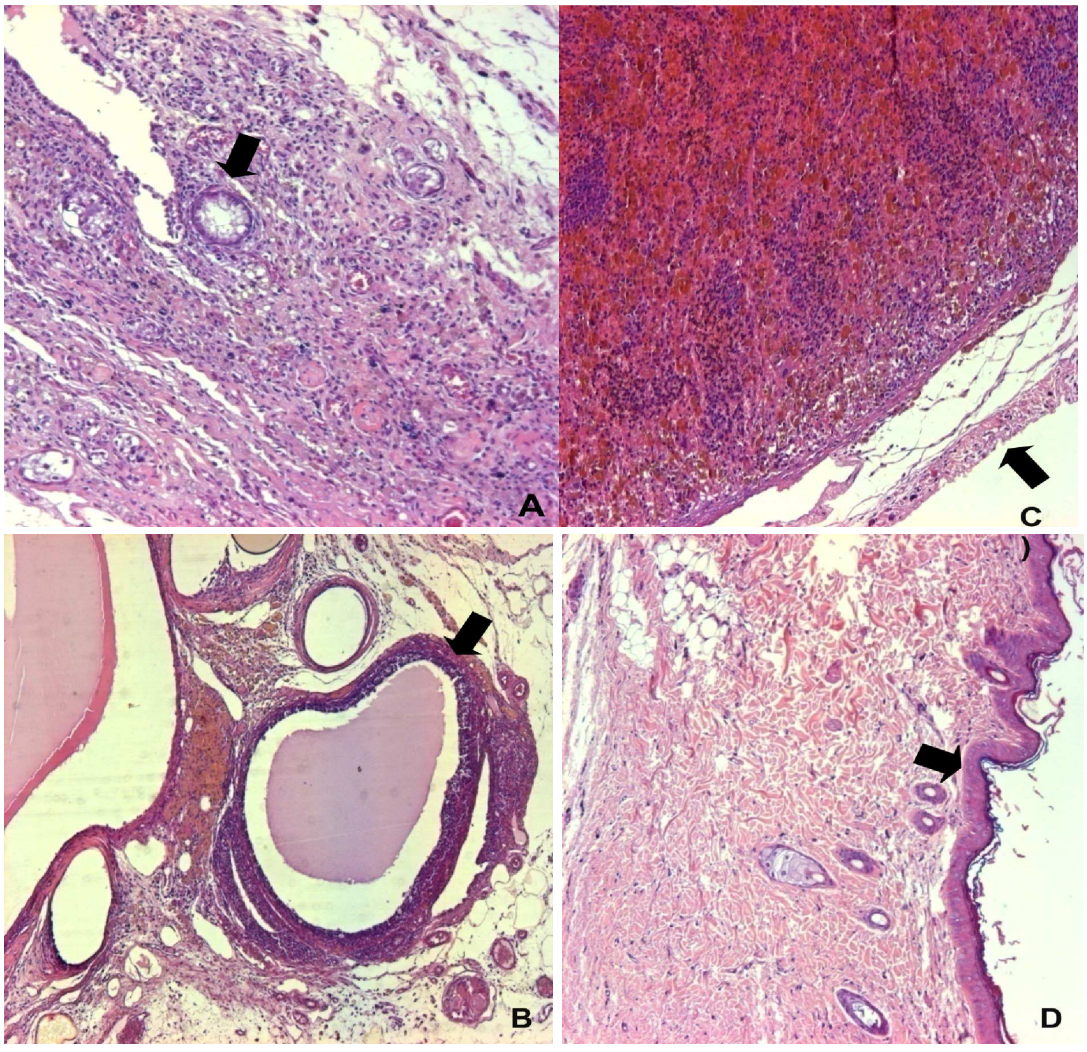

Figure 1 - *Histological sections studied preserved in mature coconut water. (HE, 100x).*

A) ovarian parenchyma with fibrous tissue and inflammation, with a preserved ovarian follicle (arrow); B) ovarian tissue with follicular cysts indicating tissue degeneration (arrow); C) splenic hemorrhagic tissue with lymphatic follicles, sinusoids capillaries and intact splenic capsule (arrow); D) skin tissue with epidermis (arrow) and dermis with hair follicles and fibrous connective tissue.

culture[15]. In this study, the coconut water solutions were as effective as the other solutions in the preservation of splenic implants, ovarian and skin. The difficulty in relating the difference between the tissue preservation solution in the study could be due to the short preservation period (six hours) sufficient to determine the maximum time conservative capacity of each solution.

Other authors have reported that the coconut water can be as effective as saline for ovarian follicle preservation under certain conditions[16]. This information would justify the difficulty to highlight differences between the preservation solutions such as Ringer lactate and Belzer. Moreover, this period is sufficient in practice to transport the donor tissue to its implantation in the recipient.

The 3-indole-acetic acid (IAA), present in coconut water, the main plant hormone, can bind to animal growth factors of ovarian tissue and increase its action[15]. However, the present study showed no benefits of coconut-based solutions in the preservation of tissues, which could be due to the presence of substances such as IAA, except for better histological ovarian preservation in mature coconut solution regarding modified coconut solutions and Belzer.

The modified coconut electrolytic solution had a composition similar to the Belzer solution and was subjected to a physico-chemical process of sterilization and pH change, which may have altered the natural properties of the coconut water[17], justifying the inadequate preservation of ovarian tissue, as well as by Belzer solution. The highest levels of FSH may suggest a lower effectiveness of the Belzer solution for preservation of ovarian function.

One of the main properties of coconut water is attributed to its antioxidant activity, on the ascorbic acid and glutathione content[3]. The antioxidant activity necessary for the preservation solutions[18] decreases by exposing the coconut water to heat. The highest concentration of potassium in the Belzer and modified coconut solutions could be a factor in explaining the worst preservation capacity, because of the ovarian tissue characteristics[19]. However, the mature coconut water, which has high levels of potassium, was as effective as other substances in the preservation of the implants in the study, with a tendency to better histological preservation of the skin and ovaries.

The absence of glucose in the Belzer solution, the presence of inert substrates as responsible for the osmotic concentration and its high viscosity[20] may have impaired the preservation of ovarian tissue and perhaps the skin tissue. Other authors observed that preserving substances enriched with nutrient showed better preservation of some tissues such as liver, pancreas and small intestine compared with the Belzer solution[21].

Coconut water was as effective as the other solutions in the preservation of skin implants. Some change in the chemical composition of coconut water with its aging, sugar changes or other microelements, and reduced enzyme activity, may explain the better preservation of the implants in this solution[22].

This study showed that the coconut water-based solutions were as effective as the other solutions in the preservation of the spleen, ovary and skin of rats for six hours. There is a need to strengthen the findings of this study with studies of other tissues and organs, as well as a greater range of animal species. There is also the need to establish the maximum amount of tissue preservation in chilled coconut water. The coconut water solutions preserved tissue vitality of the spleen, ovary and skin of rats for six hours, while maintaining their function. According to the progress of works to search for a preservation solution, this work could lead to a new, useful patent for Brazil.

R E S U M O

Objetivo: *verificar a eficácia da água de coco na preservação de tecidos para transplante.* ***Métodos:*** *cinquenta ratas* Wistar *foram distribuídas aleatoriamente em cinco grupos, de acordo com as seguintes soluções de preservação para enxertos teciduais: Grupo 1- Ringer lactato, Grupo 2- Solução de Belzer, Grupo 3- Água de coco maduro, Grupo 4- Água de coco verde, Grupo 5- Água de coco modificada. No Grupo 5, a água de coco verde foi modificada à semelhança da solução de Belzer. De cada animal, retirou-se o baço, os ovários e um segmento de pele do dorso. Esses tecidos foram preservados durante seis horas em uma das soluções. Em seguida, os enxertos foram reimplantados. A recuperação da função dos tecidos implantados foi avaliada 90 dias após a cirurgia, por meio de cintilografia esplênica, exames de sangue. Os tecidos implantados foram coletados para estudo anatomopatológico.* ***Resultados:*** *as dosagens séricas não apresentaram diferença entre os cinco grupos, exceto pelos animais do Grupo 5, que apresentaram valores mais elevados de IgG do que o Grupo 1,e pelas diferenças em relação ao FSH entre os grupos 1 e 2 (p<0,001), 4 e 2 (p=0,03), 5 e 2 (p=0,01). A cintilografia esplênica não foi diferente entre os grupos. O tecido ovariano foi melhor preservado em água de coco maduro (p<0,007).* ***Conclusão:*** *as soluções à base de água de coco preservam baço, ovário e pele de rato durante seis horas, mantendo sua função normal.*

Descritores: *Cocos, Soluções para preservação de órgãos, Transplante autógeno, Baço, Pele, Ovário.*

REFERENCES

1. Southard JH, Belzer FO. Organ preservation. AnnuRev Med.1995;46:235-47.
2. Todo S, Podesta L, Ueda Y, Imventarza O, Casavilla A, Oks A, et al. Comparison of UW with other solutions for liver preservation in dogs. Clin Transplant.1989;3(5):253-9.

3. Silva AE, Cavalcante LF, Rodrigues BA, Rodrigues JL. The influence of powdered coconut water (ACP-318®) in in vitro maturation of canine oocytes. Reprod Domest Anim.2010;45(6):1042-6.
4. Mühlbacher F, Langer F, Mittermayer C. Preservations solutions for transplantation. Transplant Proc.1999;31(5):2069-70.
5. Braga AA, Malagó R, Anacleto TP,Silva CR, Andreollo NA, Fernandes FL. Histological aspects of autologous transplantation of different fragments of the spleen in rats. Acta Cir Bras.2012;27(12):880-4.
6. Marques RG, Caetano CE, Diestel CF, Lima E, Portela MC,Oliveira AV, et al. Critical mass of splenic autotransplant needed for the development of phagocytic activity in rats. Clin Exp Immunol.2012;170(1):77-85.
7. Díaz-García C, Milenkovic M, Groth K,Dahm-Kähler P, Olausson M, Brännström M. Ovarian cortex transplantation in the baboon: comparison of four different intra-abdominal transplantation sites. Hum Reprod.2011;26(12):3303-11.
8. Kamran A, Javad FM, Sahram F, Jaber MS. A comparison of survival and secondary contraction in expanded versus conventional full-thickness skin grafts: an experimental study in rats. Eplasty.2012,12:e20.
9. Petroianu A. Esplenectomia subtotal e anastomose esplenorrenal proximal para o tratamento da hipertensão portal. Rev bras cir.1983;73(2):101-4.
10. Vasconcellos LS, Alberti LR, Petroianu A, Nunes MB. Viabilidade e função endócrina de auto-implantes ovarianos com drenagem pela veia porta ou cava. Reprod clim. 2001;16(4):259-63.
11. Petroianu A, Alberti LR, Vasconcellos LS. Allogeneic and autologous ovarian orthotopic transplantation without a vascular pedicle: morphological, endocrinologic and natural pregnancy assessment. J Obstet Gynaecol Res.2007;33(1):24-31.
12. Alberti LR, Vasconcellos LS, PetroianuA. Avaliação endócrina e morfológica de tranplante autógeno de ovários íntegros e fatiados em coelhas. Rev bras anal clin.2007;39(1):63-6.
13. Sajtos E, Balint A, Brath E,Nemeth N, Peto K, Kovacs J, Galuska L, et al. Long-term following-up of viability of spleen autotransplants in the Beagle canine model. Acta Cir Bras.2012;27(2):95-101.
14. Di Carlo I, Pulvirenti E, Toro A. A new technique for spleen autotransplantation. Surg Innov.2012;19(2):156-61.
15. Lima GL, Costa LL, Cavalcanti DM,Rodrigues CM, Freire FA, Fontenele-Neto JD, et al. Short-term storage of canine preantral ovarian follicles using a powdered coconut water (ACP)-based medium. Theriogenology.2010;74(1):146-52.
16. Costa SHF, Santos RR, Ferreira MAL,Machado VP, Rodrigues APR, Ohashi OM, et al. Preservation of goat preantral follicules in saline or coconut water solution. Bras J vet Res anim Sci.2002;39(6):324-30.
17. Awua AK, Doe ED, Agyare R. Exploring the influence of sterilisation and storage on some physicochemical properties of coconut (Cocos nucifera L.) water. BMC Res Notes.2011;4:451.
18. Doliñska B, Ostró¿ka-Cieœlik A, Caban A, Rimantas K, Leszczyñska L, Ryszka F. Influence of trace elements on stabilization of aqueous solutions of ascorbic acid.Biol Trace Elem Res.2012;150(1-3):509-12.
19. Arnaoutakis GJ, Allen JG, Merlo CA, Baumgartner WA, Conte JV, Shah AS.Low potassium dextran is superior to University of Wisconsin solution in high-risk lung transplant recipients. J Heart Lung Transplant. 2010;29(12):1380-7.
20. Guibert EE, Petrenko AY, Balaban CL, Somov AY, Rodriguez JV, Fuller BJ.Organ preservation: current concepts and new strategies for the next decade. Transfus Med Hemother.2011;38(2):125-42.
21. Kimura Y, Okitsu T, Xibao L, Teramae H, Okonogi A, Toyoda K, et al.Improved hypothermic short-term storage of isolated mouse islets by adding serum to preservation solutions. Islets.2013,5(1):45-52.
22. Vigliar R, Sdepanian VL, Fagundes-Neto U. Perfil bioquímico da água de coco de coqueiros de região não litorânea. J Pediatr.2006;82(4):308-12.

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Use of the amniotic membrane to cover the peritoneal cavity in the reconstruction of the abdominal wall with polypropylene mesh in rats

Uso da membrana amniótica como cobertura da cavidade abdominal na reconstrução da parede com tela de polipropileno em ratos

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ABSTRACT

Objective: to evaluate the efficacy of the amniotic membrane used with polypropylene mesh against the formation of adhesions and its influence on healing. **Methods**: twenty five female Wistar rats were anesthetized for creating a parietal defect in the anterior abdominal wall. Its correction was made with polypropylene mesh alone and associated with amniotic membrane. In the control group (n=11), the screen was inserted alone. In group A (n=7) we interposed the amniotic membrane between the screen and the abdominal wall. In group B, the amniotic membrane was placed on the mesh, covering it. After seven days, the animals were euthanized for macroscopic and microscopic evaluation of healing. **Results**: adhesions were observed in all animals except one in the control group. Severe inflammation was observed in all animals in groups A and B and in three of the control group, with significant difference between them (A and B with p=0.01). Pronounced angiogenic activity was noted in one animal in the control group, six in group A and four in group B, with a significant difference between the control group and group A (p=0.002) and group B (p=0.05). The scar collagen was predominantly mature, except in five animals of the control group, with significant difference between the control group and group A (p=0.05) and group B (p=0.05). **Conclusion**: The amniotic membrane did not alter the formation of adhesions in the first postoperative week. There were also pronounced inflammation, high angiogenic activity and predominance of mature collagen fibers, regardless of the anatomical plane that it was inserted in.

Key words: Tissue Adhesions. Amnion. Abdominal Wall. Rats. Collagen.

INTRODUCTION

The incisional hernia is a common condition. Lima[1] described that Kozoll and McVay reported incidence of incisional hernia in 5.7% of laparostomies performed in private hospitals and 11.1% in public hospitals.

Currently, the treatment of incisional hernias, as well as the repair of abdominal wall defects with loss of aponeurotic tissue, has been made with the use of polypropylene meshes. The polypropylene prosthesis can be inserted both in the above-aponeurotic and the sub-aponeurotic positions, and in the latter option it can be allocated in the pre-peritoneal or intra-abdominal region.

Studies have shown that the best position for the placement of the polypropylene mesh is in the pre-peritoneal subaponeurotic position. However, in many situations, such as the giant hernias or those multi-relapsed, the large wall resections, such as tumors, or in the loss of large amounts of tissue wall, as in trauma, it is not possible to cover the prosthesis with the peritoneum. In these cases, the polypropylene mesh is placed in direct contact with the organs and intra-abdominal tissues, resulting in the onset of adhesions and consequent intestinal obstructionor fistula. Many techniques and biological and synthetic materialshave been used to minimize these changes, such as coverage of the abdominal cavity with omentum, bovine pericardium prosthesis with organic and inorganic component, among others,but without ideal results.

Lately, some authors have suggested the use of amniotic membrane in the repair of tissue defects. Since the first half of the last century, some researchers have been studying the use of amniotic membrane in the reconstitution of tissue lesions, especially the skin, as recommended by Fontenla *et al.*[2]. Davis, in 1910, announced the intention of injecting amniotic sac fragments in order favoring the open wound granulation, and

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subsequently in eye tissues[3]. Fontenla *et al*.[2] and del Campo *et al*.[4], report that in 1995, Kim and Tseng reintroduced the use of amniotic membrane in the treatment of ocular lesions, ophthalmology being the specialty where more research is made on the use of amniotic membrane today. There are other studies on its use for burns[5,6], varicose ulcers[5,7], neovagina reconstruction[5,8], urinary bladder[5,9], nerve damage[5,10], mouth sores[5,11], adhesions control and early healing of peritoneal lesions[5,12], among others.

The study of clinical use of amniotic membrane is of increasing importance due to its low antigenicity, antimicrobial activity, ability to decrease exudate and adhesions, to accelerate epithelization, reducing the local pain, actingas a substrate for tissue growth, among many other actions[5].

Based on literature data, it is possible to imagine that, due to its properties that favor the restructuring of the damaged portions of the tissue, the amniotic membrane could be used as biological coverage of the abdominal cavity in the abdominal wall reconstruction using polypropylene prosthesis, representing an alternative in cases where there is no viable peritoneum. Its action at different stages of the healing process (inflammation, proliferation and maturation) could bring beneficial effects, such as decreased adhesions and reconstitution of the peritoneum[13].

This study aimed to evaluate the efficacy of the amniotic membrane associated with a polypropylene mesh and its influence on adhesion formation and wound healing.

METHODS

This study was approved by the Ethicsin Research Committee of the Universidade José do Rosário Vellano (UNIFENAS) under 25A/2008 number and developed in accordance with the rules of the Brazilian College of Animal Experimentation.

We used 25 female Wistar rats, weighing 400g and about six months old. The animals were from the Central Animal Laboratory of the Universidade Federal de Minas Gerais and were kept in the animal house of the Universidade José do Rosário Vellano, Bonaventure Campus, Belo Horizonte. Throughout the study, animals were subjected to natural conditions in their own cages, up to five per cage and fed standard chow and water *ad libitum*.

The animals were randomly divided into three groups: control group (n=11): animals with defect in the abdominal wall repaired with polypropylene mesh in intra-abdominal position. Group A (n=7): animals with defects in the abdominal wall repaired with polypropylene mesh in intra-abdominal position and amniotic membrane interposed between the implant and the abdominal wall. Group B (n=7): Animals with defects in the abdominal wall repaired with polypropylene mesh in intra-abdominal position and amniotic membrane covering it.

The preparation of the amniotic membrane[5] occurred in the Research Laboratory of the Faculty of Medicine, Universidade Federal de Minas Gerais (FM/UFMG). It was obtained from an adult femalerabbit from the UFMG Veterinary School. The rabbit was surgically subjected to pregnancy interruption, and from each fetus the placenta was collected along with the fetal membranes. The amniotic membranes were isolated from other fetal membranes and placed in metal trays containing sterile 0.9% saline solution in sufficient quantity to cover them, in order to wash the tissue, removing clots. This solution was exchanged six times, until the membrane was clean. After washing, the amniotic membranes were immersed in a Becker flask containing 500ml of phosphate-buffered saline (SSC), pH 7.2, containing 0.15M/mL sodium chloride and 6.5mM/mL potassium phosphate (Buffer PBS®- Laborclin Ltda., Pinhais, Brazil) for 40 minutes. Thereafter, each membrane was carefully laid on a sterile nitrocellulose paper (Hybond - ECL®, Amersham Pharmacia Biotech, Buckhingham shire, England) with a pore size of 0.2 microns thickness and dimensions 20cm x 20cm. The stromal side of the membrane was placed in contact with the nitrocellulose paper and then the excess paper was cut, forming strips of 10cm x 8cm, which were stored in sterile plastic containers. This material was completely immersed in a 98% glycerol solution and kept refrigerated at 8°C until the date of their use, which occurred two weeks after preparation and conservation.

The creation of defects in the abdominal wall was performed using clean technique, but not aseptic. The animals were anesthetized with intraperitoneal injection of ketamine hydrochloride solution (50mg/kg) and xylazine (8mg/kg). After anesthesia weincised the skin and subcutaneous tissue and created a defect in the abdominal wall in the mesogastrium region, through the resection of a 1.0cm diameter fragment of muscle-aponeurotic layer and the parietal peritoneum[13].

The abdominal defect was corrected using a polypropylene mesh of approximately 2.7cm x 4.0cm (Marlex mesh, CR BARD, Salt Lake City, UT). In the control group the prosthesis was inserted into the intra-abdominal position, spanning the parietal defect, with its major axis in the longitudinal direction, and sutured to the abdominal wall with simple stitches with 5-0polyglactin in the four corners of the prosthesis. The intestines were protected with an omentum coverage in an attempt to minimize contact with the prosthesis. Then we proceeded to the synthesis of the skin and subcutaneous tissue with 2-0 chromic catgut running suture and finally wound antisepsis with 10% aqueous povidone-iodine (PVP). In the other groups, the surgical technique for the treatment of the defect was similar; in group A, we inserted the amniotic membrane between the prosthesis and the abdominal wall; and in group B, the amniotic membrane was positioned underneath the mesh, creating acover on its abdominal surface (Figure 1).

In the first 12 hours after surgery the animals were fed with oral 20% glucose solution and, from there, water and standard rodent chow *ad libitum*. For analgesia, all animals received nalbuphine hydrochloride injection 3mg/kg/day (12/12 hours) within the first 48 postoperative hours. The first dose was taken at surgery due to the synergistic anesthetic effect.

The macroscopic assessment occurred seven days after the abdominal walldefect correction. The animals were again anesthetized and subjected to a U-shaped laparotomy around the sides and bottom edges of the prosthesis. Then we carried out the inventory of the peritoneal cavity in order to observe the presence of fistulas, abscesses and adhesions between the implant and the abdominal contents. Adhesions, when present, were classified according to the force applied to loosen the attached structures like the following: Grade I (loose) - easily detaching at manipulation; Grade II (firm) - easily detaching atstructurestraction; and Grade III (very firm) - not detaching easily at structures traction. Results were recorded in an appropriate protocol for statistical evaluation.

Biopsy specimens were collected spanning the full thickness of the abdominal wall and the polypropylene mesh that was in direct contact (Control group), and the amniotic tissue, in the case of animals in which the membrane wasimplanted (groups A and B).

The specimens preserved in 10% formalin were embedded in paraffin, submitted to section of 4,0ìm thick, mounted on glass slides and stained with hematoxylin-eosin. The tissue sections were included in the slide, so as to meet all the layers of the abdominal wall, in addition to the polypropylene mesh, and amniotic membrane (in the case of groups A and B). The slides were analyzed at 40x magnification by a single pathologist blinded to the study groups, to evaluate the following parameters:Inflammatory reaction -analyzed the presence or absence of inflammatory activity and, in the presence of inflammation, this was classified as mild, moderate or severe;Predominant inflammatory infiltrate type - the fields were evaluated in order to classify the inflammatory infiltrate in acute or chronic according to the predominant cell type: polymorphonuclear, mononuclear or mixed; Granulation changes - search for common giants inflammatory cells, common in the inflammatory processes stimulated by substances or allergens agents (foreign body reaction); Angiogenesis - search for neovascularization and, when present, classified as mild, moderate or severe, according to the activity and amount of angioblasts and other cells associated with angiogenesis; Proportion macrophage/fibroblast - analyzed the prevalence of macrophages or fibroblasts in the scar tissue, by counting these cells; Proportion of collagen fibers - the type of collagen fiber (immature or mature) predominantly deposited in the scar matrix. All results were recorded in their own protocols for subsequent statistical evaluation .

At the end of the collection of the abdominal wall biopsy material, animals, still under anesthesia, were killed by exsanguination via the abdominal aorta section on the seventh day[14].

The collected data were analyzed, the differences were considered significant at $p<0.05$. Quantitative variables were compared using the Kruskal-Wallis test and the qualitative variables, by Fischer test.

RESULTS

No animal had intra-abdominal abscess. Most animals had adhesions between the polypropylene prosthesis and the omentum and, more rarely, the intesti-

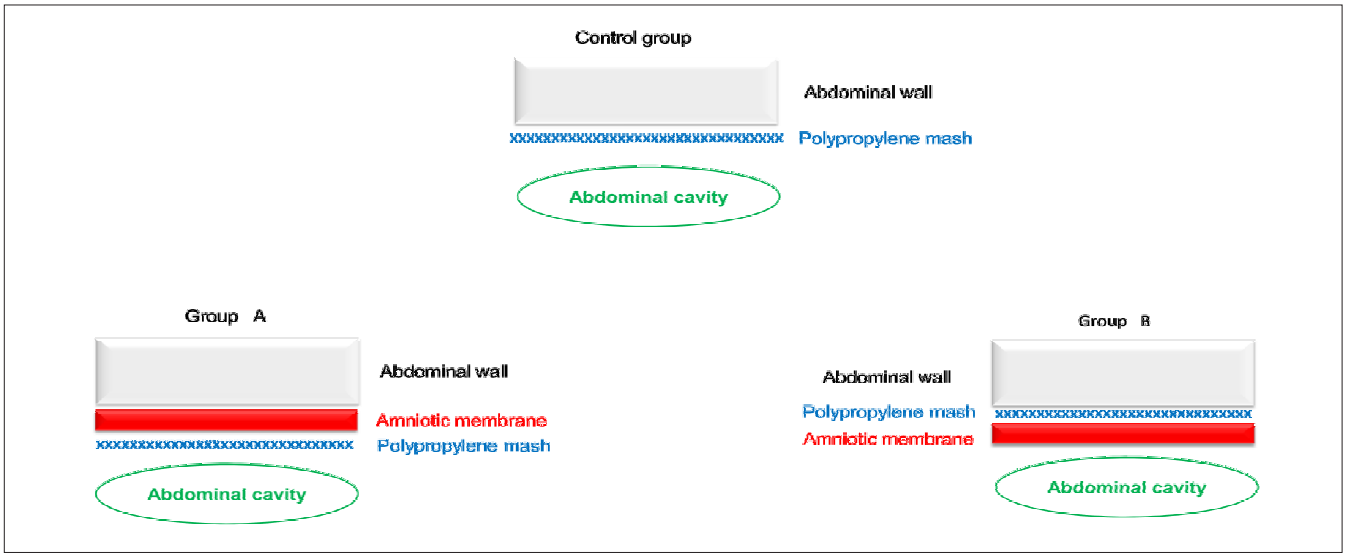

Figure 1 - *Schematic drawing showing the attachment position of the polypropylene prosthesis and insertion of amniotic membrane in the study groups with respect to the wall and the abdominal cavity.*

nal loops, but one Animal in the Control group. There was no significant difference when the groups were compared. Similarly, there was no difference between groups when comparing the degree of adhesions (Table 1).

There was inflammation in all animals, except for one animal of the Control group. The intensity of the inflammatory process was marked in all animals of groups A and B, with the difference whencompared with the control group, both with p=0.01 (Figure 2).

There was a predominance of mononuclear infiltrate over polymorphonuclear or mixed infiltrates, but no difference when each type of cell infiltrate was compared between groups. Angiogenesis was present in all animals, being classified as sharp predominantly in groups A and B, with a significant difference when compared with the control group, with p=0.002 and p=0.05, respectively (Figure 2).

There was a predominance of fibroblasts overmacrophages in all groups, being more intense in groups A and B, but without significant differences when compared to fibroblasts from each group together. Collagens deposited in the wound areas were mainly mature fibers, with the exception of five animals of the control group, in which prevailed immature collagen fibers. There was statistical difference in the predominance of immature collagen fibers in the control group compared with groups A (p=0.05) and B (p=0.05), respectively (Table 2, Figure 3).

DISCUSSION

The use of polypropylene mesh in various abdominal wall defects is common[1]. In our country, in dire financial constraints for public health sustainability, the search for new therapeutic alternatives, associated or isolated, is very important. Amniotic membrane obtained from the placenta[14] is a tissue rich in stem cells. It can be used in its fresh form, after processing, or conserved form and maintained in stock solution. In fresh form, pluripotent cells multiply rapidly, forming a tissue similar to those around it, but there is the drawback of the short time to use, since it deteriorates rapidly.

The conservation of amniotic membrane in stock solution increases its usage time.However, some studies have reported the loss of part of the living tissue, the material preserved retaining cells and growth factors sufficient to possibly stimulate healing and accelerate the repair process tissue[15,16].

In general, adhesions arise from any tissue damage in the first week after injury[17,18]. The healing time or termination of that cell proliferation is dependent on the extent of the lesion and the healing process leads to migration of fibroblasts, macrophages and giant cells. Fibroblasts promote the initial deposit of fibrin and collagen[18]. The higher tissue injury, the more increased collagen and fibrindeposition, making the peritoneal fibrinolysis and increasing the adhesive capacity of the wound line, progressing to the formation of adhesions[17,18].

In this study, we used thepreserved amniotic membrane and the observation time was a week after the initial tissue injury. The presence of the amniotic membrane

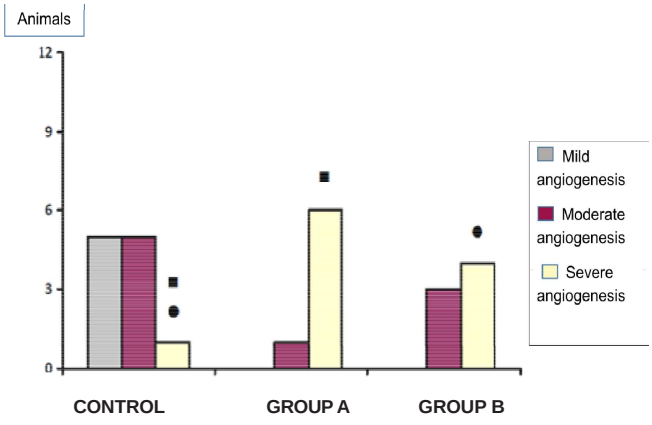

Figure 2 - *Wistar rats with mild angiogenesis activity, moderate or severe scarring in the region of abdominal wall defects corrected with polypropylene mesh use (Control) associated with amniotic membrane in the prosthesis surface region (A) or deep (B).*

■ *p = 0.002* ●*p = 0.05*

Table 1 - Evaluation of macroscopic parameters of the abdominal cavity of rats after treatment of abdominal defect with use of polypropylene prosthesis, with or without the use of amniotic membrane.

Parameter studied	Group						p value
	Control (n=11)		The study (n=07)		B study (n=07)		
	N	%	N	%	N	%	
Adhesions	10	91	07	100	07	100	ns
Grade I Adhesions	03	27.3	03	43.0	05	71.5	ns
Grade II Adhesions	06	54.6	02	28.5	02	28.5	ns
Grade III Adhesions	01	9.1	02	28.5	0	0	ns
Abscesses	0	0	0	0	0	0	ns

did not change the formation of adhesions between the polypropylene mesh and the peritoneal content. This may be due to the short time of observation. Despite the healing stimulus and the formation covering tissue on the inserted polypropylene mesh, there wasprobably not enough time for this tissueto organize, thus allowing the adhesion between the prosthesis and the intra-abdominal tissues.

Angiogenesis occurred significantly in animals where the amniotic membrane was inserted, indicating the likely presence of proinflammatory substances in the conserved membrane. In addition, the amniotic membrane changed the type of collagen fibers found in the repair process.

The predominance of mature collagen fibers was observed in all animals in which the membrane was inserted, which did not occur in other animals. This demonstrates that the presence of the membrane accelerates the healing process with mature repair tissue formation, already at the early stage of tissue repair.

The association of the amniotic membrane with the polypropylene mesh in the treatment of abdominal wall defects of Wistar rats did not alter the formation of adhesions after the first week of operation. However, the amniotic membrane was associated with a marked increased inflammation and angiogenesis activity and the predominance of mature collagen fibers, regardless of the anatomical plane in which it was inserted, accelerating healing.

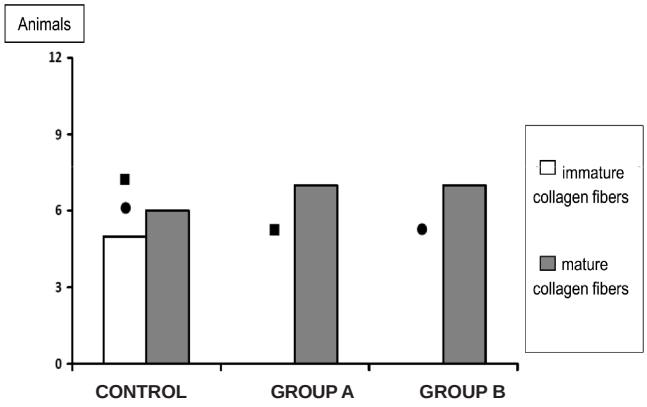

Figure 3 - *Wistar rats with a predominance of immature or mature collagen fibers in scar region of abdominal wall defects corrected with polypropylene mesh use (Control) associated with amniotic membrane in the prosthesis surface region (A) or deep (B).*

Table 2 - Evaluation of microscopic parameters of the abdominal wall of rats subjected to treatment of abdominal defect with use of polypropylene mesh associated or not to amniotic membrane.

Study parameter		Group						p value
		Control (n=11)		A study (n=07)		B study (n=07)		
		N	%	N	%	N	%	
Inflammation Degree*	Take	0	0	0	0	0	0	
	Moderate	07	63.6	0	0	0	0	a = 0.01
	Sharp	03[a, b]	27.3	07th	100	07[b]	100	b = 0.01
Type of inflammatory infiltrate	PMN	0	0	0	0	0	0	
	Mono	09	81.8	07	100	06	85.7	NS
	Mixed	02	18.2	0	0	01	14.3	
Activity of angiogenesis	Mild	05	45.4	0	0	0	0	
	Moderate	05	45.4	01	14.3	03	42.9	c = 0.002
	Intense	01[(e), (f)]	9.2	06[c]	85.7	04[d]	57.1	d = 0.05
Fibro/macro Ratio**	Fibroblast	07	63.6	07	100	07	100	
	Macrophage	04	46.4	0	0	0	0	NS
Collagen fibers	Immature	05[(e), (f)]	54.6	0[and]	0	0[f]	0	e = 0.05
	Mature	06	45.4	07	100	07	100	f = 0.05

** In one Control Group animal, the intensity of inflammation has not been classified.*
** * Ratio between Fibroblasts and Macrophages.*

RESUMO

Objetivo: *avaliar a eficácia da membrana amniótica usada com tela de polipropileno contra a formação de aderências e sua influência na cicatrização.* ***Métodos****: vinte e cinco ratas Wistar foram anestesiadas para criação de um defeito parietal na parede abdominal anterior. Sua correção foi feita com tela de polipropileno isolada e associada à membrana amniótica. No grupo Controle (n=11), a tela foi inserida isoladamente intra-abdominal. No grupo A (n=7), interpôs-se a membrana amniótica entre a tela e a parede abdominal. No grupo B, a membrana amniótica foi colocada sobre a tela, recobrindo-a. Após sete dias, os animais foram eutanasiados para avaliação macroscópica e microscópica da cicatrização.* ***Resultados****: aderências foram observadas em todos os animais, exceto em um do grupo Controle. Inflamação acentuada foi observada em todos os animais dos grupos A e B e em três do grupo Controle, com diferença significativa entre eles (A e B com p=0,01). Acentuada atividade angiogênica foi notada em um animal do grupo Controle, seis do grupo A e quatro do grupo B, com diferença significativa entre o grupo Controle e os grupos A (p=0,002) e B (p=0,05). O colágeno cicatricial foi predominantemente maduro, exceto em cinco animais do grupo Controle, com diferença significativa entre o grupo Controle e os grupos A (p=0,05) e B (p=0,05).* ***Conclusão:*** *a presença da membrana amniótica não alterou a formação de aderências na primeira semana de pós-operatório. Associou-se à inflamação acentuada, elevada atividade angiogênica e predomínio de fibras colágenas maduras, independente do plano anatômico em que foi inserida.*

Descritores: *Aderências Teciduais. Membrana Amniótica. Parede Abdominal. Ratos. Colágeno.*

REFERENCES

1. Lima JM. Tratamento cirúrgico das hérnias incisionais: experiência pessoal usando a malha de polipropileno monofilamentar-márlex. Rev Col Bras Cir. 2002;29(2):78-82.
2. Fontenla JR, Vázquez X, Díaz D, Gatell J, Pita D. Membrana amniótica. Características, efectos y aplicaciones em oftalmologia. Jano. 2003;64(1465):53-68.
3. Meller D, Pauklin M, Thomasen H, Westekemper H, Steuhl KP. Amniotic membrane transplantation in the human eye. Dtsch Arztebi Int. 2011;108(14):243-8.
4. del Campo Z, Gris O. Aplicaciones de la membrana amniótica en patologia ocular. Annals d'Oftalmologia. 2002;10(3):128-41.
5. Duarte IGL, Durval-Araújo I. Amniotic membrane as a biological dressing in infected wound healing in rabbits. Acta Cir Bras. 2014;29(5):334-9.
6. Singh R, Chacharkar MP. Dried gamma-irradiated amniotic membrane as dressing in burn wound care. J Tissue Viability. 2011;20(2):49-54.
7. Singh R, Chouhan US, Purohit S, Gupta P, Kumar P, Kumar A, et al. Radiation processed amniotic membranes in the treatment of non-healing ulcers of different etiologies. Cell Tissue Bank. 2004;5(2):129-34.
8. Carvalho BR, Reis RM, Moura MD, Lara LAS, Nogueira AA, Ferriani RA. Neovaginoplastia com membrana amniótica na síndrome de Mayer-Rokitansky-Küster-Hauser. Rev Bras Ginecol Obstet. 2007;29(12):619-24.
9. Fishman IJ, Flores FN, Scott FB, Spjut HJ, Morrow B. Use of fresh placental membranes for bladder reconstruction. J Urol. 1987;138(5):1291-4.
10. Hasegawa M, Fujisawa H, Hayashi Y, Yamashita J. Autologous amnion graft for repair of myelomeningocele: technical note and clinical implication. J Clin Neurosci. 2004;11(4):408-11.
11. Kesting MR, Loeffelbein DJ, Classen M, Slotta-Huspenina J, Hasler RJ, Jacobsen F, et al. Repair of oronasal fistulas with human amniotic membrane in minipigs. Br J Oral Maxillofac Surg. 2010;48(2):131-5.
12. Ozeren S, Corakci A, Erik A, Yûcesoy G, Yûcesoy I, Karabacak O. The effects of human membrane and fibrin sealant in the prevention of postoperative adhesion formation in the rabbit ovary model. Aust N Z J Obstet Gynaecol. 1998;38(2):207-9.
13. Tsuis S, Ellis H. Healing of abdominal incisional hernia in infant rats. Br J Surg. 1991;78(8):927-9.
14. Kesting MR, Wolff KD, Mücke T, Demtroeder C, Kreutzer K, Schulte M, et al. A bioartificial surgical patch from multilayered human amniotic membrane-In vivo investigations in a rat model. J Biomed Mater Res B Appl Biomater. 2009;90(2):930-8.
15. Paggiaro AO, Mathor MB, Carvalho VF, Polo E, Alessi MS, Herson MR, et al. Estabelecimento de protocolo de glicerolização de membranas amnióticas para uso como curativo biológico. Rev Bras Queimaduras. 2010;9(1):2-6.
16. Hennerbichler S, Reichl B, Pleiner D, Gabriel C, Eibl J, Redl H. The influence of various storage conditions on cells viability in amniotic membrane. Cell Tessue Bank. 2007;8(1):1-8.
17. Palma MLM, Foz Filho RPP. Aderências intra-abdominais em equinos. Rev Educ Contin CRMV-SP. 2005;8(2):123-34.
18. Diogo-Filho A, Lazarini BCM, Vieira-Junyor F, Silva GJ, Gomes HL. Avaliação daderências pós-oopertórioas em ratos submetidos à peritoniostomia com tela de polipropileno associada à nitrofurazona. Arq Gastroenterol. 2004;41(4):245-9.

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Closure of large wounds using rubber bands in rabbits

Fechamento de grandes feridas com fita elástica de borracha em coelhos

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ABSTRACT

Objective: to verify the effectiveness of the rubber elastic band in the treatment of large wounds of the body wall of rabbits by means of traction of its edges. **Methods**: we studied 30 New Zealand rabbits, divided into three groups (n=10): Group 1- healing by secondary intention; Group 2- removal and eutopic repositioning of skin as full thickness skin graft; Group 3- Approximation of wound edges with elastic rubber band. In all animals, we removed a segment of the back skin and subcutaneous tissue down to the fascia, in accordance with an acrylic mold of 8cm long by 12cm wide. All animals were observed for 21 days. **Results**: two animals of groups 1 and 2 had wound abscess. In Group 2, there was partial or total graft loss in 90% of animals. The complete closure of the wounds was observed in four animals of Group 1, six of Group 2 and eight of Group 3. There was no difference between the scar resistance values of groups 2 and 3, which were higher than those in Group 1. The scars of the three groups were characterized by the presence of mature connective tissue mixed with blood vessels and inflammatory infiltration, predominantly polymorphonuclear. **Conclusion**: the tensile strength of the wound edges with rubber elastic band is as efficient as the skin graft to treat rabbits' large body wounds.

Key words: Abdominal Wound Closure Techniques. Surgical Wound Dehiscence. Wound Healing. Elastomers. Skin Transplantation. Connective Tissue.

INTRODUCTION

Large wounds of the body wall are a surgical challenge, especially when they complicate and cause physical limitations. These wounds are characterized by difficulty in approaching their borders and their size varies in different regions of the body. They are caused byextensive trauma, large burns, cancer, pressure ulcers, infections, vascular disorders, fractures, laparostomies, etc. Although most wounds heal without infection, dehiscence or other abnormality, they can contribute to increased morbidity and mortality and treatment costs, and result in aesthetic and functional damage[1,2].

For the choice of treatment of extensive wounds, the surgical options are the primary closure, skin grafting, local flaps and distant flaps, in order of complexity[2,3]. The treatment is based on predicting the final result to maintain the shape and function of the area to be reconstructed, with less risk of complications[3]. When there is tissue loss, the healing process is by secondary intention, by means of wound contraction. This healing occurs in open wounds or in case of dehiscence, after primary closure[2,3]. The main disadvantages of healing by secondary intention are the long time of treatment, the need for frequent dressing changes, electrolyte and protein loss through the wound, increased risk of infections, unsightly scars and prolonged regional immobilization[4].

Skin grafts are used to shorten healing time, preventing infections and cosmetic damage, when the approximation of the wound edges is not feasible. However, this method depends on the donor site availability, which is not always possible, and predisposes patients to other complications, such as infection of the donor area and aesthetic commitment[2,3].

The objective of this study was to verify the effectiveness of the rubber elastic band in the treatment of large wounds of the body wall of rabbits by means of traction of its edges.

METHODS

We studied 30 White New Zealand male rabbits (*Oryctogalus cuniculus*) from the experimental farm of the

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Veterinary School of the Universidade Federal de Minas Gerais (UFMG). At baseline, all rabbits were four months old and weighed 2,840 ± 254 grams. These rabbits were randomly assigned to three groups and had wounds inflictedin the dorsal part of their bodies (n=10): Group 1, spontaneous healing by secondary intention; Group 2, total autogenous skin grafting; Group 3, Approximation of borders through traction with elastic rubber band.

This work followed the technical standards of research and animal testing[5,6], in accordance with Law 11.794, and was approved by the Ethics Committee for Animal Experimentation of the Federal University of Minas Gerais - CETEA / UFMG, under number 145/2009.

Anesthesia was induced with an intramuscular injection in the gluteal region of 2% xylazine hydrochloride (Calmiun®, Agener Union, São Paulo), 10mg/kg, associated with 10% ketamine hydrochloride (Dopalen®, Vetbrands, England), 60mg/kg. After extensive shaving the back of the animals, we performed antisepsis with polyvinylpyrrolidone solution (PVPI®), followed by alcoholic solution of 2% iodine, and placement of surgical drapes.

In all animals, the wound consisted of the removal of the skin segment and underlying subcutaneous tissue of the back down to themusculo-aponeurotic fascia. The wound followed a mold made of acrylic, measuring 12cm long and 8cm wide.

In Group 1, after removal of the skin, we passed four supporting stitches, 3.0 cm distant from each other, using 3-0 monofilament nylon sutures. The purpose of these guidelines was to anchor the wound edges in laterolateral sense, avoiding its extension by skin retraction (Figure 1A).

In Group 2, we removed all the subcutaneous tissue from the excised segment with scalpel and Metzembaun scissors. The skin consisted of all its layers down to the hypodermis was placed on the wound, as a full thickness skin graft (Figure 1B). At the end of the procedure, a Brown dressing was made with gauze fixed on the graft for six equidistant points past the wound edges with 2-0 monofilament nylon thread. This dressing kept the graft property for five days.

In Group 3, the approximation of the wound edges was obtained by means of a rubber elastic band (gominha), previously sterilized by autoclaving. The suture of these bands to the edges was initiated with a single stitch on one of the wound edges. Then, the elastic was crossed over itself, forming a "X" and fixed to the skin around one inch from the edge of the wound, with separate single stitches using 3-0 monofilament nylon. During the passage of the stitches, the band was kept under moderate traction by the auxiliary. This rubber strip is crossed several times, forming consecutive "XX" to the opposite vertex of the wound (Figure 1C).

After surgery, antibiotic prophylaxis was performed by subcutaneous injection of amoxicillin (Bactrosina®, Bayer, SP), 20mg / kg every 24 hours for ten days. Analgesia was achieved by oral administration of dipyrone (Novalgina®, Sanofi Aventis Pharmaceuticals, England) at a dose of 25mg/kg every 12 hours, during the first ten days postoperatively.

We washed the wounds of all rabbits daily with 0.9% saline. In Group 1, after cleaning, gauze pads soaked in petroleum jelly (Vaseline net Farmax®, Farmax, Divinópolis) were placed on the wound. In Group 2, Brown dressingcompresses were soaked in petroleum jelly daily until the fifth postoperative day. After this period, the dressing was removed and new gauze soaked in petrolatum was applied daily after cleansing of the wound with 0.9% saline. In Group 3, the wounds were covered with dry gauze, so that there was no impairment of the elastic rubber band. The trunk of all the animals of the three groups was bandaged with crepe bandages to prevent contamination of wounds and the removal of dressings by therabbit.

To prevent rabbits from biting the operated area, we placed a plastic craniocervical isolation collar in all of them. This collar was adapted from a surgical helmet for dogs. For this, a wide cut in the plastic was made in a half moon shape, coinciding with the mouth of the animals. Its fixation in the rabbits' neck useda crepe bandage pierced between the forelimbs and the cervical region to allow free movement and the intake of water and food[7].

At the end of the follow-up period, the rabbits underwent reoperation under anesthesia with ketamine (100mg/kg). We removed two skin fragments from the scar - one for histological analysis and the other for the scar

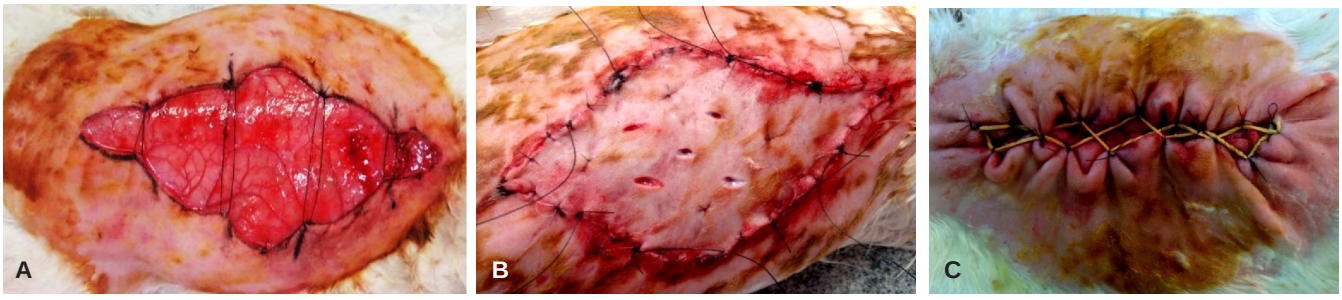

Figure 1 - *Wound aspect in animals of Groups 1, 2 and 3 after completion of the associated procedures.*
A) Final appearance of the wound in rabbit of Group 1 after installation of the supporting stitches. B) Final appearance of the graft in a Group 2rabbit. C) Full Approximation of wound edges with elastic rubber band.

tensile strength test. These skin segments measured 4cm long and 1cm wide and contained the scar of the wound in their central part. The site chosen for collecting skin fragments was the same in all animals regardless of the appearance of the scar at the final stage, and was conducted 10cm from theinsertionof the rabbits' ears.

The tissue sections prepared for histology were stained with hematoxylin and eosin (HE) and Masson trichrome. At histological evaluation, we considered: granulation tissue, young scar tissue, mature scar tissue (fibrosis), inflammatory infiltrate, granulomatous inflammation and the presence of abscesses.

To measure the scar resistance force, the removed skin fragment was clamped at both ends by two 14cm, 30g Mayo Hegar needle holders. One of the needle holders was attached to a metal support, while the other was tied to a plastic bucket with a capacity of five gallons. A water stream at a constant flow of 650ml / min filled the bucket until the rupture of the skin fragment. We measured the liquid volume, converted in grams, which was added to the mass of the bucket and, the string and the needle holder strapped to it (520g). We calculated the force to rupture the fragments using the formula: Force (Newton) = Total Mass (grams) x Acceleration due to gravity ($9.8m/s^2$).

The acceleration used was the one of the water falling on the bucket, which is the gravity acceleration, $9.8m/s^2$. Once the force required to rupture the scar was found, we obtained the scar rupture tension, from the formula: scar tension (megapascals) = force (Newton) / area ($400mm\square$).

The data were presented as mean ±standard error of the mean. To compare continuous variables in different groups, we verified the data normality using the Kolmogorov-Smirnov test, followed by analysis of variance (ANOVA) and multiple comparison Tukey test or the Kruskal-Wallis test for nonparametric data. Categorical variables were compared using the Fisher's exact test. All results were considered significant for a probability of significance greater than or equal to 95% (pd"0.05).

RESULTS

All animals could drink water and food without difficulty throughout the experiment.

There was no difference between groups as to animals weight of prior to operations (p=0.1910) and the last day of follow-up (p=0.0791). There was a reduction in weight between the preoperative and the tenth POD in group 1, p=0.0305, in group 2, p=0.0004 and in group 3, p=0.0027 (Table 1).

The macroscopic examination showed that two animals in Group 1 and Group 2 presented wound abscess, but none Group 3 had this complication. In Group 1, all rabbits had bleeding in the wound during the first three postoperative days. In Group 2 and Group 3, no rabbit showed blood loss. In Group 1, there were crusting and fibrin exudates inthe wounds of all animals. In Group 2, there was fibrinous exudate in two animals. There was total necrosis of the graft in three animals and partial necrosis of the transplanted tissue in six rabbits. In seven animals in Group 3, there was dehiscence of the suture between the eighth and 12th postoperative day, with rupture of the skin at the site of attachment points. In five animals, there was a local inflammatory reaction and fibrinous exudate, which reversed with wound cleaning.

There was no difference between groups in the number of wounds healed at 21 days (p=0.1989). There was complete wound closure in four animals of the group 1, six of Group 2 and eight of the Group 3.

When comparing the scar rupture strength and tension, we found that Group 3 values were not different from those found in Group 2, but both were higher than those in Group 1 (p=0.0177) (Table 2).

Table 1 - Values (mean ±standard error of the mean) of the weight of the animals in Groups 1, 2 and 3, obtained preoperatively, in the tenth and 21st DPO.

Group	Weight (grams)		
	Preoperative	10° POD	21° POD
1	2740 ± 229[AD]	2419 ± 276[A]	2600 ± 300[E]
2	2783 ± 172[BD]	2478 ± 187 [B]	2713 ± 181[E]
3	2995 ± 291[CD]	2756 ± 267[C]	2911 ± 237[E]

Group 1 –Healing by secondary intention
Group 2 –Skin grafting
Group 3 –Traction of the wound edges by elastic rubber band
POD –postoperative day
A –p = 0,0305
B –p = 0,0004
C –p = 0,0027
D –p = 0,1910
E –p = 0,0791

The histological findings did not differ among the three groups and were characterized by the presence of an extensive fibrosis area consisting of mature connective tissue mixed with blood vessels of the dermis and accompanying inflammatory infiltrate, consisting predominantly of polymorphonuclear cells.

DISCUSSION

Despite the large number of techniques and products available for the treatment of extensive wounds, failures are still widespread. Among the barriers to treatment, the difficulty in closing the skin is of great importance, for it brings risk of infections and other comorbidities, prolonged hospital stay and encumber treatment. The most commonly used techniques in reconstruction are complex and may contribute to increased morbidity[8].

The use of elastic rubber band for large wound closure was first described in 1986 by Cohn *et al.*[9] in the treatment of fasciotomies. These surgeons used elastic bands transfixing the wound and secured to the skin by staples. The biggest problem of this technique was the need of daily returns to the operating room, which made treatment difficult. Since then, the elastic band has been used in intervention of various types of wounds, including compartmental syndrome[10,11], extensive fasciotomy wounds[12-15], open fractures[16], injuries from burns[17] and large wounds of the body wall[15,18].

In this study, we observed partial or total graft loss in 90% in Group 2, indicating the risk of failure of these procedures on animals. Rabbits, likeother animals, are very active, jeopardizing the vascularization of the graft from the wound bed during the inosculationphase[19]. Although widely used in humans, some grafts are rarely indicated in the treatment of extensive wounds in animals because of the possibility of complications and graft tissue loss[20,21].

The use of elastic bands to traction the wound edges is an effective resource in the treatment of large wounds of the body wall[9-18]. This closure occurs by skin stretching, using the viscoelastic properties of the skin[12,13,16,18]. The biomechanical properties of the skin, resulting from the interaction between extracellular matrix components, allow it to be extended. This property is used in other techniques for closure of large skin defects, especially in tissue loss due to traumas and skin tumors[19,22].

In the technique described in this work, it is appropriate to assume that all skin stretching phases are present: intrinsic extensibility, alignment of collagen fibers and cell hyperplasia. The skin elasticity and rigidity are mainly related to the thickness of its dermis and subcutaneous tissue[23]. The viscoelastic properties include, among other factors, the immediate distension capacity of the skin and the resilience of its normal size after stretching. The immediate skin expansion by pulling its edges is guaranteed by its intrinsic extensibility. This property determines how much the skin can be incised in order to obtain a primary closure safely[24].

The gradual stretching of the skin is stimulated by mechanical drag. When a load is applied to the skin, the tissue increases in length over time and, consequently, the force required to maintain this strain gradually decreases[24] due to the arrangement of collagen fibers[25]. When at rest, these collagen fibers are wavy and, with stretching, the undulations flatten, the fibers extending in the same direction of the traction. As the drift increases, a greater number of fibers get aligned, to form a structure of parallel collagen fibers, resistant to stretching[25,26].

Hyperplasia also plays an important role in tissue growth and results from the continuous stretching of the skin, which responds with cell proliferation and tissue growth[27,28]. On the other hand, fast stretching under intense traction causes disruption of collagen fibers, culminating in the formation of stretch marks[26,28]. Excessive stretching can also cause distension and collapse of the small vessels of the skin, leading to ischemic necrosis of the edges of the wound and dehiscence[13,27].

The use of elastic traction, as proposed in this research technique, allows dynamic stretchingand has the advantage of maintaining a moderate and continuous

Table 2 - Values (mean ± standard error of the mean) of scar rupture force (Newton) and tension (Megapascal) in rabbits of groups 1, 2 e 3.

Group	Force	Voltage
1[ABC]	10,696.0 ± 2313.2	26.7 ± 5.8
2[ABD]	18,050.4 ± 4809.5	45.1 ± 12.0
3[ACD]	15,624.9 ± 6046.5	39.0 ± 15.1

Group 1 –Healing by secondary intention
Group 2 –Skin grafting
Group 3 –Traction of the wound edges by elastic rubber band
A –p = 0,0265
B –p< 0,05
C –p< 0,05
D –p> 0,05

traction of the wound edges, thanks to the elasticity of the rubber, which favors the juxtaposition of the edges to complete wound closure[29]. The pulled skin has the same characteristics regarding color, sensitivity, hair follicles and other pre-existing attachments in the wound[26,29], which can be proven by clinical and histopathological findings of this study, which were not different from healing by grafting. Thus, the final aesthetic result is better than that obtained with grafting.

In this research, the final scar after closing with elastic bandshowed adequate morphological maturation and good scar resistance forthe stage it was in.

The wound closure by approximation of its edges with elastic rubber band does not depend on special experience of the surgeon or on sophisticated features. Greater care must be taken to maintain the band in moderate traction, in order not to break it and allow a continuous traction of the skin without risk of the stitches cutting it or causing its ischemia. The tension control depends on the surgeon care, since there is no feature to prevent the excessive elastic stretch. In addition, the technique proposed herein can be performed under local anesthesia, on an outpatient surgical condition.

This technique has been successfully used in large human chronic wounds arising from laparostomies, removal of tumors, fasciotomies, burns and trauma[15,18]. However, this is the first experimental work showing efficiency of traction of the large acute wounds edges of by anelastic rubber band on animals.

The closure of large wounds of the body wall of rabbits by means of traction of its edges with rubber elastic band is effective, simple, easy to perform, feasible and cost-effective, and should be considered in the surgical treatment of humans and animals. This technique was more effective than healing by secondary intention and as effective as the closing by grafting.

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R E S U M O

Objetivos*: verificar a eficácia da fita elástica de borracha no tratamento de grandes feridas de parede corpórea de coelhos por meio da tração de suas bordas.* ***Métodos:*** *foram estudados 30 coelhos da raça Nova Zelândia, distribuídos em três grupos (n=10): Grupo 1. Cicatrização por segunda intenção. Grupo 2. Retirada e reposicionamento eutópico da pele como enxerto de pele total. Grupo 3. Aproximação das bordas da ferida com fita elástica de borracha. Em todos os animais, foi retirado segmento de pele e tecido subcutâneo até a fáscia musculoaponeurótica do dorso, de acordo com um molde de acrílico, com 12cm de comprimento por 8cm de largura. Todos os animais foram acompanhados durante 21 dias.* ***Resultados****: dois animais dos grupos 1 e 2 apresentaram abscesso na ferida. No Grupo 2, houve perda parcial ou total do enxerto em 90% dos animais. O fechamento completo das feridas foi observado em quatro animais do Grupo 1, seis do Grupo 2 e oito do Grupo 3. Não houve diferença entre os valores de resistência cicatricial dos grupos 2 e 3, que foram maiores do que os do Grupo 1. As cicatrizes dos três grupos caracterizaram-se pela presença de tecido conjuntivo maduro entremeado por vasos sanguíneos e infiltrado inflamatório, predominantemente polimorfonuclear.* ***Conclusão:*** *a tração das bordas da ferida com fita elástica de borracha constitui método tão eficaz quanto o enxerto de pele para tratar grandes feridas de parede corpórea de coelhos.*

Descritores*: Técnicas de Fechamento de Ferimentos Abdominais. Deiscência da Ferida Operatória. Cicatrização de Feridas. Elastômeros. Enxertia de Pele. Tecido Conjuntivo.*

REFERENCES

1. Kirkland KB, Briggs JP, Trivette SL, Wilkinson WE, Sexton DJ. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. Infect Control Hosp Epidemiol. 1999;20(11):725-30.
2. Ferreira MC, Tuma P Jr, Carvalho VF, Kamamoto F. Complex wounds. Clinics. 2006;61(6):571-8.
3. Teixeira Neto N, Chi A, Paggiaro AO, Ferreira MC. Tratamento cirúrgico das feridas complexas. Rev Med. 2010;89(3/4):147-52.
4. Park H, Copeland C, Henry S, Barbul A. Complex wounds and their management. Surg Clin North Am. 2010;90(6):1181-94.
5. Hoff C. Sounding board. Immoral and moral uses of animals. N Eng J Med. 1980;302(2):115-8.
6. Petroianu A. Aspectos éticos na pesquisa em animais. Acta cir bras. 1996;11(3):157-64.
7. Ivo CS, Ivo MB, Salles PGO, Rosário RCV, Nunes TA. Device for craniocervical isolation in rabbits. Acta Cir Bras. 2009;24(4):316-20.
8. Parrett BM, Matros E, Pribaz JJ, Orgill DP. Lower extremity trauma: trends in the management of soft-tissue reconstruction of open tibia-fibula fractures. Plast Reconstr Surg. 2006;117(4):1315-22; discussion 1323-4.
9. Cohn BT, Shall J, Berkowitz M. Forearm fasciotomy for acute compartment syndrome: a new technique for delayed primary closure. Orthopedics. 1986;9(9):1243-6.
10. Raskin KB. Acute vascular injuries of the upper extremity. Hand Clin. 1993;9(1):115-30.
11. Harrah J, Gates R, Carl J, Harrah JD. A simpler, less expensive technique for delayed primary closure of fasciotomias. Am J Surg. 2000;180(1): 55-7.
12. Asgari MM, Spinelli HM. The vessel loop shoelace technique for closure of fasciotomy wounds. Ann Plast Surg. 2000;44(2):225-9.

13. Taylor RC, Reitsma BJ, Sarazin S, Bell MG. Early results using a dynamic method for delayed primary closure of fasciotomy wounds. J Am Coll Surg. 2003;197(5):872-8.
14. Ismavel R, Samuel S, Boopalan PR, Chittaranjan SB. A simple solution for wound coverage by skin stretching. J Orthop Trauma. 2011;25(3):127-32.
15. Santos ELN, Oliveira RA. Sutura elástica para o tratamento de grandes feridas. Rev Bras Cir Plást. 2012;27(3):475-7.
16. Schnirring-Judge MA, Anderson EC. Vessel loop closure technique in open fractures and other complex wounds in the foot and ankle. J Foot Ankle Surg. 2009;48(6):692-9.
17. Fan J, Wang J. The "silicone suture" for tissue expansion without an expander: a new device for repair of soft-tissue defects after burns. Plast Reconstr Surg. 2004;114(2):484-8; discussion 489-90.
18. Petroianu A. Síntese de grandes feridas da parede corpórea com tira elástica de borracha. ABCD Arq Bras Cir Dig. 2010;23(1):16-8.
19. Perlis CS, Dufresne RG Jr. Immediate skin stretching with towel clips and needles. Dermatol Surg. 2005;31(6):697-8.
20. Swaim SF. Advances in wound healing in small animal practice: current status and lines of development. Vet Dermatol. 1997;8(4):249-57.
21. Beardsley SL, Schrader SC. Treatment of dogs with wounds of the limbs caused by shearing forces: 98 cases (1975-1993). J Am Vet Med Assoc. 1995;207(8):1071-5.
22. Lam AC, Nguyen QH, Tahery DP, Cohen BH, Sasaki GH, Moy RL. Decrease in skin-closing tension intraoperatively with suture tension adjustment reel, balloon expansion, and undermining. J Dermatol Surg Oncol. 1994;20(6):368-71.
23. Cua AB, Wilhelm KP, Maibach HI. Elastic properties of human skin: relation to age, sex, and anatomical region. Arch Dermatol Res. 1990;282(5):283-8.
24. Liang MD, Briggs P, Heckler FR, Futrell JW. Presuturing—a new technique for closing large skin defects: clinical and experimental studies. Plast Reconstr Surg. 1988;81(5):694-702.
25. Gibson T, Kenedi RM, Craik JE. The mobile micro-architecture of dermal collagen: a bio-engineering study. Br J Surg. 1965;52(10):764-70.
26. Melis P, Noorlander ML, van der Horst CM, van Noorden CJ. Rapid alignment of collagen fibers in the dermis of undermined and not undermined skin stretched with a skin-stretching device. Plast Reconstr Surg. 2002;109(2):674-80; discussion 681-2.
27. Pietramaggiori G, Liu P, Scherer SS, Kaipainen A, Prsa MJ, Mayer H, et al. Tensile forces stimulate vascular remodeling and epidermal cell proliferation in living skin. Ann Surg. 2007;246(5):896-902.
28. Daya M, Nair V. Traction-assisted dermatogenesis by serial intermittent skin tape application. Plast Reconstr Surg. 2008;122(4):1047-54.
29. Harris I. Gradual closure of fasciotomy wounds using a vessel loop shoelace. Injury. 1993;24(8):565-6.

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Importance of bone assessment and prevention of osteoporotic fracture in patients with prostate cancer in the gonadotropic hormone analogues use

Importância da avaliação óssea e da prevenção da fratura osteoporótica em pacientes com câncer de proìstata em uso de anaìlogos do hormônio gonadotrófico

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A B S T R A C T

The antiandrogenic therapy (ADT) for prostate cancer represents an additional risk factor for the development of osteoporosis and fragility fractures. Still, bone health of patients on ADT is often not evaluated. After literature research we found that simple preventive measures can prevent bone loss in these patients, resulting in more cost-effective solutions to the public health system and family when compared to the treatment of fractures.

Key words: Prostatic Neoplasms. Osteoporosis. Hormones. Gonadotropin Releasing Hormone/analogues & derivatives. Testosterone/antagonists & inhibitors.

INTRODUCTION

Prostate cancer (PCa) has its highest incidence among men 50-70 years of age[1]. There are several available methods for treatment of patients with PCa, such as active surveillance, resection, radiotherapy and androgen deprivation. Gonadotropin-releasing hormone analogs (GnRHa) may be indicated as adjunctive therapy in the treatment of metastases or as the therapy of choice in biochemical recurrence of primary disease[2].

From the age of 40 on, there is deterioration in bone health. Maternal family history of osteoporosis, smoking, diabetes mellitus, alcoholism and drug use increase the risk of developing osteoporosis[3-5]. Although the risk to bone health is recognized, usually patients using GnRHaare not evaluated for osteoporosis. Often the bone mineral density (BMD) before the start of antiandrogenic therapy (ADT) is not performed, and in many cases, analysis of bone health is performed only after a major adverse outcome (fracture) has occurred[6-11].

Fractures cause a significant increase in morbidity and mortality of patients during the first year after its occurrence. Its cost to the public health system is much higher than a proper investigation associated with the treatment of osteoporosis in patients with ADT. The psychosocial cost is also high for the patient's family, because patients with fractures require more intensive care, with frequent visits to the doctor, physical therapy and home assistance to perform daily activities[12,13].

The relevance of this review is to arouse attention to the research and monitoring of bone health in patients with PCa undergoing ADT, contributing to the improvement in their treatment and monitoring.

Bone health and sex hormones

Until puberty, there is no difference between genders as to skeletal growth. Since then, the influence of hormones becomes larger and promotes in man a greater periosteal apposition, characterized by longer bones, of more external and internal perimeter and greater volume of cortical bone compared with women. Therefore, in adulthood, men have a higher bone mass (larger bone), bone mineral density being higher, although the bulk density does not differ between genders[3,14].

The distinct pattern of structural modeling and bone tissue increase between men and women is related to different hormone concentrations: basically higher testosterone levels in males. Testosterone is normally metabolizedto estrogen (17β-estradiol) by the aromatase enzyme found in adipose tissue and bone.

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Bone cells express three types of steroid receptors: one androgen (AR) and two estrogen (ERα and ERβ). Several studies suggest that most of the effects of testosterone on bone cells is mediated by aromatization, allowing their binding to estrogen receptors and subsequent synthesis of mRNA and production of proteins necessary for the formation and resorption of the bone matrix[3,13-15]. It is believed that the hormones produced in the testis might influence bone metabolism by other mechanisms. A recent study suggests that there is intense communication between the testicle and the bone, mediated by various routes, such as insulin-like growth factor 3 (IGF-3), endogenous synthesis of vitamin D and calcitonin for the production of bone cells. However, more information is needed to confirm these hypotheses[16].

In addition to the accumulation of bone mass in menbeing greater than in women, bone loss rate of the former is slower over aging. This is because the decrease in the rates of sex hormones in man are more gradual than in women[3,14-17]. From the age of 40 on, there is gradual replacement of skeletal muscle tissue with fat. In the bone there is a decrease in bone density at a rate of 0.5-1% per year[3,14,17-19]. A study in men between 50 and 100 years old confirmed the role of the decline in bioavailable free testosterone and in the loss of bone mass during aging[19].

It is estimated that, in the male population of the United States over 65 years of age, approximately 1.5 million will develop osteoporosis. In many cases, this will occur in association with one or more hazardous conditions, i.e., alcoholism, diabetes, vitamin deficiency, chronic use of corticosteroids, GnRH analogues etc[20-22]. In Brazil, two studies were carried out on the prevalence of fragility fractures in the general population. Both evaluated individuals over the age of 40 years and their results concur with theinternational ones. The first[18] evaluated 325 men living in the city of São Paulo and observed osteoporosis in 15.4%, diagnoses by bonedensitometry or fracture. The second was nationwide and was published in two parts[23,24]. In it were evaluated 725 men with a mean age 58.4 ± 12.8 years and the prevalence of fractures was 12.8%.

The standards for diagnosis of osteoporosis / osteopenia used in most studies have been based on female values[6,7,10,21,23-28]. Some authors have questioned whether the use of these measured parameters in the female population could not be underestimating the incidence of bone disease in men[14]. For them, if the diagnostic criteria were adjusted for gender, the incidence of bone disease in humans could have a 13% increase[3].

Prostate Cancer

Prostate cancer (PCa) is the second leading cause of death from cancer and the most common cancer in men in the United States and Brazil. In 2010, its incidence was greater than 196,000 new cases[29]. An estimated 8,500 patients have the disease in locally advanced or advanced stages at diagnosis, which makes them eligible for antiandrogenic therapy[29].

In Brazil, in 2010, the National Institute of Câncer(INCA) estimated the average age of diagnosis of PCa in 65 years[1]. The estimated incidence of new cases was 52,350 and in the same year, 26,600 deaths had PCa as their main etiology[1]. In the estimate published for the year 2014, the overall incidence increased to 68,800 new cases[28].

Even after successful initial treatment with external beam radiotherapy, brachytherapy or resection, nearly 40% of patients with locally advanced PCa will display biochemical recurrence at any time, that is, increase in the total PSA (PSAT)[30].

The role of hormones in the promotion and development of cancer was discovered in 1941 by Huggins and Hodges. His studies identified the affinity of prostate cells by testosterone, which resulted in Huggins being contemplatedwith the Nobel Prize for Medicine and Physiology in 1966. Since then, drugs that antagonize the action of testosterone have been used in the treatment of PCa[31,32].

Therapies based on the use of estrogens have been the treatment of choice for prostatic cancer in the past, but side effects in other systems, such as increase in cardiovascular and thromboembolic events, led to the search for new drugs[20,21]. Currently, the antiandrogenic drugs most commonly prescribed for the PCa are the GnRHa[2,33-35].

Pharmacology

The gonadotropin hormone (GnRH) is a peptide synthesized in the hypothalamus in the pre-optic core. After synthesis, GnRH is transported via vesicles through the axons to the anterior pituitary gland. In the pituitary gland, GnRH stimulates the production and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

The GnRHa act by binding to receptors on the pituitary gland in a reversible way. Initially, GnRHa stimulate the secretion of gonadotropic hormones, leading to transient paradoxical increase of this hormone in the bloodstream, which increases the concentration of testosterone (flare effect)[36]. Due to this feature, GnRHais usedalong peripheral androgen inhibitors in the early treatment, preventing the advancement of cancer[36,37]. However, after three weeks of saturation of pituitary receptors, secretion of testosterone reaches levels seen in surgically castrated patients[37].

Clinical effects

The ADT hormonal changes the male pattern from eugonadism for hypogonadism in a short period (usually between 30 and 90 days). This abrupt change in androgen concentrations leads patients to complain of symptoms of acute hormonal deficiency, such as hot flashes, emotional lability, headache, fluid retention and nausea. In the long term, patients may develop gynecomastia, weight gain, decreased libido, bone loss and fractures[7,8,10,13,25,31,35,37,38].

Antiandrogenic therapy, bone loss and fractures

The age range of patients with prostate cancer is in itself a risk factor for bone disease[7,8,10,20-23]. In Brazil, the average estimated age for the diagnosis of PCa is 65 years[1,28].

After ADT initiation, bone loss occurs more intensely in the first 24 months, reaching apeak rate of 4-6% per year. After this initial period, the rate of bone loss decreases, remaining constant at 2% per year[7,9,15,20,21,38]. Even so, the loss of 2% annual bone mass is higher than the physiological loss by natural aging, ranging from 0.5 to 1% per year[19,22,27].

The literature shows that approximately 5% to 10% of patients in ADTregimen will present with fractures after two years of treatment. The risk increases with therapy time[2,13,38-40]. Other studies confirm the presence of bone disease after a long period of ADT, with prevalence of 31% and 51% for osteoporosis and osteopenia, respectively, in patients with a treatment period of less than ten years[38].

Intermittent use of GnRHa did not show any protective effect on the loss of bone density compared with continuous ADT[9,27,38]. In a study where patients had undetectable PSAT levels and had received the internationally recommended dietary supplementation of calcium and vitamin D, complete recovery of bone mineral density (BMD) at the pre ADT levels was not achieved even after a year of discontinuation of medication. The use of GnRHa further increases the risk of fractures[3,6,8,10,12,13,15,20-22,25,31,33,38,39].

COMMENTS

Despite the many literature data, an assessment of bone health is still usually neglected in ADT patients. Studies show that most doctors who work directly in the treatment of prostate cancer (urologists and / or oncologists) do not question their patients about bone symptoms[40].

In 2013, the National Osteoporosis Foundation (NOF) updated its protocol for patients at risk of developing osteoporosis[22]. It recommends that all patients above 50 years of age, before starting treatment with medications that can cause bone loss, be subjected to an assessment of their bone mineral density (BMD) by bone densitometry (DXA)[4,7,8,10,22,26,27].

There is no consensus on how to treat bone loss induced by the use of GnRHa and other medications. The literature seems to agree that exercise (aerobic and anaerobic load), sun exposure and appropriate dietary supplementation with calcium and vitamin D can reduce it, but not preventit[6-8,10,27].

Vitamin D deficiency is very common in the elderly, especially in the osteoporotic population. Studies in countries where sun exposure is more constant throughout the year (South and Central America, Africa and Middle East), have shown that vitamin D levels do not usually vary much according to the seasons and in more extreme latitudes countries (North America, Europe, Northern Asia)[3,14].

Although Brazil is a tropical country, national studies show that our people may experience a deficiency of vitamin D. In São Paulo researchers found that the late winter vitamin D rates were lower when comparedwith late summer ones in the studiedsubjects[41].

The aGnRHs are not the only drugs that induce osteoporosis[3,4,14]. Drugs such as glucocorticoids, aromatase inhibitors, proton pump inhibitors, thiazide diuretics, deposit contraceptives, unfractionated heparin, among others, also have deleterious effects recognized in bone health. The Brazilian Society of Rheumatology suggests that the cutoff points for the treatment and prevention of osteoporosis in male patients on corticosteroid therapy regimen for more than three months are, respectively, -1.8 DP and -1.0 DP[42]. Another study suggests that patients using aromatase inhibitors also have cut-off points for initiation of treatment reduced for -1.5 DP[3,16].

Although the reviewed literature does not provide enough data for this comparison, patients using GnRHa also feature a large bone loss, markedly in the first 24 months[2,13,38,40]. So maybe comparative studies were to be conducted to verify that,in patients using GnRHa, the cutoff levels for bone disease treatment initiation should be diminished, as suggested in patients taking aromatase inhibitors and corticosteroids.

RECOMMENDATIONS

Patients taking medications associated with bone loss must perform densitometry prior to treatment start. Those with normal bone mineral density (BMD) and low risk of developing osteoporosis should receive only nutritional supplementation, in order to reach 1200 mg / day of elemental calcium and 800 to 1000 IU / day of vitamin D, accompanied by physical activity. The monitoring of BMD and bone densitometry should be annual when in the presence of these drugs[4,6-8,10,22,27,42,43]. Patients with moderate to high risk (osteopenia / pre-ADT osteoporosis) who have been submitted to measuresfor patients with low risk, should undergo more aggressive treatment with bisphosphonates[4,6-8,10,22,27,32,42]. Injectable bisphosphonates appear to be more effective in preserving bone mass loss when compared with the oral ones[2,8-10,34,36,37]. The best results were achieved with the use of injectable zolendronic acid, even when performed in a single annual dose of 5 mg[8,36]. The denosumab (Dmab), a powerful anti-reabsortion drug,was recently approved for treatment of men with non-metastatic prostate cancer in ADT. Patients who received 60mg subcutaneous. Dmab vs placebo, every six months, obtained reduction in the incidence of vertebral fractures anddisplayedincreased BMD to 62% after 36 months[44].

The cost of fracture prophylaxis is significantly lower than the hospital costs of a fracture episode[4,13,36]. In

2001, it was estimated that a hip fracture cost about 12,000 pounds to the UK health system, while a year of therapy with bisphosphonates, which reduces the risk of fracture by 50%, cost 335 pounds / year[13]. In Brazil, it was estimated that the cost of a hospital osteoporotic hip fracture in the Supplementary Health System reaches R$ 24,000.00[45].

FINAL CONSIDERATIONS

Bone loss associated with antiandrogenictherapy in patients with prostate cancer is underestimated by physicians around the world. The economic and social costs for the treatment of osteoporotic fractures are high. After hospital discharge, patients often need physical therapy to help them return to their normal activities. In some cases, full recovery is never reached, and affected individuals will need assistance to enable them to perform their daily activities for the rest of their lives. The adoption of measures to avoid the appearance of fractures should be encouraged due to their benefits to affected individuals and their families, and the high costs that a fragility fracture imposes to the health system in general.

R E S U M O

A terapia antiandrogênica (TAD) para câncer de próstata representa um fator de risco adicional para o desenvolvimento de osteoporose e fraturas de fragilidade. Mesmo assim, a saúde óssea dos pacientes sob TAD frequentemente não é avaliada. Após pesquisa na literatura, observamos que medidas preventivas simples podem prevenir a perda de massa óssea nestes pacientes, resultando em soluções mais custo-efetivas para o Sistema Público de Saúde e familiares quando comparadas ao tratamento das fraturas.

Descritores*: Neoplasia da Próstata. Hormônios. Osteoporose. Hormônio Liberador de Gonadotropina/análagos & derivados. Testosterona/antagonistas & inibidores.*

REFERENCES

1. Faria EF, Carvalhal GF, Vieira RA, Silva TB, Mauad EC, Tobias-Machado M, ET al. Comparison of clinical and pathologic findings of prostate cancers detected through screening versus conventional referral in Brazil.ClinGenitourin Cancer. 2011;9(2):104-8.
2. Loblaw DA, Virgo KS, Nam R, Somerfield MR, Ben-Josef E, Mendelson DS, et al. Initial hormonal management of androgen-sensitive non metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J ClinOncol. 2007;25(12):1596-605.
3. Khosla S, Amin S, Orwoll E. Osteoporosis in men. Endocr Rev. 2008;29(4):411-64.
4. DavidgePitts CJ, Kearns AE. Update on medications with adverse skeletal effects. Mayo Clin Proc. 2011;86(4):338-43.
5. Watts NB, Adler RA, Bilezikian JP, Drake MT, Eastell R, Orwoll ES, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. J ClinEndocrinolMetab. 2012;97(6):1802-22.
6. Diamond TH, Higano CS, Smith MR, Guise TA, Singer FR. Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. Cancer. 2004;100(5):892-9.
7. Guise TA. Bone loss and fracture risk associated with cancer therapy. Oncologist. 2006;11(10):1121-31.
8. Body JJ, Bergmann P, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, et al. Management of cancer treatment-induced bone loss in early breast and prostate cancer — a consensus paper of the Belgian Bone Club. Osteoporos Int. 2007;18(11):1439-50.
9. Higano CS. Androgen-deprivation-therapy-induced fractures in men with nonmetastatic prostate cancer: what do we really know? Nat ClinPract Urol. 2008;5(1):24-34.
10. Body JJ. Prevention and treatment of side-effects of systemic treatment: bone loss. Ann Oncol. 2010;21Suppl 7:vii180-5.
11. Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. J Urol. 2013;189(1 Suppl):S34-42; discussion S43-4.
12. Townsend MF, Sanders WH, Northway RO, Graham SD Jr. Bone fractures associated with luteinizing hormone-releasing hormone agonists used in the treatment of prostate carcinoma. Cancer. 1997;79(3):542-50.
13. Peters JP, Fairney A, Kyd P, Patel A, Rogers S, Webster JJ, et al. Bone loss associated with the use of LHRH agonists in prostate cancer. Prostate Cancer Prostatic Dis. 2001;4(3):161-6.
14. Vanderschueren D, Vandenput L, Boonen S, Lindberg MK, Bouillon R, Ohlsson C. Androgens and bone. Endocr Rev. 2004;25(3):389-425.
15. Falahati-Nini A, Riggs BL, Atkinson EJ, O'Fallon WM, Eastell R, Khosla S. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. J Clin Invest. 2000;106(12):1553-60.
16. Ferlin A, Selice R, Carraro U, Foresta C. Testicular function and bone metabolism—beyond testosterone. Nat Rev Endocrinol. 2013;9(9):548-54.
17. Taxel P, Kennedy DG, Fall PM, Willard AK, Clive JM, Raisz LG. The effect of aromatase inhibition on sex steroids, gonadotropins, and markers of bone turnover in older men. J Clin Endocrinol Metab. 2001;86(6):2869-74.
18. Tanaka T, Latorre MR, Jaime PC, Florindo AA, Pippa MG, Zerbini CA. Risk factors for proximal femur osteoporosis in men aged 50 years or older. Osteoporos Int. 2001;12(11):942-9.
19. Lopes RF, Ferreira SA, Coeli CM, Farias ML. Low body mass index and declining sex steroids explain most age-related bone loss in Brazilian men. Osteoporos Int. 2009;20(7):1175-82.
20. Smith MR, McGovern FJ, Fallon MA, Schoenfeld D, Kantoff PW, Finkelstein JS. Low bone mineral density in hormone-naïve men with prostate carcinoma. Cancer. 2001;91(12):2238-45.
21. Smith MR. Diagnosis and management of treatment-related osteoporosis in men with prostate carcinoma. Cancer. 2003;97(3 Suppl):789-95.

22. National Osteoporosis Foundation. 2013 Clinician's guide to prevention and treatment of osteoporosis [Internet]. Washington, DC: NationalOsteoporosis Foundation. [Acessado: 14 dez 2013]. Disponível em: http://nof.org/files/nof/public/content/resource/913/files/580.pdf
23. Pinheiro MM, Ciconelli RM, Martini LA, Ferraz MB. Clinical Risk factors for osteoporosis fractures in Brazilian women and men: the Brazilian Osteoporosis Study (BRAZOS). Osteoporos Int. 2009;20(3):399-408.
24. Pinheiro Mde M, Ciconelli RM, Martini LA, Ferraz MB. Risk factors for recurrent falls among Brazilian women and men: the Brazilian Osteoporosis Study (BRAZOS). Cad SaudePublica. 2010;26(1):89-96.
25. Hatano T, Oishi Y, Furuta A, Iwamuro S, Tashiro K. Incidence of bone fracture in patients receiving luteinizing hormone-releasing hormone agonists for prostate cancer. BJU Int. 2000;86(4):449-52.
26. Diamond TH, Bucci J, Kersley JH, Aslan P, Lynch WB, Bryant C. Osteoporosis and spinal fractures in men with prostate cancer: risk factors and effects of androgen deprivation therapy. J Urol. 2004;172(2):529-32.
27. Higano C, Shields A, Wood N, Brown J, Tangen C. Bone mineral density in patients with prostate cancer without bone metastases treated with intermittent androgen suppression. Urology. 2004;64(6):1182-6.
28. Brasil. Ministério da Saúde. Instituto Nacional de Câncer José de Alencar Gomes da Silva. Estimativa 2014: incidência do câncer no Brasil [Internet]. Rio de Janeiro: INCA. 2013. [Acessado: 07 mai 2014]. Disponível em: http://www.inca.gov.br/estimativa/2014/sintese-de-resultados-comentarios.asp
29. United States of America. Center for Diseases Control and Prevention. Prostate Cancer: Prostate Cancer Statistics [Internet]. Chamblee: CDC 2013. [Acessado: 14 dez 2013]. Disponível em: http://www.cdc.gov/cancer/prostate/statistics/index.htm
30. United States of America. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology-v.2.2014. Prostate Cancer [Internet]. Fort Washington: NCCN.org. [Acessado: 02 jan 2014]. Disponível em: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
31. Oefelein MG, Ricchuiti V, Conrad W, Seftel A, Bodner D, Goldman H, et al. Skeletal fracture associated with androgen suppression induced osteoporosis: the clinical incidence and risk factors for patients with prostate cancer. J Urol. 2001;166(5):1724-8.
32. Charles B. Huggins, MD, 1901-1997. Acessado em 14 de dezembro de 2013. Disponível em: http://www.uchospitals.edu/news/1997/19970113-huggins.html
33. Serpa Neto A, Tobias-Machado M, Esteves MA, Senra MD, Wroclawski ML, Fonseca FL, et al.Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2012;15(1):36-44.
34. Miyaji Y, Saika T, Yamamoto Y, Kusaka N, Arata R, Ebara S, et al. Effects of gonadotropin-releasing hormone agonists on bone metabolism markers and bone mineral density in patients with prostate cancer. Urology. 2004;64(1):128-31.
35. Morgans AK, Smith MR. Bone-targeted agents: preventing skeletal complications in prostate cancer. UrolClin North Am. 2012;39(4):533-46.
36. Klotz LH, McNeill IY, Kebabdjian M, Zhang L, Chin JL; Canadian Urology Research Consortium. A phase 3, double-blind, randomised, parallel-group, placebo-controlled study of oral weekly alendronate for the prevention of androgen deprivation bone loss in nonmetastatic prostate cancer: the Cancer and Osteoporosis Research with Alendronate and Leuprolide (CORAL) study. Eur Urol. 2013;63(5):927-35.
37. Cançado BL, Miranda LC, Fleiuss ML, Madeira M. Bone mineral density in prostate cancer patients with drug induced hypogonadism. J EndocrinolDiabetes Obes. 2014;2(1):1017.
38. Weston R, Hussain A, George E, Parr NJ. Testosterone recovery and changes in bone mineral density after stopping long-term luteinizing hormone-releasing hormone analogue therapy in osteoporotic patients with prostate cancer. BJU Int. 2005;95(6):776-9.
39. Ahmadi H, Daneshmand S. Androgen deprivation therapy: evidence-based management of side effects. BJU Int. 2013;111(4):543-8.
40. Tanvetyanon T. Physician practices of bone density testing and drug prescribing to prevent or treat osteoporosis during androgen deprivation therapy. Cancer. 2005;103(2):237-41. Erratum in: Cancer. 2006;106(11):2530.
41. Unger MD, Cuppari L, Titan SM, Magalhães MC, Sassaki AL, dos Reis LM, et al. Vitamin D status in a sunny country: where has the sun gone? ClinNutr. 2010;29(6):784-8.
42. Pereira RM, Carvalho JF, Paula AP, Zerbini C, Domiciano DS, Gonçalves H, et al. Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis.Rev Bras Reumatol. 2012;52(4):569-93.
43. Lee CE, Leslie WD, Lau YK. A pilot study of exercise in men with prostate cancer receiving androgen deprivation therapy. BMC Cancer. 2012;12:103.
44. Smith MR, Egerdie B, Hernández Toriz N, Feldman R, Tammela TL, Saad F, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. NEngl J Med. 2009;361(8):745-55.
45. Araújo DV, Oliveira JHA, Bracco OL. Custo da fratura osteoporótica de fêmur no sistema suplementar de saúde brasileiro. Arq Bras Endocrinol Metab. 2005;49(6):897-901.

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Treatment of gastrointestinal stromal tumor (GIST) during bariatric surgery

Tratamento de tumor gastrointestinal estromal (GIST) durante cirurgia bariátrica

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A B S T R A C T

The gastrointestinal stromal tumor (GIST) is a rare mesenchymal tumor. One should pay special attention when the GIST comes in obese patients during surgery. The laparoscopic resections with standard techniques, such as gastric bypass, have been described with good results. However, GIST resection associated sleeve gastrectomy for the treatment of obesity is rare, but can be done safely, depending on the location of the tumor.

Key words: Obesity. Obesity, Morbid. Bariatric Surgery. Gastrectomy. Postoperative Complications. Gastrointestinal Stromal Tumors.

INTRODUCTION

The gastrointestinal stromal tumor (GIST - Gastrointestinal Stromal Tumor) is a rare mesenchymal tumor, though the most common in the digestive tract 1. The clinical presentation depends on its location, which can be from the esophagus to the anus, and it is more common in the stomach (60%). Surgical treatment is the gold standard and should be indicated as soon as the diagnosis is made 2.

GIST can be asymptomatic, diagnosed with routine examinations, or even recognized during laparoscopy. Laparoscopic resection with already standardized techniques, such as gastric bypass, have been described with good results 3. But resection of gastric GIST during vertical gastroplasty is rare 4.

TECHNIQUE

We report an alternative surgical strategy to treat patients with GIST that need to be submitted to surgical treatment of obesity. The technique used was the vertical banded gastroplasty in a patient 54 years of age, male gender, morbid obesity (weight: 109kg, height: 1,59m, BMI: 43), with type II diabetes, hypertension and severe hepatic steatosis. Preoperative endoscopy found a submucosal, hypervascular lesion, located in the posterior wall of the gastric fundus, measuring approximately four centimeters in diameter. The results of four biopsies were inconclusive. Computed tomography of the abdomen showed no other abnormalities.

At laparoscopic inventory, we could not find the tumor. We then opted for a digestive endoscopy for perioperative marking of the lesion with perilesional injection of methylene blue. We started by the release of the greater curvature of the stomach with the sealing of the left gastroepiploic vessels for greater mobilization of the stomach and visualization of the posterior lesion. We followed with the gastric release to identify with certainty the marking on the posterior wall around the lesion (Figure 1). We emphasize that we routinely do the stapling of the sleeve first, releasing the vascularization only after completely dividing the stomach,, according to the standardization of the described technique. However, in this case described we chose the variation of the surgical procedure to better visualize the tumor. We introduced the Fouchet-type 32 gastric catheter for the sleeve calibration (Figure 2). We performed the first two shots with a 45 mm load for thick tissue, keeping the distance of three centimeters from the pylorus. This distance is important to prevent the narrowing of the *incisura angularis* and hence a gastric fistula. We continued the to gastroplasty with 60mm load for normal tissue. The last two shots were made with 45mm loads for thin tissue, fully encompassing the lesion under direct vision (Figure 1). We then Tested the integrity of the sleeve with the introduction of methylene blue by the Fouchet catheter. We removed the specimen and placed a 19FR silicone drain in abdominal cavity.

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The next day, the patient started oral intake of clear fluids and was discharged on the second day after surgery. Histopathology confirmed GIST without mitotic activity (index 0x50 in high-power field). Immunohistochemical examination showed positive CD117 and CD34 cells. Six months after the operation the patient had lost 23 Kg in weight. The medications used prior to gastric resection were stopped (insulin, captopril and hydrochlorothiazide).

DISCUSSION

The incidence of previously undiagnosed diseases encountered during operations to treat obesity is estimated at 2%, and gastric GIST, around 0.8% of patients 5. Since GIST is an tumor of the submucosa and / or muscle layers of the digestive tract, endoscopy can be falsely negative. When a GIST is found in a obese patient, ones must give special attention to the gastric study, because during gastric bypass, undiagnosed disease may remain in the excluded stomach, which will be inaccessible to routine exams 2. During the sleeve preparation, although there resection and continuity of the normal transit, one should pay attention to the exact location of the lesion so as to ascertain the possibility and feasibility of safely using this technique without causing stenosis or tortuosity in the staple line (Figure 2). Stenosis of the *incisura angularis* allows for the existence of fistula in the His angle that can be very serious, even causing the patient's death 6.

According to the criteria established by the National Institutes of Health, our case of GIST can be considered a benign tumor. Therefore, we deemed the resection curative with safety margins and, therefore, treatment with Imatinib was not indicated.

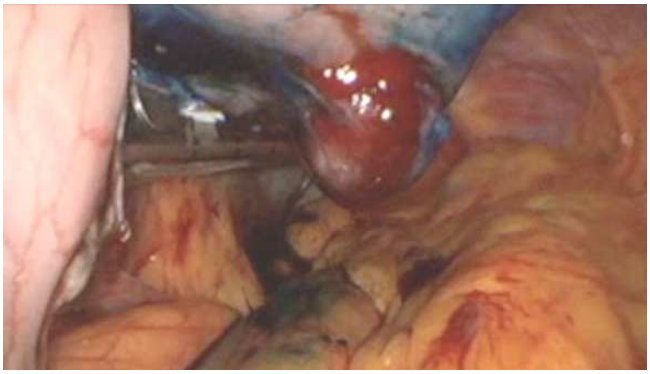

Figure 1 - *Gastroplasty with resection of the lesion.*

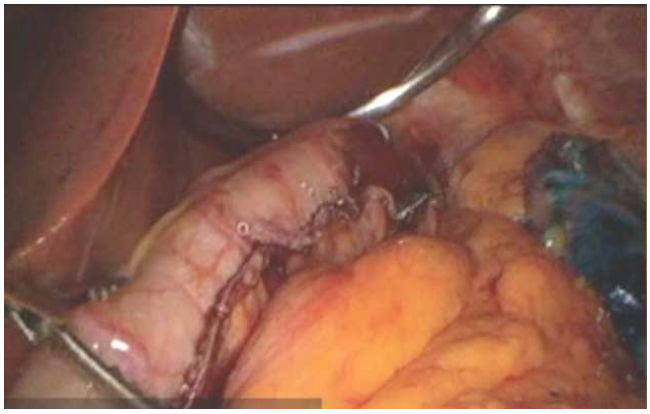

Figure 2 - *Final appearance of the sleeve.*

R E S U M O

O tumor estromal gastrointestinal (GIST) é um tumor mesenquimal raro. Deve-se ter atenção especial quando o GIST apresenta-se em pacientes obesos durante o ato operatório. As ressecções laparoscópicas com técnicas padronizadas, como o bypass gástrico, têm sido descritos com bons resultados. Porém, a ressecção de GIST associada à gastrectomia vertical para o tratamento para a obesidade é rara, mas pode ser feito com segurança, dependendo da localização do tumor.

Descritores: *Obesidade. Obesidade Mórbida. Cirurgia Bariátrica. Gastrectomia. Complicações Pós-Operatórias. Tumores do Estroma Gastrointestinal.*

REFERENCES

1. Graadt van Roggen JF, van Velthuysen ML, Hogendoorn PC. The histopathological differential diagnosis of gastrointestinal stromal tumours. J Clin Pathol. 2001;54(2):96-102.
2. Saund MS, Demetri GD, Ashley SW. Gastrointestinal stromal tumors (GIST). Curr Opin Gastrointerol. 2004;20(2):89-94.
3. Sanchez BR, Morton JM, Curet MJ, Alami RS, Safadi BY. Incidental finding of gastrointestinal stromal tumors (GISTs) during laparoscopic gastric bypass. Obes Surg. 2005;15(10):1384-8.
4. Beltran MA, Pujado B, Meìndez PE, Gonzaìles FJ, Margulis DI, Contreras MA, Cruces KS. Gastric gastrointestinal stromal tumor (GIST) incidentally found and resected during laparoscopic sleeve gastrectomy. Obes Surg. 2010;20(3):393-6.
5. Finnell CW, Madan AK, Ternovits CA, Menachery SJ, Tichansky DS. Unexpected pathology during laparoscopic bariatric surgery. Surg Endosc. 2007;21(6):867-9.
6. Stol A, Gugelmin G, Lampa-Júnior VM, Frigulha C, Selbach RA. Complicações e óbitos nas operações para tratar a obesidade mórbida. ABCD, arq bras cir dig. 2011;24(4):282-4.

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