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Have the current and promising therapeutic options changed the surgeon's role in the treatment of pancreatic cancer?

As atuais e promissoras opções terapêuticas modificaram o papel do cirurgião no tratamento do câncer de pâncreas?

Emilio Vicente MD PhD FACS[1], Yolanda Quijano Md PhD[1].

Pancreatic cancer (PC) has been a poor prognosis tumor for many years. The general factors that have always contributed to this, such as the anatomical location of the gland with its extensive lymphatic connections and the absence of clinical symptoms that allow an early diagnosis, add up to the scarce accomplishment of radical surgical procedures capable of achieving free-margins resections and the absence of effective chemo and radiotherapeutic procedures. Due to these circumstances, survival results have been very disappointing. Thus, a marked skepticism about this disease has been spread among patients and medical professionals[1].

In the last ten years, notable therapeutic changes have occurred. Through them, it was possible to prove a slow but progressive improvement in results, with special repercussion in some reference groups that, due to their large series, have a wide experience in this field[2].

The diagnostic methodology has improved remarkably. Through radiology, endoscopy and radioisotopes, it is now possible to detect patients with disseminated and / or locally advanced disease. The greatest problem arises in the evaluation of vascular involvement. In our country, the combination of helical computed tomography and echo-endoscopy allows us to preoperatively detect 75% of patients with PC who will require arterial or venous resection associated with pancreatic resection. The study of these patients should be as broad as possible to clearly define local commitment and its possible dissemination. The goal is to operate only those patients who may benefit from an oncologic resection, avoiding unnecessary procedures (surgeries with positive margins) that in some occasions surpass 40% of the operated patients[3].

Venous infiltration of pancreatic tumors located in the cephalic position or on the isthmus was considered a criterion of irresectability for a long time. The technical complexity and the apparent small oncological benefit seemed to justify this attitude. Currently this criterion has been clearly overcome. A better surgical technique in the field of vascular surgery, achieved by specialists in pancreatic surgery, has made venous resection a standard procedure in the treatment of suchh patients. In order to obtain free margins, about 30% of our patients require venous resection.

From an oncological perspective, a question that currently does not have a clear answer is whether vascular invasion is always a sign of greater aggressiveness and, consequently, worse prognosis. In some patients it may be considered as such, especially in large lesions. However, in others, the aforementioned invasion stems only from an "unfavorable anatomical tumor location" and does not represent greater biological aggressiveness. Similar results obtained in many PC patients treated with or without vascular resection support the latter theory.

Arterial resection represents a different, though controversial, scenario. Virtually all clinical guidelines consider patients with this type of vascular involvement to be inoperable and unresectable. The first descriptions of combined pancreatic and arterial resections occurred in lesions located in the pancreatic body with invasion of the celiac trunk. The modified Appleby technique[4], described in 1953, allows its realization without the need to perform hepatic revascularization. The hepatic vascularization is maintained through the pancreato-duodenal branches of the superior mesenteric artery. The

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gastroduodenal artery must be preserved. The surgical challenge of this technique is the arterial resection, but the most complex part from the technical point of view is the subsequent reconstruction[5].

Few groups in the world carry out resections of the common or proper hepatic artery, right hepatic artery or superior mesenteric artery in patients with PC. We established a rigorous selection criterion: non-disseminated lesions no larger than 3 cm and always after receiving a neoadjuvant treatment (radiochemical) for at least three months[6].

On the other hand, vascular resection may in some occasions constitute an important technical necessity. Lymphadenectomy performed over arterial axes with intense perineural involvement may in some cases lead to arterial wall lesions, including rupture. The clinical manifestation is the presence of hemorrhage, in some cases massive, by the formation of arterial pseudoaneurysms. If occurring in the early postoperative days, this usually has a dramatic evolution. In those cases in which, after completion of lymphadenectomy, there are important changes in the artery characteristics, it should be resected[7].

Of all the factors that contribute to increase PC patients'survival, the most important is the obtaining free margins. Therefore, vascular resection in selected patients can not and should not be a limiting factor to this goal, although this clearly increases the risk of the operation, especially if the resection is double, arterial and venous. Any PCpatient who will undergo surgery requires that the surgical team, in addition to trying to obtain an R0 resection, have a sufficient degree of experience in vascular surgery to be able to perform it.

Another important aspect is to determine the real therapeutic benefit in these patients. It is difficult to establish it. Only the neoadjuvant treatment allows knowing the patient who, at least theoretically, can benefit. Patients with disease progression during or after neoadjuvant treatment should not be candidates for surgical treatment. Therefore, due to the difficulty in establishing adequate preoperative staging (perineural involvement), neoadjuvant treatment should be performed in all PCpatients.

In certain cases, other factorsinfluence patients' survival in an unknown way. Like other groups, we have described prolonged survival in patients with PC, with or without multidisciplinary treatments. In general, these patients are carriers of small, well-differentiated tumors with no involvement of lymph nodes and / or resection margins. Some patients, however, had prolonged survival despite presenting with locally advanced tumors and poor prognostic factors, including metastases. These results demonstrate the heterogeneity of PCbiological behavior. In most cases, the biology of cancer, rather than the classic pathological factors, determinespatients' prognosis. But it is certain that there is an essential requirement to obtain a prolonged survival: the accomplishment of a radical surgery with free margins.

The new concepts on PC characteristics are opening new hopeful therapeutic perspectives. PC had a dense stroma. Pancreatic star cells (or myofibroblasts)play an important role in the formation and replacement of the stroma. This is not only a mechanical barrier, but is involved in the formation and progression to metastases. Stromal cells express a variety of proteins that are associated with resistance to treatment. These proteins represent new therapeutic targets. Therapy directed to the modification of the stroma allows to increase tumor vascularization, with consequent increased diffusion and, mainly, of the clinical efficacy of drugs on pancreatic tumors[8,9].

In addition, within the tumors a subpopulation of neoplastic cells with pluripotential properties was identified. In PC these stem cells (1 to 5% of the tumor population) are resistant to radiation and chemotherapy, which could explain their inefficacy and the recent interest in directing treatment to these specific cells[10].

New drugs include small molecules that inhibit signaling pathways and oncogenes. The recognition that both the tumor microenvironment and the neoplastic stem cells are critical elements of PC led to the development of agents, such as the inhibitors of the hedgehog signaling pathway, that block these components. The availability of preclinical models torecapitulate the complexity of this disease helps to establish strategies and priorities for the development of new drugs and innovative therapies.

Ultimately, the PC genomic complexity demonstrates the heterogeneity of this type of cancer and advises individualization of treatment methods.

The role of the surgeon today is clearly defined in the treatment of PC: select patients who, according to their clinical situation and the characteristics of the disease, can benefit from the surgical treatment, and perform an R0 resection as safely as possible. This role has not changed in recent years, and it is still certain that there are more and more arguments to keep it.

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Profile of the appendectomies performed in the Brazilian Public Health System

Perfil das apendicectomias realizadas no Sistema Público de Saúde do Brasil

Fernanda dos Santos[1]; Gabriel Flamarim Cavasana[1]; Tercio de Campos, TCBC-SP[1].

ABSTRACT

Objective: *to analyze the profile of appendectomies performed in the Brazilian Public Health System (SUS) and to compare the laparoscopic and laparotomic techniques of appendectomy.* **Methods:** *This work used information from DataSus from 2008 to 2014 (http://datasus.saude.gov.br). We compared the data of patients submitted to laparotomic appendectomy with those submitted to laparoscopic one.* **Results:** *when comparing the total growth of appendectomies, the laparoscopic route increased 279.7%, while the increase in laparotomic surgery was 25% (p <0.001) in the study period. With regard to medical and hospital costs, laparoscopic appendectomy accounted for only 2.6% of the total expenditure on appendectomies performed by the Unified Health System (SUS) hospitals, with an average cost 7.6% lower than that of laparotomy procedures, but without statistical significance. The mortality rate was 57.1% lower in the laparoscopic approach when compared with laparotomy.* **Conclusion:** *there has been a significant increase in the laparoscopic route in the treatment of appendicitis, but the method is still rarely used in SUS patients. The costs of laparoscopic appendectomy were similar to those observed in laparotomic access.*

Keywords: *Appendicitis. Laparoscopy. Appendectomy. Health Expenditures.*

INTRODUCTION

Acute appendicitis is the most common cause of acute abdomen in the child, adolescent, and young adult, with a peak incidence in the 2nd and 3rd decades of life[1]. In 1894, McBurney established the surgical treatment as the best way to handle acute appendicitis, and in 1983, Kurt Semm, a German gynecologist, performed the first laparoscopic appendectomy[2]. Despite the description of the success of the clinical treatment of acute appendicitis by some authors, appendectomy, either laparotomic or laparoscopic, continues to be the treatment of choice[3,4]. Technical variations of these access routes are described in the literature, depending on the stage of the disease and its evolution, the patient's clinical situation, the surgeon's experience, aesthetic aspects, the patient's anatomy and the availability of local resources.

The classic laparotomic approach is through the McBurney[5] incision. The laparoscopic approach, usually performed through three ports, is a minimally invasive method and associated with a lower incidence of postoperative pain[6,7].

It is of extreme relevance that studies are made to compare the techniques and encourage the training of professionals with the modern surgical methods, when these are superior. Santos Júnior and Guimarães emphasize the evidence-based surgical practice on the importance of research with high scientific background[8].

The objective of this study is to analyze the profile of appendectomies performed at SUS and to compare the laparoscopic and laparotomic techniques.

METHODS

This work used DataSus information from 2008 to 2014 (http://datasus.saude.gov.br). To obtain the data, the we used the Portuguese terms for "appendectomy" and "videolaparoscopic appendectomy". The analyzed variables were: total number of hospitalizations, total hospitalization costs, mean hospitalization costs, mean length of stay and mortality rate. We compared the data of patients submitted to laparotomic appendectomy with those submitted to laparoscopic one. We placed the data in an Excel spreadsheet and exposed it in charts. For statistical analysis, w used the Chi-square test, considering p <0.05 as significant. The work was approved by the Ethics and Research Committee of the

1 - Anhembi Morumbi University, Sao Paulo, Sao Paulo State, Brazil

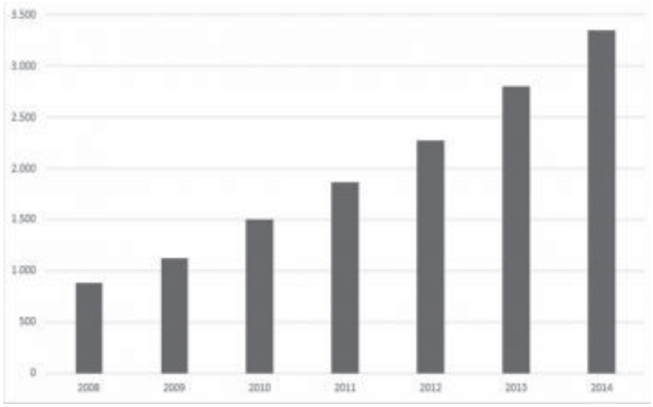

Figure 1. *Evolution of the number of laparoscopic appendectomies between 2008 and 2014.*

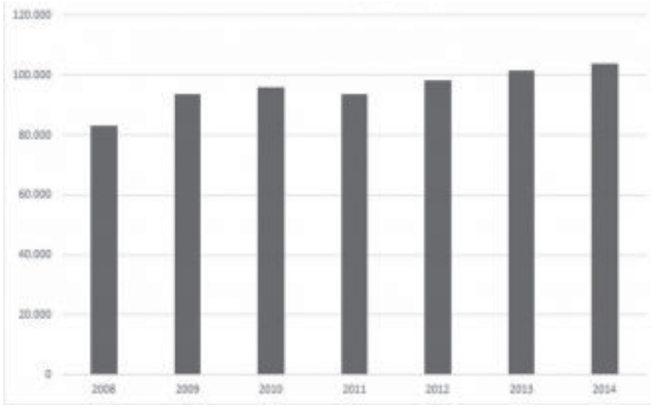

Figure 2. *Evolution of the number of appendectomies by laparotomy between 2008 and 2014.*

Anhembi Morumbi University of São Paulo, approval number: CAAE 57409016800005492.

RESULTS

The total number of appendectomies was 684,278 in this period, with a mean of 97,754 per year. Of this, 2% were laparoscopic, representing 13,801 procedures in absolute values. When comparing the total growth between the years 2008 and 2014, the laparoscopic route increased by 279.7%, while the increase in appendectomy by laparotomy was 25% ($p < 0.001$) (Figures 1 and 2).

The number of laparoscopic surgeries in the South Region of the country corresponded to 57% of the total number of those performed in Brazil, followed by the Southeast Region, with 29%. The laparotomic route was used in these regions in 21% and 41% of the total number of surgeries, respectively (Figure 3).

The total cost of surgeries performed, counting medical and hospital expenses, was R$ 318,207,595.08. Of this total, surgeries with laparoscopic access accounted for 2.6%, with an expenditure of R$ 8,137,417.59, while for the laparotomic procedures the total expenses were R$ 310,070,177.49. The average cost of the laparoscopic surgeries was R$ 500.06, 7.6% less than that of conventional surgeries, which had an average cost of R$ 537.88, however without a statistically significant difference.

The mean length of hospital stay with laparotomies was 3.8 days, while with laparoscopy, 3.6 days, with no statistical difference.

The mortality rate was 57.1% lower in the laparoscopic route when compared with the laparotomic one during the seven years of analysis (0.12% x 0.28%), a statistically significant difference (Figure 4).

DISCUSSION

Acute appendicitis is the most common intra-abdominal pathological condition requiring surgical intervention. Thus, it is extremely relevant that reference services have surgeons trained to perform the surgical technique that brings greater benefits to the patient and that can deal with eventual complications of the surgical procedure[9]. Most appendectomies in SUS patients are still performed through laparotomy. There is no consensus in the literature regarding the benefit of the laparoscopic route in relation to the laparotomic one, especially when regarding costs and mortality. Although the laparoscopic approach requires specific instruments and greater technical qualification, our study demonstrated that there was no increase in hospitalization costs when using the laparoscopic route. However, the need for specific equipment associated with the need for surgeon training justifies the lesser use of the laparoscopic technique in SUS. There are a number of surgeons who still do not master the laparoscopic technique, and the material needed to perform the procedure is not widely available in hospitals attending SUS patients. But considering that only 2% of the surgical treatments of acute appendicitis were performed laparoscopically in the period studied and that this has a 7.6% lower cost in relation to the

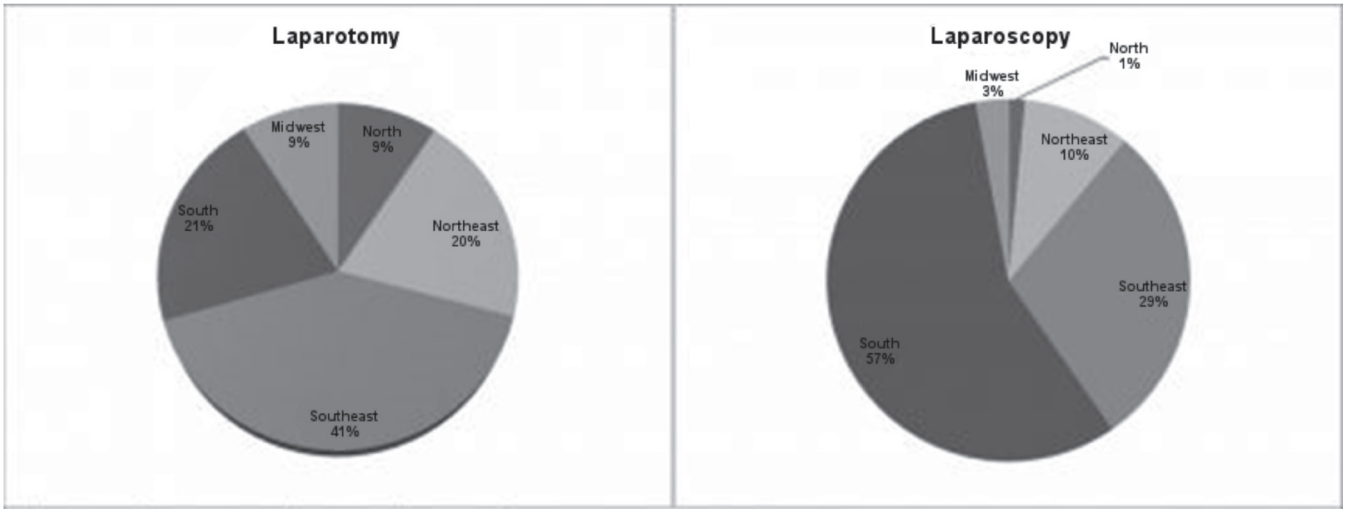

Figure 3. *Distribution of laparoscopic and laparotomic surgeries in Brazil's five regions between 2008 and 2014.*

laparotomic route, taking into account the figures raised in this work, if all surgeries had been performed laparoscopically, there would be a reduction in the total cost of approximately R$ 23 million.

In addition, laparoscopic surgery is a less invasive method with less repercussions, both systemic and in the abdominal wall[10,11]. In this study with SUS patients, there was a 57.1% reduction in the mortality rate in relation to laparotomy. It should be considered, however, that there was no comparison between the access routes by gravity of the cases and. It is possibly that more complicated patients had the initial approach by laparotomy.

Contrary to what we observed in our study, most patients with acute appendicitis operated in private hospitals are preferably submitted to laparoscopic surgery[12]. This reality, however, is already beginning to change, since we observed a significant increase in the number of laparoscopic procedures in the Study period, well above the increase in open appendectomies. The Southern Region of Brazil was where the largest number of laparoscopic surgeries were performed, possibly due to the easier access to equipment and to the surgeons training.

Early recovery, less need for analgesics, earlier return to daily activities and better aesthetic results are major factors in favor of laparoscopic appendectomy[11,13,14]. Our results, however, did not show a significant difference in patients' mean hospital stay. Sozutek *et al.*[15] conducted prospective, randomized study and found a significant difference in length of hospital stay, in which the laparoscopic route showed a reduction of 0.8 days in relation to the laparotomy ($p < 0.05$). In our country, this fact could contribute to increase the availability of beds in SUS hospitals.

The tendency is that laparoscopic surgery becomes the method of choice for appendectomies, as reported by Coccolini *et al.*[16] in a recent literature systematic review. The method was superior in cases of obese and female patients[1], besides facilitating the exploration of the entire abdominal cavity when necessary, allowing differential diagnoses and cleaning of the cavity[6]. In patients with peritoneal adhesions due to previous surgeries, with generalized peritonitis or with previous intra-abdominal inflammatory diseases, laparoscopic surgery may present greater technical difficulty and greater chance of conversion to laparotomy[10,12].

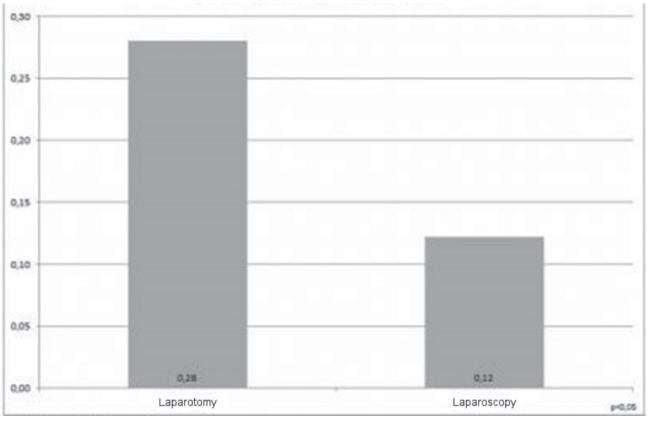

Figure 4. *General mortality rate according to the access route.*

This paper presents some limitations. One of these occurs due to the restriction of the information in the DataSus, since this database does not allow to widely evaluate the patients' epidemiological profile. Variables such as gender, ethnicity, age range, comorbidities prior to admission, complications related to the main disease, degree of inflammation of the appendix are also not available in this database. Groups of patients were similar, which could somehow compromise the final analysis. A better development in the database, especially considering clinical and surgical urgencies, can be useful in the planning of strategies for the best service of the population in the emergency services. In addition, it uses data only from patients treated at SUS hospitals, not allowing the analysis of patients operated in private medical services. On the other hand, the series obtained by this database is considerable and the most extensive so far in the country.

Thus, the present study suggests that the laparoscopic route has a growth potential for the treatment of acute appendicitis in Brazil, with the possibility of reducing treatment costs.

R E S U M O

Objetivo: analisar o perfil das apendicectomias realizadas no Sistema de Saúde Pública (SUS) do Brasil e comparar as técnicas de apendicectomia, por via laparoscópica e laparotômica. **Método:** este trabalho utilizou informações do DataSus de 2008 a 2014 (http://datasus.saude.gov.br). Foram comparados os dados dos doentes submetidos à apendicectomia laparotômica com aqueles submetidos à apendicectomia laparoscópica. **Resultados:** ao se comparar o crescimento total das apendicectomias, a via laparoscópica aumentou 279,7%, enquanto o aumento da cirurgia laparotômica foi 25% (p<0,001) no período do estudo. Com relação aos custos com despesas médicas e hospitalares, a apendicectomia vídeo-laparoscópica representou apenas 2,6% do gasto total em apendicectomias realizadas por hospitais do Sistema Único de Saúde (SUS) com custo médio 7,6% inferior ao das cirurgias por via laparotômica, porém sem significância estatística. A taxa de mortalidade foi 57,1% menor na via laparoscópica quando comparado com a laparotômica. **Conclusão:** vem havendo um aumento significativo da via laparoscópica no tratamento das apendicites, mas o método ainda é pouco utilizado nos doentes do SUS. Os custos da apendicectomia laparoscópica se mostraram semelhantes aos observados nos acessos laparotômicos.

Descritores: Apendicite. Apendicectomia. Laparoscopia. Gastos em Saúde

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Lower extremity reconstruction: epidemiology, management and outcomes of patients of the Federal District North Wing Regional Hospital

Reconstrução de membros inferiores: perfil, manejo e evolução dos pacientes do Hospital Regional da Asa Norte do Distrito Federal

Jefferson Lessa Soares Macedo, TCBC-DF[1,2]; Simone Corrêa Rosa[1,3]; Daniel Lobo Botelho[1]; Clendes Pereira dos Santos[1]; Murilo Neves de Queiroz[2]; Tabatha Gonçalves Andrade Castelo Branco Gomes[2].

ABSTRACT

Objective: *to evaluate the management of lower limbs complex traumatic injuries by analyzing their characteristics, types, conduct and evolution, with emphasis on surgical treatment.* **Methods:** *we conducted a prospective study of patients treated by Plastic Surgery at a regional hospital of the Federal District during a one-year period. We collected data through serial evaluations and telephone contact records.* **Results:** *we studied 40 patients, with a mean age of 25.6 years, predominantly male (62.5%). The most frequent wounds were of the distal third of the lower limb (37.5%). Bone or tendon exposures occurred in 55% had and there was a 35% rate of exposed lower limb fractures. The treatments employed were skin grafting (57.5%), local fasciocutaneous flap (15%), muscle flap (12.5%), cross-leg fasciocutaneous flap, reverse sural flap (12.5%) and microsurgical flap (2.5%). Short-term evaluation showed that 35 patients had excellent or good results (87.5%), four had a regular result (10%), and one had an unsatisfactory result (2.5%). In the long term, of the 18 patients who answered the questionnaire, ten resumed walking, even with support, in the first three months after surgery (55.6%).* **Conclusion:** *young men involved in motorcycle accidents during leisure time represented the profile of patients with lower limb trauma requiring surgical reconstruction; the distal third of the leg was the most affected region. Grafting was the most used technique for reconstruction and postoperative functional evaluation showed that, despite complex lesions, most patients evolved with a favorable healing process and successful functional evolution.*

Keywords: *Lower Extremity. Wounds and Injuries. Injury Severity Score. Surgery, Plastic.*

INTRODUCTION

Trauma is one of the main causes of preventable death and one of the main mechanisms of complex wound formation affecting young adults and a large part of the economically active population[1].

Lower limb wounds reach a variable spectrum, and are generally caused by high-energy trauma, with extensive skin loss and impaired tissue viability, associated with amputations of limbs or fingers, lacerations, crushing and exposures of noble tissues[1]. Over the last 30 years, advances in reconstructive surgery, such as the recognition and use of pediculated fasciocutaneous/muscular flaps and the introduction of microsurgery have broadened the therapeutic arsenal of the plastic surgeon in the treatment of traumatic injuries[1-6]. In addition, the lower limbs, especially the leg and foot, have some characteristics that make it difficult to treat wounds in this region, such as: thin skin coating; scarce subcutaneous tissue; terminal arterial vascularization; venous return made difficult by the orthostatic position; and of heavy loads for most of the time[7,8].

The evaluation, follow-up and decision of surgical treatment of these complex lesions are conducts taken by a multidisciplinary team, with the fundamental participation of the plastic surgeon. Functional recovery should always be sought, regardless of the proposed treatment, reconstruction or amputation[8,9].

The objective of this study is to present the epidemiological profile, treatment and evolution of patients sustaining lower limbtrauma treated at the Plastic

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METHODS

This is a prospective study of patients victims of lower limbtrauma admitted to the HRAN, who underwent surgical reconstruction of the lower limbs due to loss of skin cover, with and without bone exposure, from January to December 2011. Patients were admitted to the Plastic Surgery Service by direct referral from the emergency room or outpatient clinic, but only after clinical / surgical control of their fractures by orthopedics, general surgery and / or other services. All patients underwent surgical treatment of their wounds, from debridement to complete coverage of defects. None of them was submitted to second intention healing, to the use of vacuum dressing or to the use of acellular dermis replacement.

We evaluated the following variables: gender, age, trauma etiology, presence and location fractures, characteristics of the substance loss, presence of bone exposure and type of treatment established in lower limb reconstructions.

The initial basic treatment of open fractures was performed, on average, in the first 24 to 48 hours after the trauma, and consisted in all cases of mechanical and surgical cleaning associated with transskeletal traction, bipolar fixation, immobilization with a cast material, or external fixation. In cases of closed fractures, patients received plates and screws, osteosynthesis with crossed Kirschner wires, or bipolar fixation.

In the immediate postoperative period, patients were immobilized with cruropodal plaster cast. The first dressing was performed on the fifth postoperative day and stitches were removed around the 15th day. In the donor area of the skin graft, we used vaseline gauze and 10% zinc oxide cream to accelerate the healing process.

We performed the short-term postoperative assessment (one to two months) by observing the cutaneous cover, classifying wound healing in: "Excellent": no graft or flap distress; "Good": suffering of up to a third of the graft or flap; "Regular": suffering from graft or flap up to one-third with signs of infection; or "Unsatisfactory": graft or flap loss greater than one-third".

We carried out the analysis of the long-term outcome, performed at least 48 months postoperatively, through telephone contact. Patients responded to a questionnaire based on Harris Score and Vancouver International Scale for scars[10-12]. The questionnaire included seven categories: use of support for ambulation, presence of claudication, distance that can walk, postoperative period in which began to walk, pain in the operated region and quality of the scar (presence of secretion and flexibility). To consider failure in the telephone contact, we made at least six calls on three different days.

We used The SPSS version 17.0 program for data compilation, graphics assembly and epidemiological analysis.

The study was approved by the Ethics in Research Committee of the State Department of Health of the Federal District (CAAE number: 47391715.6.0000.5553, opinion number: 1,167,841).

RESULTS

During the study period, there were 40 patients with complex wounds caused by trauma to the lower limbs. The mean age was 25.6 years, ranging from two to 56 years, with a predominance of the 20-29 age group. There was a predominance of males, representing 62.5% of the sample. Regarding etiology, motorcyclist accidents (52.5%)were the most prominent,followed by run-over accidents (22.5%). Regarding the place or circumstance, leisure time was the main moment of trauma, followed by work accidents (Table 1).

The mean wound time before the evaluation by the Plastic Surgery Team was one week. Measurements of the areas requiring treatment ranged from 3x5 cm to 5x12 cm. Loss of substance from the distal third of the leg was the most frequent (37.5%), followed by lesions of the middle and upper third, respectively. Regarding fractures or other orthopedic injuries, 35%

Table 1. *Descriptive data of patients sustaining lower limb trauma attended at HRAN from January to December in 2011.*

	Number	%
Gender		
Male	25	62.5%
Female	15	37.5%
Origin		
Federal District	22	55%
Outside the Federal District	18	45%
Age group		
0-19 years	10	25%
20-29 years	20	50%
30-39 years	5	12.5%
> 39 years	5	12.5%
Type of accident		
Motorcycle	21	52.5%
Run-over	9	22.5%
Agricultural Machine	4	10%
Automotive	3	7.5%
Fall	2	5.0%
Fire arm	1	2.5%
Trauma context		
Leisure	18	45%
Work	7	17.5%
Other	15	37.5%

of the patients did not present them; 35% suffered tibial/fibular fracture; 7.5% suffered a femoral fracture; and 22.5% suffered other fractures or orthopedic injuries such as dislocation, tendon rupture and patellar fracture. Bone exposure occurred in 55% of patients and the other 45% had only soft tissue loss, without bone or tendon exposure (Table 2).

The treatment proposed for each case was in agreement with the presence or absence of bone exposure. We used total or partial skin graft for the wounds with good granulation tissue without exposure of noble structures, representing 57.5% of the procedures (Figure 1). We The flaps for major substance loss or exposure of noble structures, divided into: fasciocutaneous flap (15%), muscular flap of the medial head of the gastrocnemius (12.5%), reverse sural fasciocutaneous flap (7.5%), cross-leg fasciocutaneous flap (5%) and microsurgical anterolateral thigh fasciocutaneous flap (2.5%) (Figure 2, Table 3).

The short-term evaluation of the cutaneous cover showed that 35 patients had excellent or good results (87.5%), four had a regular result (10%) and one had an unsatisfactory result (2.5%).

Regarding the long-term evaluation, of the 18 patients who answered the questionnaire, ten started walking, even with support, in the first three months after surgery (55.6%), three in the second trimester (16.7%), two in the second semester (11.1%) and the other three after one year (16.7%). Among the patients who answered the questionnaire, none was unable to walk. We assessed mobility by dividing the patients into five groups: wheelchair; walking with the aid of crutches - two or one -; walking with the aid of a walking stick; walking without assistance. Four years after the surgical procedure to cover the loss of leg substance due to trauma, 88.9% of the patients walked without assistance and 11.1% with the help of a walking stick or a crutch. Regarding claudication, 44.4% of the patients reported no pain or only mild pain without functional impairment, 38.9% reported moderate claudication, which made it impossible to run, and 16.7% reported severe claudication, with intense pain. We measured the distance the patients could walk in blocks, with 22.2% being able to walk unlimited distances, 50% able to walk long distances (more than three blocks), 16.7%, a maximum of two or three blocks, and only 11.1% could walk only indoors (Table 4).

Table 2. *Characteristics of the substance loss area of patients sustaining lower limb trauma attended at HRAN from January to December in 2011.*

	Number	%
Substance loss área of leg		
Proximal 1/3	12	30%
Medium 1/3	13	32.5%
Distal 1/3	15	37.5%
Bone exposure		
Yes	22	55%
No	18	45%
Presence of open fracture		
Yes	15	37.5%
No	25	62.5%

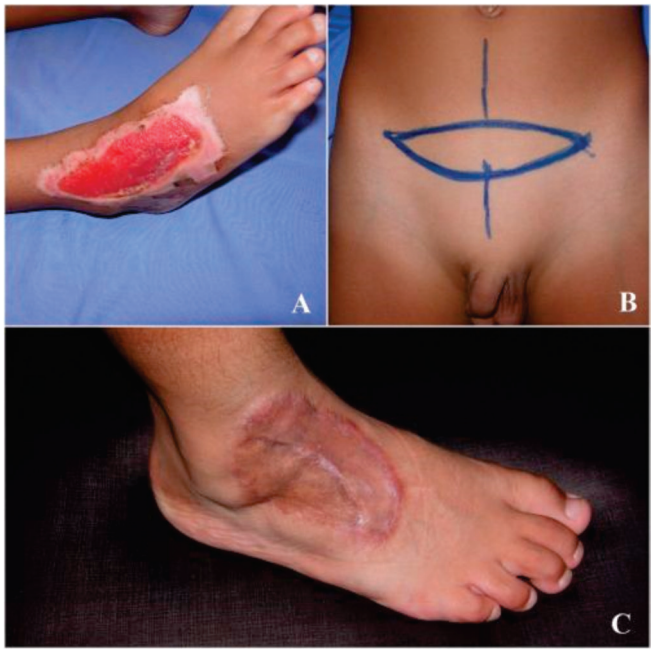

Figure 1. *A) An 8-year-old child who was a run-over victim, with loss of substance on the back of the right foot, without bone or tendon exposure. B) Skin graft donor area. C) Two months after skin graft on the foot dorsum.*

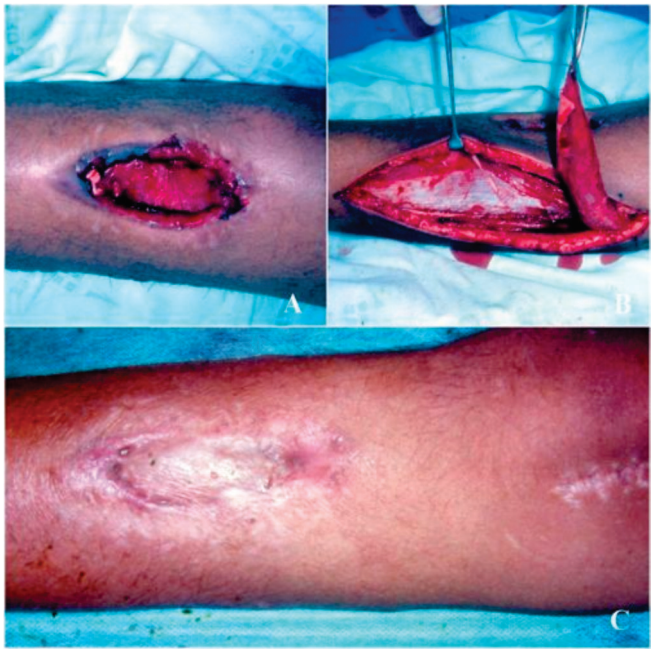

Figure 2. *A) A 22-year-old patient victim of motorcycle accident, with bone exposure of the middle third of leg. B) Release of the medial head of the gastrocnemius muscle. Positioning of the muscular flap in the middle third of the leg. C) Skin graft over the Gastrocnemius medial head muscular flap, four months after the procedure.*

Only one patient reported severe pain in the reconstructed region, with serious limitations to daily activities.Five patients reported moderate, tolerable pain, and seven, occasional pain, without compromising activities. Five patients reported no pain after reconstruction of the lesion. We evaluated the scars in two aspects: presence of secretion and flexibility in the region. Fifteen patients reported dry scarring (83.3%) and three patients remained with secretion outflow (16.7%). Regarding flexibility, 16 patients (88.9%) reported some movement limitation and only two reported no functional limitation due to the scar (Table 4).

DISCUSSION

The treatment of wounds with loss of substance in lower limbs due to trauma, infection or vascular processes is a challenge to surgeons and often requires the use of specialized techniques to cover bones, tendons, nerves, vessels and osteosynthesis materials. In this study, we verified, by the mean age of 25.6 years of the victims of accidents involving the lower limbs, that this type of trauma mainly affects the part of the society that is economically active, bringing great socioeconomic impact. In addition, the major cause of these accidents is related to motorcycle use and pedestrian involvement (run-overs), which are gradually increasing in large cities and capitals, probably due to the increase in vehicular traffic and difficulties in adapting cities to high demand for public transportation, emphasizing the importance of public policies for traffic safety. This type of trauma has a high socioeconomic cost, leading to work absence for long periods, as has been verified in other studies[13-15].

Although most of the patients involved in the traumas were in leisure time (45%), a good portion of the injured (17.5%) were in their working hours or in the home-work path, which constitutes a work accident in Brazil.

The aim of surgical treatment in lower limb reconstructions is maximum limb functional recovery and return to work activities. Therefore, many studies advocate the early surgical coverage of complex wounds to avoid surgical site infection, ensure better bone remodeling, and shorten hospital stay[16-18]. Other studies have proposed a protocol that includes a series of surgical procedures from debridement to stabilization of the

Table 3. *Distribution of surgical treatment types and the level of the lesion in patients sustaining lower limb trauma attended at HRAN[1], from January to December in 2011.*

Level of the injury	Graft[2]	Muscle flap[3]	Neighborhood Flap[4 ‘]	Reverse sural flap[4 ‘’]	Cross Leg[5]	Micro surgical[6]	Total
Proximal 1/3	9 (22.5%)	3 (7.5%)	0	0	0	0	12 (30%)
Medium1/3	4 (10%)	2 (5%)	5 (12.5%)	0	2 (5%)	0	13 (32.5%)
Distal 1/3	10 (25%)	0	1 (2.5%)	3 (7.5%)	0	1 (2.5%)	15 (37.5%)
Total	23 (57.5%)	5 (12.5%)	6 (15%)	3 (7.5%)	2 (5%)	1 (2.5%)	

[1]HRAN= North Wing Regional Hospital; [2]Sole skin grafting; [3]Gastrocnemius medial head muscle flap; [4 ‘]Neighbourhood Fasciocutaneous Flap; [4 ‘’]Reverse Sural Fasciocutaneous Flap; [5]Cross-leg Fasciocutaneous Flap; [6]Microsurgical Anterolateral Thigh Flap.

wound, avoiding further complications[19,20]. In our study, performed in a hospital that does not have a polytrauma service, the majority of patients had outpatient admission for elective hospitalization at the Plastic Surgery Service for surgical programming, after clinical and hemodynamic stabilization, wound infection control, adequate debridement and fractures stabilization. Therefore, patients who were victims of traumatic or operative amputation were excluded.

The vascular conditions of the limb, both arterial and venous, should be carefully evaluated, both preoperatively and postoperatively. Circulatory diseases may be present and the trauma itself may render unfeasible apparently well-planned flaps.

The present study shows that 55% of the patients presented bone exposure, and 35% had a tibial/fibular fracture. We treated most patients with bone exposure with flaps for coverage, while patients who did not show bone exposure were treated with skin grafts. When they presented good granulation tissue without exposure of noble structures, the treatment of choice was partial or total skin grafting and outpatient monitoring of the healing process. In other situations, such as poor granulation tissue or exposure to noble structures such as bone, tendon, or vascular-nervous pedicles, the treatment consisted of fasciocutaneous or muscular flaps, according to the location of the wound bed, size, neighboring tissue structures and vascular preservation of the affected limb. We decided not to use negative pressure dressings because, despite reducing the bloody area and the complexity of the wound, they are contraindicated in wounds with exposure of blood vessels or nerves, bone or tendon.

The high grafting rate (57.5% of the patients) used in this period is due to the characteristics of the lesions associated with the treatment of the wound bed, debridements and dressings, allowing the coverage with granulation tissue and good receptor bed for skin grafting. We used skin grafts in cases of substance loss that presented good granulation tissue, but without bone, tendon or vascular-nervous pedicles exposure. The formation of wound granulation tissue was stimulated with surgical debridements of the devitalized tissueand alginate or zinc oxidedressings.

The treatment with flaps obeyed guidelines already established in the literature, according to the area of substance loss, but there is still no consensus on the type of biological flap to be used, fasciocutaneous or myocutaneous[21]. This type of approach divides the leg in thirds to facilitate the choice of flap as a surgical option for wound coverage. The lower third of the leg had the most frequent substance loss, 37.5% of the patients, the surgical options being: skin grafts, reverse flow

Table 4. *Functional postoperative evaluation of patients victims of lower limbs trauma attended at HRAN from January to December in 2011, four years after the surgical procedure.*

Support	
None	16
Cane	1
Crutch	1
Claudication	
None	5
Light, without hampering function (goes down stairs, runs)	3
Moderate (can't run)	7
Severe	3
How far can you go	
Unlimited	4
Far, more than three blocks	9
At most two or three blocks	3
Only indoors	2
How long took to walk after surgery (even with support)	
Doesn't walk	0
First quarter	10
Second quarter	3
Second semester	2
After one year	3
Pain in the region	
None	5
Casual, doesn't compromise activities	7
Moderate, tolerable pain, but makes concessions to pain	5
Sharp pain, serious limitation to activities	1
SCAR	
Dry	15
Secretion output	3
Flexibility in the scar area	
With limitation of movement	16
Without limitation of movement	2

fasciocutaneous flaps, and neighborhood fasciocutaneous flaps. We treated calcaneal and ankle substance losses (7.5% each) with reverse sural fasciocutaneous flap and free microsurgical anterolateral thigh fasciocutaneous flap, respectively. The second most affected area of the leg was the middle third, totaling 32.5% of the cases, being treated with skin grafts, neighborhood fasciocutaneous flaps, cross-leg fasciocutaneous flaps or Gastrocnemius medial head muscular flap[9,22,23].

The Gastrocnemius medial head muscular flap is a good option to cover bony exposures of the upper and middle third of the leg and does not leave motor sequelae. We performed it in five patients (12.5%). Similar results have been observed in other studies, including the concomitant use of the soleus muscle in cases of large bone exposure[7,24]. Distal reverse pedicle flaps, such as the reverse sural, have proved to be of great utility and versatility, especially for lesions of the distal third of the leg[25]. We used this flap in three patients.

The microsurgical flap remains one of the main options for limb reconstruction, especially in the lower third of the leg and foot, when there is no donor area for the reverse sural flap. However, microsurgical techniques require specialized training and there are no specialists in most hospitals to perform them. We used this technique in only one patient (2.5%) with loss of foot substance and no donor area for the reverse sural flap.

We indicated cross-leg flaps in two patients (5%) with substances losses from the lower third of the leg that did not present a donor area for the reverse sural flap or local fasciocutaneous flaps; also, microsurgery was not available at the time. The cross-leg flap has the disadvantage of prolonged immobilization and uncomfortable resting positions.

The repair surgery of lower limb wounds currently has an arsenal of procedures capable of solving most cases. Whenever possible, one should choosesimple and non-invasive procedures, to achieve an early rehabilitation of these patients.

Our study showed that young men involved in motorcycle accidents during leisure time represented the profile of patients with lower limb trauma who required

surgical reconstruction, the distal third of the leg being the most affected region. Grafting was the most used technique for reconstruction and postoperative functional evaluation showed that, despite complex lesions, most patients evolved with a favorable healing process and successful functional evolution.

R E S U M O

Objetivo: avaliar o tratamento de feridas traumáticas complexas de membros inferiores analisando suas características, tipos, condutas e evolução, com ênfase no tratamento cirúrgico. **Métodos:** estudo prospectivo de pacientes tratados pela Cirurgia Plástica em um hospital regional do Distrito Federal no período de um ano. Os dados foram coletados através de avaliações seriadas e registro de contatos telefônicos. **Resultados:** foram estudados 40 pacientes com média de idade de 25,6 anos, predominantemente homens (62,5%). As feridas do terço distal do membro inferior foram mais frequentes (37,5%). 55% apresentavam exposições óssea ou tendinosa e 35%, fraturas expostas do membro inferior. O tratamento foi enxerto de pele (57,5%), retalho fascio-cutâneo local (15%), retalho muscular (12,5%), retalho fascio-cutâneo de perna cruzada, retalho sural reverso (12,5%) e retalho microcirúrgico (2,5%). A avaliação em curto prazo evidenciou que 35 pacientes tiveram resultado excelente ou bom (87,5%), quatro tiveram resultado regular (10%), e um teve resultado insatisfatório (2,5%). Em longo prazo, dos 18 pacientes que responderam ao questionário, dez deambularam, mesmo que com apoio, no primeiro trimestre após a cirurgia (55,6%). **Conclusão:** nosso estudo mostrou que o perfil dos pacientes com trauma de membros inferiores que necessitaram de reconstrução cirúrgica foi representado por homens jovens, envolvidos em acidentes motociclísticos, durante situação de lazer, sendo o terço distal da perna a região mais acometida. A enxertia foi a técnica mais utilizada para reconstrução e a avaliação funcional pós-operatória demonstrou que, apesar de lesões complexas, a maioria dos pacientes evoluiu com processo de cicatrização favorável e sucesso na evolução funcional.

Descritores: Extremidade Inferior. Ferimentos e Lesões. Escala de Gravidade do Ferimento. Cirurgia Plástica.

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Conversion of Plastic Surgery meeting abstract presentations to full manuscripts: a brazilian perspective

Conversão dos resumos apresentados em congressos de Cirurgia Plástica em manuscritos completos: uma perspectiva brasileira

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A B S T R A C T

Objective: *to assess the conversion rate of Plastic Surgery meeting abstract presentations to full manuscript publications and examine factors associated with this conversion.* **Methods:** *we assessed the abstracts presented at the 47th and 48th Brazilian Congresses of Plastic Surgery by cross-referencing with multiple databases. We analyzed the Abstracts' characteristics associated with full manuscript publications.* **Results:** *of the 200 abstracts presented, 50 abstracts were subsequently published in full, giving the conference a conversion rate of 25%. The mean time to publish was 15.00±13.75 months. In total, there were 4.93±1.63 authors per abstract and 67.8±163 subjects per abstract; 43.5% of the abstracts were of retrospective studies; 69% comprised the plastic surgery topics head and neck, and chest and trunk, and 88.5% had no statistical analysis. Overall, 80% of the manuscripts were published in plastic surgery journals, 76% had no impact factor and 52% had no citations. Bivariate and multivariate analyses revealed the presence of statistical analysis to be the most significant (p<0.05) predictive factor of conversion of abstracts into full manuscripts.* **Conclusion:** *the conversion rate found from this bibliometric research appeared a bit lower than the conversion trend of international plastic surgery meetings, and statistical analysis was a determinant of conversion success.*

Keywords: *Meeting abstracts. Manuscripts. Publications*

INTRODUCTION

Brazil's scientific production has increased substantially, reaching an average growth rate of 10.7% per year[1]. However, as presentations of abstracts at different Brazilian medical meetings have been accompanied by a relatively low conversion rate into full manuscript publications in peer-reviewed, indexed journals[2-8], this scientific growth could potentially be higher. Therefore, a continuous analysis of the conversion rate should be performed to encourage members of each academic society to publish full manuscripts[2-8].

In this context, there has been no data about the conversion rate from Brazilian Plastic Surgery meetings, although international Plastic Surgery meetings have been analyzed[9-13]. In addition, we are not aware of any investigation of possible predicting factors for the publication of plastic surgery meeting abstracts as full manuscripts[9-13].

Thus, the purposes of this quantitative, descriptive, bibliometric study were to assess the conversion rate of Brazilian plastic surgery meeting abstracts into full peer-reviewed, indexed manuscripts and to examine possible predicting factors of this conversion. We hypothesized that despite increased diffusion of the necessity of full manuscript publications within the Brazilian plastic surgery community[14,15], the conversion rate after Brazilian plastic surgery meeting presentations would be inferior than the international plastic surgery trends[9-13].

METHODS

Identification of abstracts

Two independent authors identified and analyzed the abstracts through examination of the online supplements published by the Brazilian Society of Plastic Surgery (*Sociedade Brasileira de Cirurgia Plástica* – SBCP) from the 47th and 48th Brazilian Congresses of

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Plastic Surgery, held in 2010 and 2011, respectively. We recorded the following quantitative bibliometric data for each individual abstract: year (2010 or 2011; periods 1 and 2, respectively); number of authors (1-3, 4-5, or >6); plastic surgery topic (head and neck; chest and trunk; extremities; general; or others) according to designation in the meeting programs; number of included subjects (1, 2–10, 11–50, 51–100, or >101); presence of statistical analysis; and study designs (randomized clinical trial, systematic review, simple review, prospective study, retrospective study, case series, case reports, and others)[2-8,16-18].

Full manuscript publication search

We identified the publications in peer-reviewed journals by a standardized searching of the Medline (PubMed), ISI Web of Knowledge, SciELO, Lilacs, and Google Scholar databases through March 2015. We used the last name and the first letter of the first name of the first author of the abstracts. If we dis not find an exact match or if there were no results to a search, we repeated the process using the second and the last authors of the abstracts. If the result included no publication or several publications with the same author, we applied an additional criterion, such as another author or keywords from the title or text of the abstract to expand or simplify the search. Whenever we retrieveda peer-reviewed manuscript, we compared the abstract information with those of the full publication to establish whether they matched in accordance with the stringent criteria previously used[16-18].

For each matching publication, we recorded the following data: period between the abstract presentation and the publication (<12 months; 12-36 months; >36 months); journal name; database indexing journal (ISI Web of Knowledge and Medline; Medline; SciELO; or Lilacs); impact factor of the journal according to the Thompson Reuters Journal Citation Report® on the date of publication; language of the publication (English, Portuguese, or English/Portuguese); and the number of citations of the manuscript according to Google Scholar and ISI Web of Knowledge (if indexed journal)[6,9,12,16-18].

Statistical analyses

For the descriptive analysis, we used the mean and standard deviations for numerical variables and percentages for categorical variables. We defined the conversion rate as the ratio between the number of subsequently published articles in peer-reviewed journals and the total number of abstracts presented at the scientific meetings[18]. We performed intra- and inter-period (period 1 versus period 2) comparisons. We used Analysis of Variance, Equality of Two Proportions, Paired Student's T, Chi-Square, and Confidence Interval for the Mean tests for statistical comparisons. We performed bivariate and multivariate logistic regression analyses to determine which independent abstract variables (number of authors, number of subjects, plastic surgery topic, presence of statistical analysis and study designs) were significant predictors for the conversion of abstracts into full manuscripts (dependent variable). We also calculated theinterobserver reliability between the two authors who collected all of the data. We performed all analyses using the software program Statistical Package for Social Science (SPSS version 20.0 for Windows, Chicago, IL, USA). We considered as significant values with a confidence interval of 95% ($p < 0.05$).

RESULTS

We included two hundred meeting abstracts in this bibliometric study, with an excellent interobserver agreement (all values between 0.86 and 0.99) for all evaluated abstracts and manuscript variables.

Meeting abstract characteristics

Overall, there was a significant (all $p < 0.05$) predominance in the proportion of abstracts including: more than six authors; 11-50 subjects/abstract; head and neck, and chest and trunk plastic surgery topics; absence of statistical analysis; and retrospective study design. The inter-period analyses revealed a significant

Table 1. *Characteristics of Plastic Surgery meeting abstracts (n=200).*

Abstrat variables	2010-2011 (n=200)	2010 (n=100)	2011 (n=100)	p-value**
Authors/abstract M±SD	4.93±1.63	5.09±1.56	4.76±1.69	0.153
1-3 n (%)	40 (20)	18 (18)	22 (22)	0.480
4-5 n (%)	52 (26)	27 (27)	25 (25)	0.747
>6 n (%)	108 (54)	55 (55)	53 (53)	0.777
p-value *	<0.001	<0.001	<0.001	–
Subjects/abstract M±SD	67.8±163	68.4±130	67.2±193	0.963
1 n (%)	22 (13.3)	4 (4.7)	18 (22.5)	<0.001
2-10 n (%)	41 (24.7)	21 (24.4)	20 (25)	0.931
11-50 n (%)	61 (36.7)	40 (46.5)	21 (26.2)	0.007
51-100 n (%)	18 (10.8)	7 (8.1)	11 (13.8)	0.245
>101 n (%)	24 (14.5)	14 (16.3)	10 (12.5)	0.489
p-value *	<0.001	<0.001	<0.001	–
Plastic surgery topic n (%)				
Head and neck	76 (38)	37 (37)	39 (39)	0.771
Chest and trunk	62 (31)	29 (29)	33 (33)	0.541
Extremities	33 (16.5)	23 (23)	10 (10)	0.013
General	25 (12.5)	11 (11)	14 (14)	0.521
"Other"	4 (2)	0 (0)	4 (4)	0.043
p-value *	<0.001	<0.001	<0.001	–
Statistical analysis n (%)				
Present/Absent	23 (11.5) / 177 (88.5)	14 (14) / 86 (86)	9 (9) / 91 (91)	0.268
p-value *	<0.001	<0.001	<0.001	–
Study designs n (%)				
Randomized clinical Trial	2 (1)	1 (1)	1 (1)	1.000
Systematic review	1 (0.5)	0 (0)	1 (1)	0.316
Simple review	15 (7.5)	7 (7)	8 (8)	0.788
Prospective study	15 (7.5)	5 (5)	10 (10)	0.179
Retrospective study	87 (43.5)	54 (54)	33 (33)	0.003
Case series	43 (21.5)	23 (23)	20 (20)	0.606
Case reports	22 (11)	4 (4)	18 (18)	0.002
Other	15 (7.5)	6 (6)	9 (9)	0.421
p-value *	<0.001	<0.001	<0.001	–
Published as full manuscript n (%)				
Yes/No	50 (25) / 150 (75)	32 (32) / 68 (68)	18(18) / 82(82)	0.022
p-value *	<0.001	<0.001	<0.001	–

*M, Mean; SD, standard deviation; *, intra-period comparisons; **, inter-period comparisons; –, not applicable;*
Note 1: sample size not stated in 34 abstracts due to study designs.

(all $p < 0.05$) increase (period 1 < period 2) in the proportion of abstracts with one subject/abstract, case reports, and "other" study designs; and a significant (all $p < 0.05$) decrease (period 1 > period 2) in the proportion of abstracts with 11-50 subjects/abstract, extremities topics, and retrospective study design (Table 1).

Full manuscript characteristics

Overall, there were 50 (25%) matching full manuscripts, and a significant (all $p < 0.05$) predominance in the proportion of abstracts published as full manuscripts within 12 months after meeting presentations, manuscripts in Portuguese, manuscripts published in plastic surgery journals, journals indexed in the SciELO database, journals without an impact factor, and manuscripts without citations. The inter-period analyses revealed a significant (all $p < 0.05$) reduction (period 1 > period 2) in the proportion of abstracts converted into full manuscripts and manuscripts in English/Portuguese languages (Table 2).

Bivariate and multivariate analyses

Bivariate analysis revealed that abstracts with 1-3 and 4-5 authors/abstract, one subject/abstract, general plastic surgery topic, and case reports were significantly (all $p < 0.05$) less converted into full manuscripts. Bivariate and multivariate analyses demonstrated that the presence of statistical analysis was the most significant (all $p > 0.05$) predictive factor of conversion success (Table 3).

DISCUSSION

Abstract presentations at scientific meetings are an integral component of medical research, in which investigators can share their results with others and meeting attendees may obtain new information[18,19]. Although acceptance of an abstract by a scientific meeting is prestigious, ideally abstracts should be followed by a full manuscript publication in peer-reviewed journals for several reasons: key novel findings and useful information should also be available to the general scientific community who did not participate in the meetings; abstracts alone have many defects, inaccuracies, and only preliminary data; abstracts have been devoid of information that is needed for evaluating validity and reliability; and abstracts are accepted for presentations without a peer-review process or have been reviewed less thoroughly than what is typical of journal manuscripts[18,19]. In addition, adverse consequences of research inaccessibility include: unnecessary duplication, delays in the dissemination of advances in patient-care strategies, harm to patients, waste of limited resources, and loss of (trust in) scientific integrity[20]. In fact, research ethical obligations require the appropriate dissemination and publication of all research outcomes[21], and empirical evidence indicates the existence of research dissemination bias, as published studies tend to be systematically different from unpublished studies[22].

It is also noteworthy that the conversion rate may be regarded as an indicator of the scientific level of a certain society's meeting[12]. Interestingly, however, a considerable proportion of medical meeting abstracts have never been published as full manuscripts[18]. In Brazil, the publication rates from different medical fields were previously established[2-8]. To the best of our knowledge, there has been no similar research from a Brazilian plastic surgery perspective, although there are recent bibliometric plastic surgery data[14,15].

Therefore, in response to an identified gap in the national plastic surgery literature, we quantified conversion rates from the major Brazilian plastic surgery meeting. Our rationale for evaluating this particular meeting was threefold: first, it is the most important scientific plastic surgery event in Brazil; second, it is applicable to a wide plastic surgery audience, as it is general in nature; and third, Brazilian Portuguese was the primary language of presentation. Plastic surgeons are invited to submit scientific abstracts that are reviewed for relevance and scientific value by a scientific committee called that Department of Scientific Events of SBCP. Our data is mainly from a plastic surgery perspective, but our bibliometric research is also important for the overall Brazilian scientific

Table 2. *Characteristics of plastic surgery full manuscripts (n=50).*

Manuscript variables	2010-2011 (n=50)	2010 (n=32)	2011 (n=18)	p-value**
Time from presentation to publication (months) M±SD	15.00±13.75	15.48±13.76	14.11±14.09	0.737
< 12 months n (%)	29 (58)	17 (53.1)	12 (66.7)	0.352
12-36 months n (%)	19 (38)	13 (40.6)	6 (33.3)	0.610
> 36 months n (%)	2 (4)	2 (6.3)	0 (0)	0.279
p-value *	<0.001	<0.001	<0.001	–
Publication language n (%)				
English	13 (26)	7 (21.9)	6 (33.3)	0.343
Portuguese	25 (50)	13 (40.6)	12 (66.7)	0.063
English/Portuguese	12 (24)	12 (37.5)	0 (0)	0.002
p-value *	<0.001	<0.001	<0.001	–
Journals n (%)				
Brazilian Journal of Plastic Surgery	22 (44)	14 (43.8)	8 (44.4)	0.651
Plastic and Reconstructive Surgery	5 (10)	3 (9.3)	2 (11.1)	0.817
Brazilian Journal of Craniomaxillofacial Surgery	5 (10)	4 (12.5)	1 (5.6)	0.451
Catarinense Medicine Archives	5 (10)	2 (6.3)	3 (16.7)	0.224
Aesthetic Plastic Surgery	4 (8)	4 (12.5)	0 (0)	0.124
Journal of the Brazilian College of Surgeons	3 (6)	3 (9.3)	0 (0)	0.187
Brazilian Journal of Head and Neck Surgery	2 (4)	2 (6.3)	0 (0)	0.287
Others	4 (8)	0 (0)	4 (22.2)	<0.05
p-value *	<0.001	<0.001	<0.001	–
Database indexing journal n (%)				
Medline and ISI	13 (26)	7 (21.9)	6 (33.2)	0.282
Medline	3 (6)	2 (6.2)	1 (5.6)	0.200
SciELO and Lilacs	1 (2)	0 (0)	1 (5.6)	0.159
SciELO	19 (38)	14 (43.8)	5 (27.8)	0.369
Lilacs	14 (28)	9 (28.1)	5 (27.8)	0.873
p-value *	<0.001	<0.001	<0.001	–
Impact factor n (%)				
Present / Absent	13 (26) / 36 (74)	7 (21.9) / 25 (78.1)	6 (33.3) / 12 (66.7)	0.343
p-value *	<0.001	<0.001	0.046	–
Manuscript citations				
Google Scholar M±SD	1.78±3.17	2.18±3.70	1.00±1.58	0.275
Yes / No n (%)	24 (48) / 26 (52)	14 (43.8) / 18 (56.2)	10 (55.6) / 8 (44.4)	0.933
p-value *	0.110	0.218	0.218	–
ISI Web of Knowledge M±SD	0.40±1.14	0.52±1.35	0.18±0.53	0.326
Yes / No n (%)	8 (16) / 42 (84)	6 (18.8) / 26 (81.2)	2 (11.1) / 16 (88.9)	0.558
p-value *	<0.001	<0.001	<0.001	–

*M, Mean; SD, standard deviation; *, intra-period comparisons; **, inter-period comparisons; –, not applicable.*

Table 3. *Bivariate and multivariate analyses for conversion rate.*

Independent variables	Bivariate analysis		Multivariate analysis (Conversion)	
	Conversion Yes / No n (%)	p-value	?	p-value
Authors / abstract				
1-3	5 (10) / 35 (23.3)	0.041	-0.041	0.954
4-5	34 (68) / 74 (49.3)	0.022		
>6	11 (22) / 41 (27.3)	0.457		
Subjects / abstract				
1	1 (2) / 21 (18.1)	0.028		
2-10	17 (34) / 24 (20.7)	0.489	0.353	0.688
11-50	23 (46) / 38 (32.7)	0.245		
51-100	4 (18) / 14 (12.1)	0.943		
> 101	5 (10) / 19 (16.4)	0.795		
Plastic surgery topic				
Head and neck	20 (40) / 56 (37.3)	0.737		
Chest and trunk	17 (34) / 45 (30)	0.596	0.281	0.570
Extremities	9 (18) / 24 (16)	0.741		
General	2 (4) / 23 (15.3)	0.036		
Others	2 (4) / 2 (1.3)	0.243		
Statistical analysis				
Present	13 (26) / 10 (6.7)	<0.001	2.010	0.008
Absent	37 (74) / 140 (93.3)			
Study designs				
Randomized clinical trial	1 (2) / 1 (0.7)	0.412		
Systematic review	0 (0) / 1 (0.7)	0.563		
Simple review	3 (6) / 12 (8)	0.642		
Prospective study	6 (12) / 9 (6)	0.163	-22.502	1.000
Retrospective study	20 (40) / 67 (44.7)	0.564		
Case series	11 (22) / 32 (21.3)	0.921		
Case reports	1 (2) / 21 (14)	0.019		
Other	8 (16) / 7 (4.7)	0.008		
Constant	–	–	-2.258	0.227

M, mean; SD, standard deviation; –, not applicable.

community, as it allows a quantitative assessment of the relative contribution from Brazilian plastic surgery investigators to the scientific scenario. It also permits the initiation of a critical reflection on actual scientific production, with potential modifications of planning by the specialty society, academic community, and governmental actions for research induction, financing, human resources training, among others, as has been proposed in other medical fields[2,7,16,17].

We showed an overall conversion rate of 25%, ranging from 32% to 18% in meetings held in 2010 and 2011, respectively. A Cochrane systematic review with meta-analysis[18] from 29,729 abstracts revealed a mean conversion rate of 44.5%, with a wide range of

conversion rates across medical specialties. Conversion rates following Brazilian scientific meetings also vary according to the assessed medical field, including: general surgery (2.6%), trauma (2.9%), angiology and vascular surgery (6.32%), cancer (16.9%), orthopedic (26.6%), and urology (39-51.3%)[2-8]. In addition, particularly from a plastic surgery perspective, our initial hypothesis proved to be right, as the overall Brazilian plastic surgery conversion rate was inferior to most of the prior international plastic surgery conversion rates (38.7%-63.7%)[9-13] and was only superior to the British Association of Plastic, Reconstructive, and Aesthetic Surgeons meeting conversion rate (20%)[9-13].

The abstract characteristics (number of subjects, number of authors, and plastic surgery topics) are in conformity with the previous bibliometric plastic surgery meeting trends[9-13]. Moreover, some of the characteristics of the manuscripts are different from previous published trends[9-13], with most abstracts being published in journals without an impact factor and only indexed in SciELO. More than 43% of the abstracts were published in the Brazilian Journal of Plastic Surgery (*Revista Brasileira de Cirurgia Plástica*), the official journal of the *SBCP*. Previous reports[9-13] also highlight that abstracts presented at meetings organized by scientific societies are preferentially submitted for publication to the official journals.

We also investigated independent abstract factors that may predict full manuscript publication, as they have not been previously investigated in the plastic surgery meeting literature[9-13]. Bivariate analysis revealed that abstracts with 1-3 and 4-5 authors/abstract and general plastic surgery topics were significantly less converted in full manuscripts. The increase in the number of authors per article has been evident in scientific literature, and may reflect a progressive complexity in academic work[23], which are potentially more likely to be published, and the increasing focus on subspecialtization of plastic surgery[24] may partially explain these findings. However, as we have not ascertained the connection, future research should test these hypotheses.

We also showed that the presence of statistical analysis was a significant determinant for conversion success, as exhibited in different societies' meetings[16,17]. Although the provision of appropriate statistical tests is an important quality criteria of abstract reporting[16], details about statistical testing were provided in only 11.5% of the evaluated abstracts; and interestingly, many retrospective studies (the major study design in our report) had a potential sample of patients, but no statistical analysis was applied. Therefore, identifying the right statistical test as an essential component of research design and ensuring that data are correctly obtained with sufficient power to address the original research hypothesis[25] should be the target of plastic surgeons in the future.

In addition, our bivariate analysis showed that abstracts with only one subject and case reports were significantly less converted into full manuscripts, whereas the study design was not significant in predicting the conversion of abstracts into full manuscripts in the multivariate analysis. Although one can assume that studies with increased methodological rigor, such as randomized clinical trials and prospective studies are likely to have higher conversion rates than case series and case reports, there are mixed results regarding the study design of meeting abstracts as a determinant factor of conversion success[16-18]. As we also showed an increase of case reports and a decrease of retrospective studies, efforts to increase publishing research with more thorough research methods in Brazilian plastic surgery must be promoted as evidence-based medicine achieves greater acceptance within the plastic surgery community[14,15].

We found that 75% of abstracts presented at the Brazilian Congress of Plastic Surgery remained unpublished after four years. The reasons why some scientific meeting abstracts remain unpublished are not entirely clear and probably act in a complex multifactorial format[19,26]. Rejection by journals may be a cause of non-publication; however, as most of the unpublished studies have not been submitted to journals, non-publication of many studies was directly caused by failure of authors

to write and submit it to journals[26]. A recent systematic review[19] revealed that among different factors (e.g., "lack of resources," "publication not an aim," "low priority," "incomplete study," and "trouble with co-authors"), "lack of time" was the most frequently reported reason and the most important reason for not subsequently publishing abstracts as full-length manuscripts. The plastic surgery literature[27] has demonstrated that a median of 177 hours is needed to take a retrospective study from idea genesis to publication, and the number of authors or subjects is not correlated with the hours spent per publication, whereas different factors (e.g., medical students, residents, and data collection) were associated with more hours spent per plastic surgery publication[27]. As we are unable to directly address the real reasons that may have influenced non-publication of abstracts, further studies should be delineated to investigate this issue.

In this context, our data reinforced previous anecdotal perceptions that regular scientific productivity has not been the rule among Brazilian plastic surgeons[14,15]. In fact, Brazil was poorly ranked (number of articles and impact factor) in recent worldwide bibliometric plastic surgery analyses[28,29], although the Brazilian plastic surgery community – with more than 5,500 plastic surgeons and 83 plastic surgery residency programs accredited by SBCP – is among one of the biggest plastic surgery communities worldwide.

Therefore, to improve conversion rates, we need major changes in the Brazilian plastic surgery research culture. Given the necessity of disseminating all research findings, mandatory full manuscript submission for publication before meeting presentation may be considered.Although this might be a radical notion and reduce the number of abstracts submitted, the result would be an increased publication yield[10,18]. Senior authors and experienced research teams should be encouraged to assist junior authors and incipient scientific groups with study completion and manuscript preparation[10,18]. In addition, the next generation of plastic surgeons should receive the knowledge that "an abstract is only a work in progress[30]," as emphasized by Dr. Joseph Murray, a Nobel laureate plastic surgeon, during the residency training process. For these culture changes, governmental, departmental and SBCP support is urgently required,for both faculties and trainees, including dedicated research time and a research infrastructure. It will be a long-term journey, but with the support of the entire Brazilian plastic surgery community, it is possible to get there.

Some inherent limitations to this study design may have influenced our results and must be considered when interpreting our findings. The variability of conversion rates may be related to the quality of meeting presentations, alterations in the criteria for abstract selection, the stringency of the publication criteria for the specialty's peer-review journals, differences of scientific profile of each specialty and medical society, and/or the inherent methodology of determining conversion rates[2-13,16-18]. Thus, the trend comparisons performed in our study should be interpreted with caution. Our results likely underestimate the overall Brazilian conversion rate after meeting presentations. Given the bibliometric nature of this study, there is the potential for selection bias; it is possible that the search strategy did not accurately identify all publications, although our methods of selection, inclusion, and analysis have been found in previous similar investigations[2-13,16-18]. We only looked at abstracts presented at one particular plastic surgery meeting, mirroring previous studies[2-9,11-13,16,17]. Thus, it is possible that the analysis of other meetings would show different rates of Brazilian plastic surgeons' contributions. Our study is also limited by the data provided by the investigators in the abstracts, as there was no information about the type of institution involved, academic status, gender of the investigators, among others. A further caveat stems from the fact that we assessed the proportional Brazilian contribution in the form of abstracts. It is conceivable that good-quality Brazilian research throughout the years analyzed was submitted for full publication without presentation at the evaluated plastic surgery meeting. Such possibility would lead to an underestimation of

Brazilian productivity. An additional limitation is that we only assessed quantitative aspects of the abstracts. Finally, a minimum 3-year period was fixed to allow time for publication of each meeting abstract, as the vast majority of publications appeared in the first three to four years after meeting presentations[2-13,16-18].

R E S U M O

Objetivo: avaliar a taxa de conversão de resumos apresentados em congressos de Cirurgia Plástica em publicações de manuscritos completos e examinar fatores associados a essa conversão. **Métodos:** resumos apresentados nos XLVII e XLVIII Congressos Brasileiros de Cirurgia Plástica foram avaliados por meio de referências cruzadas em diversos bancos de dados. Averiguaram-se as características dos resumos associadas às publicações de manuscritos completos. **Resultados:** dos 200 resumos apresentados, 50 foram posteriormente publicados na íntegra, determinando uma taxa de publicação de 25%. O tempo médio para publicação foi 15,00±13,75 meses. No total, houve 4,93±1,63 autores/resumo e 67,8±163 pacientes/resumo; 43,5% dos resumos foram estudos retrospectivos; 69% pertenciam aos tópicos crânio, cabeça e pescoço, e tórax e tronco e 88,5% não apresentavam análise estatística. No geral, 80% dos manuscritos foram publicados em revistas de Cirurgia Plástica, 76% não exibiam fator de impacto e 52% não possuíam citações. As análises bivariada e multivariada revelaram que a presença de análise estatística foi o fator preditivo significativo (p<0,05) para a conversão de resumos em manuscritos completos. **Conclusão:** a taxa de conversão deste estudo bibliométrico foi inferior à tendência de conversão descrita em congressos internacionais de Cirurgia Plástica, e a presença de análise estatística foi um determinante para o sucesso de conversão.

Descritores: Manuscritos. Cirurgia plástica. Publicações.

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Profile of thoracic trauma victims submitted to chest drainage

Perfil dos pacientes vítimas de trauma torácico submetidos à drenagem de tórax

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A B S T R A C T

Objective*: to describe and compare the variables involved in trauma victims undergoing thoracic drainage.* **Methods***: we conducted a retrospective, analytical, descriptive, cross-sectional study, with medical records of patients attended at the Trauma Service of the Curitiba Evangelical University Hospital between February 2011 and January 2014.* **Results***: there were 488 patients undergoing chest drainage, 84.7% men and 15.3% women, with an average age of 38.2 years. Attendances usually occurred at night, without predominance between open or closed mechanism, gender or age group. The majority of patients with thoracic trauma requiring drainage were diagnosed by anamnesis and physical examination (41.1%) and drained in the emergency room (80.8%). Most of the patients (66.2%) had another associated lesion, mostly some abdominal viscera. Complications were present in 16.6% (81 patients), most of them due to drainage positioning error (9.2%). The mean hospital stay was 15 days and drainage lasted for an average of 8.1 days, with no statistical difference between open and closed trauma. The clinical outcome was discharge in most cases.* **Conclusion***: the profile of patients with thoracic trauma is that of young men, attended at night, with some other associated lesion. Although diagnosis and treatment were rapid and most often without the need for complex examinations, the time of drainage, hospitalization and complications were higher than in the literature, which can be explained by the drainage being made at the Emergency Room and the presence of associated injuries.*

Keywords: *Thoracic Injuries. Drainage. Wounds and Injuries.*

INTRODUCTION

Trauma in general has been increasing in recent years and is the third leading cause of death, and the first in individuals under 40 years[1].

Chest trauma is an important cause of preventable death, especially in young men between the ages of 20 and 30. The injuries are due to auto accidents (particularly motorcycle ones) and intentional injuries, stabbing and gunshot wounds, with variable frequency according to the region studied[2-4].

Most thoracic lesions are represented by pneumothorax, hemothorax or hemopneumothorax, and can be resolved with simple procedures performed in the emergency room, such as chest drainage. Few cases (10% to 30%) require thoracotomy[5-8].

The present study aims to know the profile of the victims of thoracic trauma who underwent chest drainage at the Curitiba Evangelical University Hospital (HUEC), as well as the complications and treatments given to these patients.

METHODS

We conducted a retrospective, analytical, cross-sectional study through the analysis of medical records of patients suffering from thoracic trauma submitted to pleural drainage attended at the emergency department and admitted to the General Surgery group ward of the Curitiba Evangelical University Hospital (HUEC) between February 2011 and January 2014.

We included in the study patients of both genders, all ages, submitted to closed drainage in water seal, with or without multiple organ traumatisms, with blunt or penetrating thoracic trauma. We excluded the victims of thoracic trauma who died before the surgeon's conduct or who had conservative treatment.

We analyzed the following variables: trauma mechanism, age, gender, associated lesions, approach, clinical outcome (hospital discharge or death), hospitalization time, use of antibiotics and admission diagnosis method. Associated lesions were stratified by body segment and by involvement of parenchymal or hollow organs.

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We present the quantitative variables by means, medians, minimums, maximums and standard deviations, and qualitative ones by frequencies and percentages. We used the Student's t test for independent samples for quantitative variables when comparing the patients' groups defined by the type of trauma, open or closed. For the evaluation of the association between the type of trauma with qualitative variables, we applied the Fisher's exact test or the Chi-square test. Values of $p<0.05$ indicated statistical significance. We analyzed the data using the IBM SPSS Statistics v.20 software.

The project was approved by the Ethics in Research Committee, CAAE 49521615000000103, on 09/24/2015.

RESULTS

The study included 488 patients, 409 (84.7%) being men and 74 (15.3%) women, with a mean age of 38.2 years. There was no predominance of open (n=258; 52.9%) or closed (n=230; 47.1%) trauma. In men, open trauma was more common (n=221; 86.3%) than closed one (n=188, 82.8%) and in women closed trauma (n=39; 17.2%) was more prevalent (n=35; 13.7%), with no statistical difference between groups. We found no relationship between the type of trauma and the patient's age (Table 1). Most of the visits occurred in the early morning (n=164, 33.6%) and at night (n=146, 29.3%). In the open trauma group, most of the occurrences took place during the early morning (n=91, 36.3%) followed by the night (n=66, 22.6%), morning (n=57, 22.1%), and afternoon (n=44, 17.05%). In the victims of closed trauma the attendances occurred predominantly at night (n=77, 33.5%) followed by the early morning (n=73, 31.7%), afternoon (n=42, 18.3%) and morning (n=38, 16.5%), with no statistical difference.

In the majority of cases, thoracic injury was diagnosed through history and physical examination (n=200, 41.1%) and simple chest radiography (n=155, 31.8%), followed by computed tomography (CT) (n=129, 26.5%). Among the open traumas, anamnesis and physical examination were mostly sufficient for the diagnosis (n=146, 56.8%), followed by the use of radiography (n=76, 29.6%) and CT (n=33, 12.8%). Among the closed traumas, there was a greater need for complementary tests for diagnosis, CT being the main diagnostic medium (n=94, 40.9%), followed by radiography (n=79, 34.3%) and anamnesis and examination (n=54; 23.5%), with statistical difference between the groups ($p<0.001$).

The majority of cases were drained at the Emergency Room (n=391, 80.8%), the remainder being divided into drains inserted at the Operating Room (n=44, 9.1%), ICU (n=28; 5.8%) and infirmary (n=21; 4.3%), with unilateral drainage in 394 cases (81.7%). The main site of drainage was the Emergency Room for both open (n=198; 77.3%) and closed (n=193, 84.65%) traumas. In the open traumas the second position was occupied by drainages in Operating Room (n=31, 12.1%) followed by infirmary (n=14, 5.5%) and ICU (n=13, 5.1%). In closed traumas the second position was occupied by the ICU (n=15, 6.6%) followed by the Operating Room (n=13, 5.7%) and infirmary (n=7, 3.1%), with statistical difference between the groups (p=0.04). Unilateral drainage was more common in open traumas (n=214,

Table1. *Comparison between type of trauma and age, hospital stay and drainage time.*

Variable	Type of Trauma	N	Average	Standard Deviation	Maximum	Minimum	p value
Age (years)	Open	255	34.7	14.4	85	9	<0.001
	Closed	256	42.1	16.4	89	13	
Hospital stay (days)	Open	258	13.8	15	90	2	0.142
	Closed	230	16.3	21.8	215	1	
Drainage time (days)	Open	252	7.8	6.3	35	1	0.233
	Closed	224	8.4	6	36	1	

Table 2. *Associated injuries*

Associated Injuries	N	%
Thorax	102	20.9
Limbs	75	15.4
Traumatic Brain Injury	60	12.3
Liver	52	10.6
Hollow viscera	40	8.2
Spleen	36	7.4
Spinal Cord	19	3.4
Kidney	8	1.6
Pancreas	3	0.6
Other	3	0.6

83.6%) than in closed ones (n=180, 79.6%) and bilateral drainage was more common in closed traumas (n=46, 20, 4%) in relation to the open ones (n=42; 16,4%), with no statistical difference between the groups.

The majority of cases were pneumothorax (n=199, 40.8%) followed by hemopneumothorax (n=189, 38.7%) and hemothorax (n=94, 19.3%). In the open trauma group, the most frequent lesion was hemopneumothorax (n=118, 45.7%) followed by pneumothorax (n=82, 31.8%) and hemothorax (n=58, 22.5%). In the closed trauma group, the most frequent lesion was pneumothorax (n=117, 50.9%) followed by hemopneumothorax (n=71, 30.9%) and hemothorax (n=36, 15.65%), with statistical difference between groups ($p<0.01$).

Patients were also stratified for presence of abdominal hollow viscus injuries associated with chest trauma, which were more prevalent in the open trauma group (n=40; 15.6%) than in the closed group (n=4; 1.7%) with statistical difference ($p<0.001$). Most patients had at least one associated lesion (n=323, 66.2%), represented mostly by other abdominal injuries. The stratification of the associated lesions can be observed in table 2.

The mean hospital stay was 15 days (±18.5) and the drainage time was 8.1 days (±6.1), with no statistical difference when the open and closed groups were compared (Table 1). Complications were present in 81 patients (16.6%), being more common in the open group (n=43, 16.7%) than in the closed group (n=38, 16.5%), with no statistical difference. Complications can be observed in table 3.

The majority of patients had a good evolution and were discharged (n=401, 82.2%), without statistical difference between open (n=214, 82.9%) and closed (n=187, 81.3%) trauma. In all, 87 patients died (17.8%), with no statistical difference between the open (n=44, 17.1%) and closed (n=43, 18.7%) trauma groups. Victims of closed trauma required more ICU admission (n=98; 42.6%) than those with open trauma (n=79; 30.7%), with statistical difference ($p<0.01$).

DISCUSSION

Chest trauma is an important cause of morbidity and mortality, which affects the economically active population and results in losses of productive days and damage to the economy and the public health system. It is also a major cause of preventable deaths. It involves young people, mainly men, and its incidence varies according to the region studied and the mechanism of trauma, the penetrating ones in individuals slightly younger (average of 34.7 years) than those victims of closed traumas (average of 38.2 years)[4].

The causes are represented mainly by automobile accidents and intentional penetrating injuries. The predominance of the mechanism varies according to the region studied, with intentional penetrating trauma (stabbing and firearms) being a common cause in some Brazilian capitals (Goiânia, Manaus, São Luiz, Curitiba), while in developed countries the closed trauma represents

Table 3. *Complications.*

Complication	Frequency	Percentage
Positioning error	45	56.2
Infection	27	33.8
Fistula	5	6.3
Retained Clot	2	2.5
Persistent Bleeding	1	1.3
Total	80	100

the main cause[4,9]. We expected a greater incidence of open traumas (of violent origin) in the night and early morning, but we observed no statistical difference between open and closed traumas as a function of the moment of the trauma.

Closed trauma occurs mainly due to traffic accidents, especially motorbikes, followed by run-overs. The fall comes soon after, being an important cause in elders.

Larger thoracic injuries that affect ventilatory mechanics and that need to be recognized and managed immediately during the primary examination include hypertensive pneumothorax, open pneumothorax, flail chest and pulmonary contusion, and massive hemothorax[5]. The data showed that pneumothorax was the most frequent lesion in our service. Hemopneumothorax was the most frequent finding in open thoracic trauma, whereas pneumothorax was the most frequent in the closed one. These results differ from studies such as that of Souza[4], which showed the predominance of hemothorax as an injury in victims of traffic accidents with blunt thoracic trauma.

As stated earlier, most chest traumas are preventable causes of death. With simple, standardized and relatively inexpensive methods, it is possible to diagnose and often treat them in the Emergency Room[5,10]. The anamnesis and physical examination were sufficient for the diagnosis and consequent drainage in 41.1% of the cases. In the open traumas treated at the HUEC, anamnesis and physical examination were sufficient for diagnosis in 56.6% of the cases. However, when the closed lesions were analyzed, they were only diagnosed in 23.5%. It is a low index, which can be explained by primary care being performed by training general surgery residents and by the occurrence of minor injuries that went unnoticed in primary care and were identified in imaging tests in the secondary evaluation.

In cases where the diagnosis is doubtful, and in which the patient's clinical conditions allow to perform complementary examinations, these are indicated in the secondary examination, the chest radiography being the first choice. In many cases, it is sufficient for diagnosis, indication of treatment and follow-up[5,11]. This was the second most used diagnostic method in the present study (31.8% of cases). In the case of closed traumas, chest CT was the most requested exam, being used for diagnosis in 40.87% of cases of closed traumatisms. One explanation for this is that tomography allows the early diagnosis of other associated thoracic and abdominal lesions, which could go unnoticed at first. They are present in an expressive number of patients with thoracic traumatism. CT is also more sensitive for thoracic lesions than plain radiography[12,13] as well as a more accurate diagnostic method when complications are suspected[11].

Associated lesions are present in a significant number of thoracic traumas. In the literature, they are around 36%[13], and in our study, 66.2% of the patients had some other lesion. Most were in extremities, cranioencephalic and abdominal. This higher incidence can be justified by the large number of polytrauma patients admitted to the service.

The mean drainage time was eight days and the hospitalization time was 15 days. A similar study performed in Curitiba shows a drainage time of approximately seven days and hospitalization of ten[14]. Other works show an average of three to five days of hospitalization and five of drainage, with no difference in relation to open and closed traumas[4,11,14,15]. The longer hospitalization time can be explained by the existence of associated injuries, as well as the presence of drainage complications, which can also increase drainage time.

Chest drainage is a simple procedure but with a considerable number of complications[6], varying from drainage position error and subcutaneous insertion to late complications such as empyema[2,6]. The place the drainages are performed is believed to be associated with the high complicationrate; most of them happen in the Emergency Room, lacking aseptic conditions, which can lead to a higher incidence of infection. Some studies show that drains inserted in the Emergency Room are more likely to require drainage repositioning and, therefore, the chances of infection increase. Some authors claim that drainage by residents has a greater chance of technical failures, with a higher rate of complications[6,16,17].

Infections (33.8%) and positioning errors (52.5%) were the main complications found, which can

be reduced with drainage in a Operating Room, since in 80.8% of cases drainage was performed in the Emergency Room, where the antisepsis conditions are not ideal. Similar complication rates were found by other authors, with indices around 30%, with those of infectious origin being the most common[14]. A factor that contributes to the increase of complications is the presence of retained hemothorax, especially when it results from open wounds caused by stabbing injuries in patients over 39 years of age and with drained volume between 300 and 599 ml[11]. An explanation for this is that wounds by the knives can carry germs into the thoracic cavity and the blood retained serves as a culture medium for infections[18].

The mortality rate of 17.8% was slightly higher than those found in two emergency hospitals in São Paulo (8.3% and 9.9%) and one in Goiânia (11%)[18,19]. The international mortality rates are similar to the latter, not exceeding 10%[13,20,21]. Other studies performed in Curitiba, however, show a mortality rate similar to ours, of 17.3%[14]. The mortality discrepancy may be due to the profile of the patients treated in these hospitals, which receive more severe polytrauma patients, with mortality from other non-thoracic injuries. Likewise, the need for ICU admission was also high in a study carried out in Curitiba, reaching 27.5% of the visits[14] but still lower than ours, which reached 36.3%, higher in the victims of closed trauma. Comparing the types of trauma, there was no significant difference in the risk of death.

We conclude that victims of thoracic injury submitted to pleural drainage obey the trauma profile of the Brazilian population, being represented by a young male subject, victim of both closed and open trauma. Events usually occur at night, and the diagnosis is made by clinical examination, the drainage being performed at the emergency room. Victims usually have some associated injury, most commonly of abdominal viscera. There was no difference between the victims of open and closed trauma in relation to hospital stay, drainage time or complications, although victims of blunt trauma had a greater need for ICU admission.

R E S U M O

Objetivo: descrever e comparar as variáveis envolvidas nos pacientes vítimas de trauma torácico submetidos à drenagem de tórax. **Métodos**: estudo transversal descritivo analítico retrospectivo realizado com prontuários de pacientes atendidos no Serviço de Trauma do Hospital Universitário Evangélico de Curitiba entre fevereiro de 2011 e janeiro de 2014. **Resultados**: neste período foram atendidos 488 pacientes, 84,7% homens e 15,3% mulheres, com média de idade de 38,2 anos. Os atendimentos geralmente ocorreram à noite sem predomínio entre mecanismo aberto ou fechado e/ou em relação ao sexo ou idade. A maioria dos pacientes com trauma torácico que necessitaram de drenagem teve diagnóstico feito por anamnese e exame físico (41,1%) e foram drenados no pronto socorro (80,8%). Grande parte dos pacientes (66,2%) teve outra lesão associada, na maioria alguma víscera abdominal. Complicações estiveram presentes em 16,6% (81 pacientes), a maior parte por erro de posicionamento do dreno (9,2%). O tempo médio de internamento foi 15 dias e de drenagem, 8,1 dias, sem diferença estatística entre trauma aberto e fechado. O desfecho clínico envolveu alta na maioria dos casos. **Conclusão**: o perfil dos pacientes com trauma torácico é o de homens jovens, atendidos durante a noite, com alguma outra lesão associada. Apesar do diagnóstico e do tratamento serem feitos de modo rápido e, na maior parte das vezes, sem a necessidade de exames complexos, o tempo de drenagem, internamento e complicações foram mais alto do que na literatura, o que pode ser explicado pela drenagem no próprio pronto-socorro e pela presença de outras lesões associadas.

Descritores: Ferimentos e Lesões. Traumatismos Torácicos. Drenagem.

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Bone grafting for alveolar ridge reconstruction. Review of 166 cases.

Enxerto ósseo para reconstrução óssea alveolar. Revisão de 166 casos.

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A B S T R A C T

Objective*: to investigate the predictive factors of failure in bone grafts for alveolar ridge augmentation and implant surgery.* **Methods***: we reviewed the charts of 166 patients operated between 1995 and 2014. A total of 248 grafting procedures were performed. We submitted the data to the binomial test at 5% significance.* **Results***: grafts to gain width of the alveolar ridge (65.32%) were more frequent than sinus lifting (p<0.0001) and the number of grafts to the posterior maxilla (48.8%) was greater than in other regions (p<0.01); 6.04% of the grafts were lost. The losses in anterior (p<0.0309) and posterior (p<0.0132) maxilla were higher than in the mandible. There were 269 implants installed in the grafted areas, of which only 4.83% were lost. The number of implants lost (4.51%) in areas of onlay grafts was not statistically higher than those placed after sinus lifting (2.63%, p<0.2424). Losses were greater in the anterior (53.85%) and posterior (38.46%) maxilla than in the mandible (p<0.031). Regarding patients' age, 76.92% of the lost grafts (p<0.006) and 80% of the lost implants (p<0.001) were installed in patients over 40 years.* **Conclusion***: failure rate was higher both for grafts and dental implants in the maxilla and in patients over 40 years of age.*

Keywords: *Bone regeneration. Alveolar Bone Grafting. Dental Implants.*

INTRODUCTION

Osseointegration is considered indispensable for the success of dental implants. However, it is a complex process with many factors interfering in the formation and maintenance of the bone tissue around the implant, such as topography and surface roughness, biocompatibility and loading conditions.[1] In addition, implants installation and success require a healthy and compatible host bone bed that allows primary stability and consequently osseointegration. However, this is not always the case. Many patients have a bone tissue that has undergone posterior irradiation, osteoporosis or, more commonly, has varying degrees of bone resorption, resulting in insufficient bone volume for implant installation.[2]

The minimum ideal bone conditions for implant installation are 10mm of bone height and 1mm of bone in width on both sides of the implant. Placement of implants in areas with reduced bone quantity may be impossible or infeasible, and if performed, will cause major aesthetic and functional defects after prosthetic rehabilitation[3]. In this context, insufficient bone volume, in height or thickness, is the most common clinical problem in rehabilitation with dental implants and corresponds to a clear indication of bone grafting for increased bone availability[4-6].

In the posterior maxilla region, the bone volume is usually limited by the vertical resorption of the alveolar bone and the pneumatization of the maxillary sinus. Thus, procedures for bone augmentation are usually required through maxillary sinus lift surgeries[7-9]. In addition, bone reconstructions for vertical and horizontal bone gains are not uncommon in posterior maxilla[10]. In other maxillo-mandibular regions, bone resorption after exodontias can also be accentuated, leading to significant bone loss in height and thickness, often culminating with the atrophy of the alveolar ridge[3]. In such situations, reconstructive bone surgeries are necessary to correct the bone deficiencies. Currently there are several options available, such as: autogenous, homogenous and xenogenous grafts, and alloplastic materials. A combination of these materials has also been described in several situations, although the autogenous bone remains the gold standard[4,11,12].

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Even in the case of predictable procedures with documented long-term success, complications and failures have been reported after implant surgeries. Implant loss may involve several factors, such as early loading, surgeon experience, implants inserted in areas of poor bone quality, smoking or other systemic compromise, inadequate surgical technique, among other factors[13,14]. In this context, in the search of the best results with implant-supported rehabilitation, it is of great interest to establish the factors that lead to graft and implant failures[15]. Thus, the present study aimed to retrospectively evaluate a database of 166 patients who received bone grafts and implants from 1995 to 2014, to identify and describe the predictive factors of failures in this sample.

METHODS

This study was based on a retrospective analysis, in which we reviewed the medical records of the patients treated at the Oral Face Care Clinic (Santos, SP, Brazil) who underwent graft surgeries and dental implant installation from 1995 to 2014. All inserted implants were followed for at least four months.

Patients presented partial or total edentulism with varying degrees of vertical and horizontal atrophy of the alveolar bone crest and pneumatization of the maxillary sinus that did not allow the installation of dental implants without previous reconstruction with bone grafts. We included in this study patients of both genders, regardless of age or race. We excluded systemically compromised patients with a history of radiotherapy in the head and neck region or use of chemotherapeutic agents with active periodontal disease involving the remaining dentition and with their medical records incompletely filled. Thus, we reviewed the medical records of 166 patients who met the inclusion criteria. They undergone 248 graft surgeries, between maxillary sinus lifting surgeries and onlay grafts, and installation of 269 implants.

All reconstructive onlay surgeries were performed with autogenous bone of the mandibular retromolar area, and the maxillary sinus lifting procedures were performed with autogenous bone, Bio-Oss or by the association of the two materials. It is important to emphasize that no implant was submitted to immediate loading, and the period of osseointegration for the installation of the provisional prostheses was awaited. All patients received a prescription of 875mg of amoxicillin every 12 hours for seven days, starting with two capsules one hour before surgery, and for implant surgery, 1g of first-generation cephalosporin was prescribed for prophylaxis.

In addition, the same surgeon, with experience in the field, performed all surgeries. We organized the data in a Microsoft Excel spreadsheet and then submitted it to the Binomial Test for proportions at 5% significance (BioEstat Program, version 5.0).

RESULTS

Of the 166 patients undergoing grafts, 155 were women (62.5%) and 93 men (37.5%), a statistically significant difference ($p<0.0001$). The patients' ages ranged from 18 to 78 years, the mean age being 50.42.

Most of the surgeries were onlay grafts for thickness gain, corresponding to 65.32% (162 grafts), and 34.68% (86 grafts) were particulate grafts for maxillary sinus floor elevation ($p<0.0001$). The most common location of the grafts was the posterior maxilla, which received 121 grafts (48.8%), a percentage statistically higher than that of grafts performed in other maxillo-mandibular regions ($p<0.01$). On the other hand, the anterior region of the maxilla received 34.27% of the grafts, which was statistically higher than the proportion of grafts performed in the mandible ($p<0.0001$). Among the grafts to the mandible, the amount performed in the posterior region (31 grafts – 12.5%) was statistically higher than that performed in the anterior onr (11 grafts – 4.43%, $p<0.013$).

However, considering only the location of the 162 onlay grafts, the main site was the anterior maxilla region, with 85 grafts, followed by the posterolateral region (35 grafts) and the posterior mandible region (31 grafts). The region with the fewer onlay grafts was the

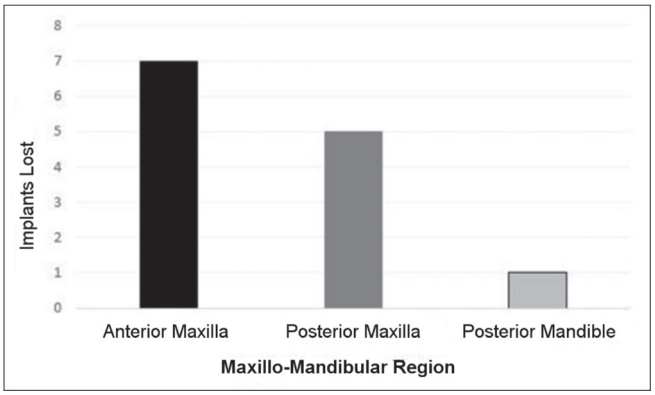

Figure 1. *Distribution of lost implants according to the maxillo-mandibular location.*

anterior mandible, with 11. The percentage of grafts performed in the anterior maxillary region (52.47%) was statistically higher than in all other regions (p<0.0001). Statistical differences were also observed between the proportion of grafts in the posterior region of the maxilla (21.60%) compared with the anterior region of the mandible (6.8%, p<0.0001), as well as between the posterior (13%) and anterior (6.8%) mandible regions (p<0.0009). We found no significant differences in the number of grafts performed between the maxilla and mandible posterior regions (p<0.5811).

In general, most grafts were performed with autogenous bone, corresponding to 219 cases (88.31%, p<0.0001). Fourteen cases were done with Bio-Oss (5.64%) and 15, with the association of Bio-Oss and autogenous bone (6.05%). When considering only the maxillary sinus regions (86 grafts), the most used material was autogenous bone, in 57 cases (66.28%).

The 248 grafted areas received 269 implants. Of these, 114 (42.37%) were inserted in the maxillary sinus area and 155 (57.63%) in an onlay block area. Of the inserted implants, 256 were osseointegrated (95.17%) and 13, lost (4.83%, p<0.0001).

Only 13 implants were installed concurrently with the reconstructive surgeries. Of the implants installed concomitantly to the grafts, only one was lost (8.33%) and the others were successful (91.67%). Of the implants installed late, 12 failed (4.68%) and 244 were osseointegrated (95.32%). Still in relation to implant losses, ten (4.51%) were located in graft sites for gain in thickness (onlay) and only three in areas of maxillary sinus floor elevation (2.63%). However, there was no statistical difference regarding implant loss according to graft type (p<0.2424).

Regarding the maxillo-mandibular location of the lost implants, only one occurred in the mandible in the posterior region. The others occurred in the maxilla, seven in the anterior region and five in the posterior one. The number of implants lost in the anterior (53.85%) and posterior (38.46%) maxilla was statistically higher than in the mandible (7.69%, p<0.0313). There was no statistical significance as for implant losses in the maxilla regions (p<0.4314, Figure 1).

We observed a greater implants loss in patients over 40 years of age, which corresponded to ten implants lost (76.92%). In patients less than 40 years of age, three implant losses (23.08%) occurred (p<0.006). Eight implant losses occurred in women and five in men. However, there was no statistical difference between the female (61.54%) and male (38.46%) genders (p<0,2393).

As for graft loss, five were in the maxillary sinus region (33.33%) and ten in onlay grafts (66.67%), and there was no statistical difference between the different types of grafts (p<0.0679). Most of the lost grafts were located in the maxilla, six (40%) in the anterior maxilla and seven (46.47%) in the posterior region. In the mandible, one graft loss occurred in the anterior region and one in the posterior mandible. There was a statistical difference in the loss of grafts in the anterior (p<0.0309) and posterior (p<0.0132) maxilla regions in relation to the mandible (Figure 2).

Eighty percent of cases of lost grafts (12 grafts) occurred in patients over 40 years and 20% of cases (three grafts) in patients under 40 years. The proportion of graft loss in patients over 40 years was statistically higher than in patients below 40 years (p<0.001).

DISCUSSION

Dental implants are being increasingly used because of their high success rates. This modality of rehabilitation is currently considered the most predictable and scientifically accepted treatment for partially or

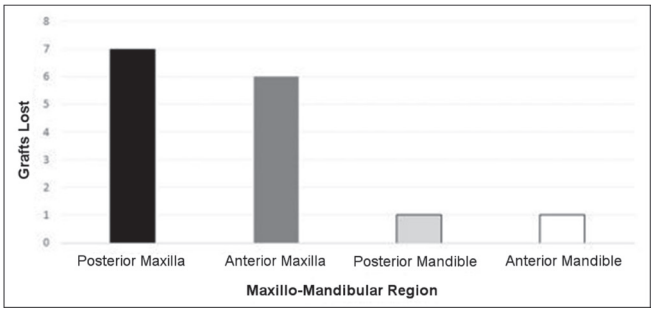

Figure 2. *Distribution of lost grafts according to the maxillo-mandibular location.*

totally edentulous patients. However, a large proportion of patients do not present sufficient bone conditions for implants installation, thus requiring previous reconstructive bone surgeries[5,16]. In this study, 269 implants were inserted in 248 grafted maxillo-mandibular regions, which displayed a success rate of 95.17%, with only 13 implants lost (4.83%). In 1986, Branemark and Albrektsson[17] evaluated implants inserted during a year for a five-year follow-up period and found a high success rate, 96.5%. However, in the systematic review of Albrektsson and Donos[18], based on 23 retrospective studies with 1312 implants followed during a five-year period, the authors found a higher success rate, which corresponded to 97.7%.

It is important to emphasize that the implants inserted in the present study were followed for a period ranging from four months to 19 years, depending on the time at which they were installed (1995 to 2014). According to Misch[10], the osseointegration of implants in grafted areas depends on the resulting bone quality. Thus, implants inserted into areas of denser bone tissue may require about two months for osseointegration, whereas in areas of less dense spongy bone tissue it may take up to four months for the same process to occur[10]. Based on this assumption, in this study we included only implants that had a minimum period of four months of follow-up, enough time to evaluate osseointegration even in regions of low bone quality.

Regarding implants loss in the grafted regions, there were no statistically significant differences in the number of implants lost in the onlay graft areas (4.51%) in relation to maxillary graft ones (2.63%, p<0.2424). Cabezas-Monjón *et al*.[3] carried out a meta-analysis with the objective of reviewing the success rates of implants inserted in areas of maxillary sinus elevation surgeries over a 10-year period. They observed that of the 3975 implants inserted, 3794 implants were successful, representing a success rate of 94.3%. In the present study, the success rate of implants in maxillary sinus area was higher, corresponding to 97.37%. However, there were no statistical differences regarding the implants success as for graft area (95.49%, p<0.2424). Another study that indicates a high success rate of implants inserted in areas of maxillary sinus grafted with autogenous bone, in this case of extrabuccal donor area, is that of Sakka and Krenkel[9]. The authors report a success rate of 94.8%. In contrast, in relation to the success of implants in onlay graft areas, in the systematic review by Clementini *et al*.[2], they observed a success rate of implants in areas of autogenous graft, which ranged from 72.8% to 97%, in most of the reviewed studies. Thus, the authors point out that the technique of autogenous onlay grafting is a reliable and predictable technique to obtain the bone volume required for the implant installation[2]. In the work of Kamal *et al*.[5], in turn, of the 379 implants inserted in areas reconstructed with autogenous bone, 15 failed (3.95%), successful implants corresponding to 96.05%.

Regarding the maxillo-mandibular location of the lost implants, more implants were lost in the anterior (53.85%) and posterior (38.46%) maxilla, which was statistically significant in relation to mandibular failure (7.69%, p<0.0313). This may have occurred because, among the situations that increase implant failures, the insertion of maxillary implants stands out, mainly in the posterior region, since it is an area of known low bone quality (type III and IV)[19]. So much so that, according to Chrcanovic *et al*.[19], most studies show a higher rate of failure of maxillary implants, with statistical differences in relation to the mandible as observed in the present study. On the other hand, other studies, like the one of Alissa and Oliver[16], did not find statistical difference in the failure of implants between the maxilla and mandible.

In addition, higher rates of implant failure have been reported in systemically compromised patients[16,19]. In the present sample, all patients were healthy without

metabolic disturbances, which may also have contributed to the low rate of implant failure (4.83%). Another factor poorly investigated in the literature that may play a role in the success of dental implants is the use of prophylactic and postoperative antibiotic therapy. Alissa and Oliver[16] found a significant statistical difference between the success of implants in patients who used antibiotics in the postoperative period and the rates of patients who did not. In the present study, all patients underwent antibiotic therapy, with the use of pre and postoperative amoxicillin for graft surgeries and first-generation cephalosporin prophylactically for implant surgeries.

For the implant inserted in a grafted area to be successful, it is indispensable that the previously performed graft reaches the expected objectives regarding the correction of bone deficiencies. Thus, the success of a bone graft is evaluated for its potential to withstand the tensions and mechanical deformations to which it is submitted. In this way, successful grafts are those that undergo revascularization and replacement by host bone after insertion into the recipient bed, without significant loss of volume and mechanical resistance[20]. In the present study, 248 grafts were performed, between surgeries for gain in thickness (onlay – 65.32%) and maxillary sinus floor elevation (34.68%), with a loss rate of only 6.04%. Most of the grafts were performed in the posterior maxilla region (48.8%), with statistical difference in relation to the number of grafts performed in the other maxillo-mandibular regions ($p<0.01$). It is important to note that implants inserted into grafted areas have a success rate that may be lower, ranging from 60 to 100%. It is speculated that the graft itself may constitute a risk factor for implant success[20]. However, in the present study, all implants were inserted into grafted areas and we do not believe in a negative graft interference in results, since there was a success rate of 95.17%. Carr *et al*.[21], in turn, report that the risk of implant failure is five times greater in areas of grafted maxillary sinus compared with the implants installed in residual bone.

Despite this, similar to the results of the present study, Alissa and Oliver[16] did not identify negative graft interference in implants' osseointegration. These same authors point out that this may have occurred because they opted for the two-stage approach, i.e. implants were only inserted after a minimum period of three months, which allowed graft maturation, obtaining initial implant stability and placement of the implant in a more adequate position[16]. Regarding the moment of implant installation, in the present study, only 4.83% of the implants were installed concomitantly with the graft. Of these, only one implant (8.33%) was lost and 91.67% were successful. However, in the study by Cabezas-Monjón *et al*.[3], the success rate of implants installed concomitantly to the graft was slightly higher, corresponding to 94%. However, according to Del Fabbro *et al*.[20], there are no significant differences in the success rate of implants, independent of the installation protocol, simultaneous or late. With regard to implants installed late, we had a success rate of 95.32%, which was similar to the rate reported in other studies (96.8%)[3]. According to Misch[10], placement of the implants after the healing period should be preferred. Nevertheless, it is important to install the implants as soon as possible to stimulate the formation and maintenance of bone tissue. In the case of autogenous grafts, a minimum period of four months should be expected[10]. Despite this, due to the small failure rate of implants inserted concomitant to the graft (8.33%) in the present study, we do not believe that the simultaneous installation of graft and implant had a negative effect on results. Similarly, other authors have evaluated the success of implants inserted concomitantly with maxillary sinus surgeries for a period of 12 to 60 months and observed a high success rate (98.8%)[8]. On the other hand, previous studies reported high failure rates, between 25 and 30%, when the implants were inserted simultaneously to the reconstruction of atrophic maxillae with autogenous iliac crest bone[22,23].

The number of implants (76.92%) and grafts lost (80%) in patients over 40 years was statistically higher than the failures in younger patients ($p <0.001$). However, the majority of studies found no significant correlations between implant loss and patient age[16,19]. However, as in the present study, Zinser *et al*.[24] found a significant interference of age in implant loss. Regarding gender, in

the present study the majority of lost implants (61.54%) and grafts (60%) occurred in women, though with no significant statistical difference (p<0.2733). This finding is in agreement with the literature, since a great part of the studies do not indicate significant differences between men and women with regard to the implant loss[16,19].

As for the origin of the materials used in the present study, all 162 onlay grafts were performed with autogenous bone. Similarly, most sinus elevation grafts (66.28%) were also performed with autogenous bone, and a small percentage of cases were performed with Bio-Oss (16.28%) or with Bio-Oss and autogenous bone combined (17.44%). In the survey of maxillary sinus elevation surgeries of Cabezas-Monjón *et al*.[3], most procedures were also performed with autogenous bone (59%), followed by the use of the association of autogenous bone with a bone substitute (24%), Isolated use of bone substitute (10%), and in 7% of cases the graft material used was not specified. The authors also report that 18% of the autogenous bone used was collected from the extraoral area. In contrast, in the present study, 100% of the autogenous graft was removed from intraocular donor areas. The percentage success of implants inserted in autogenous bone (94.40%) in the present study was higher than the overall implant survival rate of the Cabezas-Monjón *et al*. study (93%)[3].

In addition, in the present study, no implant installed in areas of Bio-Oss or Bio-Oss associated with autogenous bone was lost. Although the autogenous graft is considered the "gold standard" in reconstructive bone surgeries due to its osteogenic, osteoconductive and osteoinductive characteristics, in the present study, the highest rate of implant loss was observed in areas grafted with autogenous bone. This can be explained in part by the greater resorption of the material, which in the areas of the maxillary sinus can allow subsequent peneumatization[7]. In the systematic review of the literature by Jensen *et al*.[7], only one study was found that evaluated the survival of implants inserted in areas grafted with Bio-Oss alone (80%) or Bio-Oss associated with autogenous bone (20%). Although the highest success rate was observed in the Bio-Oss group (96%), there was no statistical difference in relation to the group where Bio-Oss was associated with autogenous bone (94%). On the other hand, Del Fabbro *et al*.[20] found a success rate of implants in sinus lift areas performed exclusively with the bone substitute (96.1%) considerably higher than with the use of autogenous bone alone (88.9%).

Regarding the location of the onlay grafts, in the present study the largest amount of grafts was located in the anterior region of maxilla (52.47%), with statistical difference in relation to the other maxillo-mandibular regions. This is understandable, since after a tooth loss, a marked buccal bone resorption occurs in the maxilla, which can lead to loss of up to 50% of the ridge width, leading to the need for reconstructive surgeries to gain thickness. In addition, the upper anterior region is the aesthetic area of the patient and great efforts therefore are required in bone reconstruction so that the implant is in a position that favors aesthetics. The reconstructions of this region can be especially delicate when the patient presents with a high smile line[10].

In this context, based on what has been discussed, it is important to identify the factors related to implant failure in regions where bone reconstruction was performed. Failures may be related to local or systemic factors[15]. In the present study, the factors most involved in implant and graft loss were local, since patients were healthy. Despite this, age had a significant influence on implant loss. Given this caveat, the authors believe that the implant losses of the present sample may be related to the vascularization, density and resorption of the bone tissue obtained after the reconstructions. This is because the quality of obtained bone tissue can interfere with the primary stability and osseointegration process, as pointed out by Sjöström *et al*.[15]. Primary stability, in turn, is an important aspect for the consolidation of osseointegration and can be affected by bone quality, surgeon skill and surgical technique[15]. Based on the assumption that in the present study all surgeries were performed by the same experienced surgeon, who used an accurate surgical technique, we do not believe that technical aspects have interfered with the implants' results. Moreover, another important aspect in assessing the success of implants is immediate loading. Most studies show higher failure

rates found in early loaded implants[15]. Nonetheless, in this study all implants were loaded late after the period of osseointegration. Thus, immediate loading was not a predictive factor of implant failure in the studied sample.

In the sample studied, there were few cases of graft and implant failure. Reconstructive and implant surgeries performed in the maxilla and in patients over 40 years showed a higher rate of failure.

R E S U M O

Objetivo: investigar os fatores preditivos de falhas em enxertos ósseos para aumento do rebordo alveolar e cirurgia de implantes. **Métodos**: os prontuários de 166 pacientes, operados entre 1995 e 2014, foram revistos. Um total de 248 enxertos foi realizado. Os dados foram submetidos ao teste binomial a 5% de significância. **Resultados**: os enxertos para ganho em espessura do rebordo alveolar (65,32%) foram mais frequentes do que levantamentos de seio maxilar (p<0,0001) e o número de enxertos para a região posterior da maxila (48,8%) foi maior do que em outras regiões (p<0,01). Foram perdidos 6,04% dos enxertos. As perdas em maxila anterior (p<0,0132) e posterior (p<0,0309) foram maiores do que na mandíbula. Foram instalados 269 implantes nas áreas enxertadas e apenas 4,83% perdidos. O número de implantes perdidos (4,51%) em áreas de enxertos em bloco não foi estatisticamente maior do que na área de seios maxilares enxertados (2,63%) (p<0,2424). As perdas foram maiores na região anterior (53,85%) e posterior (38,46%) da maxila em relação a mandíbula (p<0,031) e, 76,92% dos enxertos (p<0,006) e 80% dos implantes perdidos (p<0,001), foram instalados em pacientes com mais de 40 anos de idade. **Conclusão**: maior taxa de falhas foi observada para enxertos e implantes dentários realizados em maxila e em pacientes com mais de 40 anos de idade.

Descritores: Regeneração óssea. Transplante Ósseo. Implantes Dentários.

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Sugammadex ED90 dose to reverse the rocuronium neuromuscular blockade in obese patients

Dose ED90 de Sugamadex para reverter o bloqueio neuromuscular com rocurônio em pacientes obesos

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ABSTRACT

Objective: *to determine the ED90 (minimum effective dose in 90% of patients) of sugammadex for the reversal of rocuronium-induced moderate neuromuscular blockade (NMB) in patients with grade III obesity undergoing bariatric surgery.* **Methods:** *we conducted a prospective study with the biased coin up-and-down sequential design. We chosen the following doses: 2.0mg/Kg, 2.2mg/Kg, 2.4mg/Kg, 2.6mg/Kg, 2.8mg/Kg. The complete reversal of rocuronium-induced NMB considered a T4/T1 ratio ≥0.9 as measured by TOF. After induction of general anesthesia and calibration of the peripheral nerve stimulator and accelerometer, we injected rocuronium 0.6mg/kg. We administered propofol and remifentanil by continuous infusion, and intermittent boluses of rocuronium throughout the procedure.* **Results:** *we evaluated 31 patients, of whom 26 had displayed successful reversal of the NMB with sugammadex, and failure in five. The mean time to complete moderate NMB reversal was 213 seconds (172-300, median 25-75%). The ED90 of sugammadex calculated by regression was 2.39mg/kg, with a 95% confidence interval of 2.27-2.46 mg/kg.* **Conclusion:** *the ED90 of sugammadex in patients with grade III obesity or higher was 2.39mg/kg.*

Keywords: *Dose-Response Relationship, Drug. Obesity. Cyclodextrins.*

INTRODUCTION

The pathophysiological changes determined by obesity can affect the distribution and elimination of medications[1,2]. The majority of drugs with high lipid solubility have a high distribution volume[3]. Measures of weight correction to indicate the best scheme of drug administration in obese patients have been proposed[4-6]. A simple and easy method of calculating ideal body weight (IBW) considers height in centimeters (cm) minus 100 for men and height in centimeters less 110 for women[7].

Sugamadex, a selective binding agent that reverses rocuronium-induced neuromuscular blockade (NMB), can be rapidly distributed into the extracellular fluid, which should therefore be considered as its distribution volume (DV)[8]. This substance is used in adults of normal weight at 2mg/kg to promote reversion of moderate NMB, measured by the train-of-four (TOF) stimulus sequence (T4/T1 ≥0.9); at 4mg/kg for reversal of deep NMB; and at a dose of 16mg/kg for immediate reversal of rocuronium-induced NMB[9-13].

Results in patients with grade III obesity submitted to laparoscopic bariatric surgery under NMB indicated an optimal dose of 2mg/kg of sugammadex based on 140% of the IBW for patients with moderate neuromuscular blockade[14]. However, a prospective observational study found that 23.4% of patients required a second dose of sugammadex to reverse moderate NMB over a two-minute time interval when a dose of 2mg/kg was used in comparison with the time of reversion between non-obese subjects[15].

There are sequential evaluation methods for binary response variables used to determine the concentration or dose associated with the 50% point of the dose-response curve. The up-and-down method is commonly used in anesthesia research[16]. Briefly, the first patient with a positive response to the received dose will indicate an initial lower subsequent dose to the next patient; if the patient does not have a positive response, the next will receive a higher dose. This procedure is repeated until the end of the determined experiment[17].

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Table 1. *Anthropometric data and procedures times (median, 25-75%).*

	Successes (n=26)	Failures (n=5)
Age (years)	42 (35-45)	45 (40-52)
Height (m)	1.62 (1.55-1.73)	1.59 (1.59-1.67)
Weight (kg)	126.5 (110-149)	130 (124-130)
BMI (kg/cm^2)	49.3 (44.3-52.0)	46.7 (46.6-51.4)
Time of surgery (min)	194.5 (158.5-223.7)	220 (203.0-225.0)
Anesthesia time (min)	240 (206-295)	300 (270-305)
Time to awake (min)	10.5 (7.2-15.7)	12 (10.0-20.0)
Rocuronium total dose (mg)	96 (84.2-117.8)	100 (79.2-119.4)
Sugamadex total dose (mg)	123.6 (108-160.8)	117.6 (107.8-136.8)

BMI: body mass index.

Previous studies have suggested that reversal of NMB in morbidly obese patients could be achieved at 4mg/kg for deep blockade considering the ideal body weight, or 2mg/kg, regardless of which body weight is considered, ideal or actual[18,19].

The aim of this study was to determine the minimum effective dose of sugammadex in 90% of obese patients (ED 90) required to complete the reversal of rocuronium-induced moderate neuromuscular blockage using the up-and-down design of biased coin (BCD) in patients with grade III obesity submitted to bariatric surgery. We also recorded the mean time to NMB reversal in these patients with obesity grade III or higher.

METHODS

We conducted a prospective study using the biased coin up-and-down sequential method (BCD) to determine the ED90 of patients with obesity grade III or higher undergoing bariatric surgery receiving sugammadex for the reversal of moderate neuromuscular blockade induced by rocuronium. We studied patients operated at the Central Hospital of the Brotherhood of the São Paulo Holy Home of Mercy, from January to October 2013. The estimated sample size considered 20 patients to determine the lowest effective dose[18].

Inclusion criteria were patients older than 18 years and under 60 years, body mass index ≥40 kg/m^2, with indication of bariatric surgery and who signed the informed consent term. We did not include Patients with a history of neuromuscular disease, use of medicinal products that could interfere with neuromuscular transmission, allergy to aminosteroid-class neuromuscular blocking agents, any anticipated difficulties in managing the airways, or renal failure.

We chose the doses of sugammadex to reach the decile 0.9: 2.0mg/kg; 2.2mg/kg; 2.4mg/kg; 2.6mg/kg; 2.8mg/kg, and also considering patients' IBW. The first patient in the study received a dose of 2.4mg/kg and, if there was a negative response, the next patient would be considered to receive a next higher dose of 2.6mg/kg. However, in the case where 2.4mg/kg produced a positive response, the next patient would be randomized with a 10% probability of receiving the next dose of 2.2mg/kg and 90% probability of receiving the same dose of 2.4mg/kg. We repeated this procedure subsequently until the end of the study[17].

Complete NMB reversal occurred when the patient had a TOF T4/T1 ratio ≥0.9 within eight minutes of sugammadex infusion at the prescribed dose. In case of failure, the same dose was repeated until complete neuromuscular blockade reversal.

The anesthesia technique included denitrogenation with 100% oxygen in proclivity position, followed by intravenous (IV) infusion of fentanyl 5µg/kg IBW and propofol 2mg/kg total body weight. Soon after calibration of the peripheral nerve stimulator and accelerometer, we injected rocuronium IV at the dose of 0.6mg/kg of IBW

Table 2. *Sugamadex dose and time to complete the reversal of neuromuscular blockade (median, 25 to 75 percentile – n=31).*

Dose (mg/kg)	Success	Subjects studied	Observed probability	PAVA-adjusted probability	Time to reversion (s)
2.20	0	3	0.0	0.0	-
2.40	23	25	0.92	0.92	213 (172-300)
2.60	3	3	1.0	1.0	150 (150-229)

PAVA: *pooled-adjacent-violators algorithm.*

to NMB. We maintained anesthesia with propofol 2 to 6 mg/kg/h to keep the bispectral index (BIS) at 40 to 60, remifentanil 0.1 to 0.3 µg/kg/h and intermittent boluses of rocuronium at 0.3µg/kg of IBW, still adjusted to maintain a maximum of only two responses, T1 and T2, in TOF. Patients were referred to a stay of no less than six hour in the post-anesthetic recovery unit (PACU), in which the neuromuscular function was clinically evaluated by the TOF, both on admission and on discharge from the unit.

Patients were monitored with cardioscope, pulse oximetry, capnography (in ventilation to maintain $ETCO_2$ between 35 and 40 mmHg), noninvasive blood pressure, central temperature (forced warm air blanket maintained in the upper body), BIS, TOF (Electrodes on the ulnar nerve and accelerometer on the thumb). The four-stimulus sequence was monitored every five minutes after calibration of the monitor for each patient, and immediately after the infusion of sugammadex at 15-second intervals until T4/T1 ≥0.9 (TOFWatch SX, Organon Ltd Dublin, Ireland).

We used the statistical software R version 3.0.2 (R Foundations for Statistical Computing, Vienna, Austria), as well as the Sigma Stat statistical package for Windows version 2.03 (SPSS Inc., Chicago, IL, USA). We used the isotonic regression functions with the pooled-adjacent-violators algorithm (PAVA) to determine the ED90, and bootstrapping to calculate the respective 95% confidence interval with the statistical program R[17-19].

This study was approved by the Ethics in Research Committee of the Brotherhood of the São Paulo Holy Home of Mercy and was registered at ClinicalTrials.gov under the number: NCT02568345.

RESULTS

The ED90 of sugammadex calculated by isotonic regression was 2.39mg/kg, with a 95% confidence interval of 2.27-2.46 mg/kg), calculated by the bootstrapping method with 9,999 replicates of the sample. There were no patients with residual neuromuscular blockade at any of the three time points studied after complete reversal of moderate NMB with sugammadex.

Thirty-one patients completed the study, 24 females (77%) and seven males (23%). Anthropometric data and procedure times (median, 25 to 75%) did not differ between groups (Table 1). Twenty-six patients achieved complete reversal of moderate neuromuscular blockade with sugammadex (77% female), and five patients failed to achieve it (80% female), and the time for reversal was smaller with the higher dose (Figure 1, Table 2).

DISCUSSION

This study establishes the effective ED90 dose of sugammadex at 2.39mg/kg (95% CI: 2.27-2.46 mg/kg) for the reversal of rocuronium-induced moderate neuromuscular blockade in obese patients ≥ grade III. The biased coin design (BCD) allowed the use of small samples, reducing the time of execution and also the number of individuals tested with ineffective doses, which is interesting from an ethical point of view.

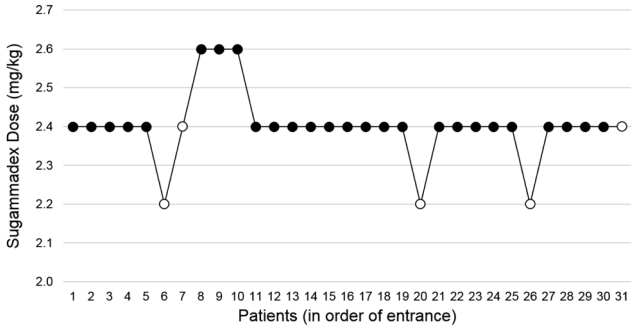

Figure 1. *Up-and-down sequence of the biased coin for administered doses (n=31). Empty circle: failure to reverse the lockade; Full circle: complete reversal of the blockade.*

In the classical up-and-down model, the doses tested are concentrated closer to the 0.5 decile (ED50), but the estimated probabilistic dose with higher efficiency should be situated close to decile 0.9 (ED90)[17]. However, The efficiency of this procedure is disputed by some authors[18,20]. Most studies with this approach in anesthesiology study 20-40 patients[21-29].

A recent study did not point out the total dose of rocuronium[14], while other investigations point to an average of 97.5mg of rocuronium for 120 minutes of surgery duration[15]. The present study observed individuals who had the moderate neuromuscular blockage successfully reversed after receiving 100.8mg of rocuronium for 194 minutes of surgery duration. An additional variable that could be difficult to compare relates to the definition of ideal body weight, since we did not base our study on expected tables for height and weight[30]. Nevertheless, our results confirm recent investigations suggesting sugammadex doses in a range of 2-4 mg/kg of ideal body weight[18,19].

Some limitations of this study are the lack of investigation for the minimal effective dose in other clinically relevant situations, such as during superficial or deep neuromuscular blockade in individuals with obesity ≥ grade III. Additional studies may examine these variables.

In conclusion, for obese grade III or higher, the ED90 dose for sugammadex to reverse rocuronium-induced neuromuscular blockade was 2.39mg/kg within a mean infusion time of 213 seconds.

R E S U M O

Objetivos: determinar a ED90 (dose mínima eficaz em 90% dos pacientes) de sugamadex para a reversão de bloqueio neuromuscular (BNM) moderado induzido pelo rocurônio em pacientes com obesidade grau III submetidos à cirurgia bariátrica. **Métodos:** estudo prospectivo com o método de projeção sequencial para cima e para baixo da moeda enviesada. As seguintes doses foram escolhidas: 2,0mg/kg^{-1}, 2,2mg/kg^{-1}, 2,4mg/kg^{-1}, 2,6mg/kg^{-1}, 2,8mg/kg^{-1}. A reversão completa de BNM induzido por rocurônio considerou uma relação T4/T1 ≥0,9 na medida do TOF. Após a indução da anestesia geral e calibração do estimulador de nervo periférico e acelerômetro, rocurônio 0,6mg/kg^{-1} foi injetado. Infusão contínua de propofol e remifentanil, e bolus intermitente de rocurônio foram injetados durante todo o procedimento. **Resultados:** trinta e um pacientes foram avaliados, 26 dos quais bem-sucedidos e cinco sem reversão completa do BNM moderado promovido pelo sugamadex. O tempo médio para completar reversão de BNM foi 213 segundos (172 a 300 segundos; mediana, 25-75%). O ED90 de sugamadex calculado pela regressão foi de 2,39mg/kg^{-1} com um intervalo de confiança de 95% (2,27 a 2,46mg/kg^{-1}). **Conclusão:** o ED90 de sugamadex em pacientes com obesidade grau III ou superior foi 2,39mg/kg^{-1}.

Descritores: Obesidade. Ciclodextrinas. Relação Dose-Resposta a Droga.

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Endovascular treatment of carotid-cavernous vascular lesions

Tratamento endovascular das lesões vasculares carótido-cavernosas

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ABSTRACT

Objective*: to evaluate the endovascular treatment of vascular lesions of the cavernous segment of the internal carotidartery (ICA) performed at our institution.* **Methods***: we conducted a descriptive, retrospective and prospective study of patients with aneurysms of the cavernous portion of the ICA or with direct carotid-cavernous fistulas (dCCF) undergoing endovascular treatment.* **Results***: we included 26 patients with intracavernous aneurysms and ten with dCCF. All aneurysms were treated with ICA occlusion. Those with dCCF were treated with occlusion in seven cases and with selective fistula occlusion in the remaining three. There was improvement of pain and ocular proptosis in all patients with dCCF. In patients with intracavernous aneurysms, the incidence of retro-orbital pain fell from 84.6% to 30.8% after treatment. The endovascular treatment decreased the dysfunction of affected cranial nerves in both groups, especially the oculomotor one.* **Conclusion***: the endovascular treatment significantly improved the symptoms in the patients studied, especially those related to pain and oculomotor nerve dysfunction.*

Keywords: *Carotid-Cavernous Sinus Fistula. Embolization, Therapeutic. Carotid Artery Injuries.*

INTRODUCTION

The treatment of lesions that compromise the cavernous sinus (CS) represents a challenge to neurosurgeons. Since Dolenc[1] has comprehensively described the microsurgical anatomy, knowledge of the CS region has spread, allowing the development of new treatment techniques.

The increasing knowledge of the topographic anatomy related to the internal carotid artery (ICA) and its relationships with bones, dura mater (DM), venous spaces and cranial nerves (CN) changed the course of neurosurgical performance in CS lesions[1]. The development of modern neuroendocrine intervention techniques has widened the range of therapeutic options for vascular affections compromising the CS. However, controversy persists regarding treatment.

The endovascular treatment of such lesions has presented several changes in recent years, especially due to the appearance of new technical resources[2]. Thus, the constant evaluation of its effectiveness is necessary to obtain better results, associated with progressively lower rates of morbidity and mortality.

The objective of the present study is to evaluate the endovascular treatment of vascular lesions - aneurysms and fistulas - that affect the intracavernous internal carotid artery in patients undergoing treatment in the São Paulo Holy Home**.**

METHODS

The project and the Informed Consent Form were previously approved by the Ethics in Research Committee under number 197/10.

It is a descriptive, retrospective and prospective study in which we evaluated 39 patients with intracavernous aneurysms (IcCAA) and direct carotid-cavernous fistulas (dCCF), of whom 36 underwent endovascular treatment in the period of January 1, 2009 to December 31, 2012. We performed retrospective assessment through medical records review and prospective outpatient visits. All individuals had an outpatient follow-up for at least one year.

We included in the study patients with a diagnosis of dCCF who underwent endovascular treatment and ICA patients with intractable pain and/or

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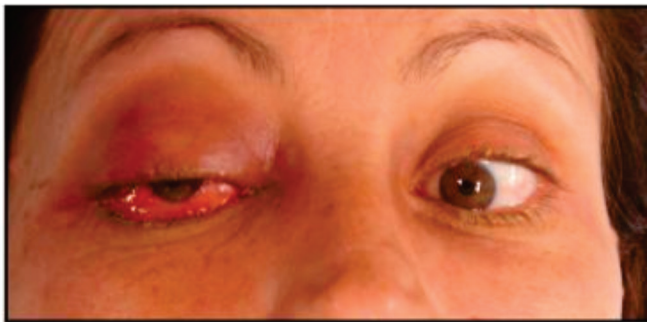

Figure 1. *Patient with dCCF presenting with proptosis, ocular hyperemia and CN VI deficit on the right.*

symptoms resulting from changes in CN III, IV, V or VI lasting less than or equal to six months and undergoing endovascular treatment.

We excluded patients who refused to participate in the study and patients with incomplete data records or for whom the variables assessment was impossible. We included the obtained data in spreadsheets and presented them in a descriptive way in tables and graphs.

RESULTS

Ten patients underwent endovascular treatment for carotido-cavernous fistulas, four of them male and six female. The mean age was 35.3 years. We observed previous trauma history in nine (90%) patients, with the mean time interval between the trauma and the definitive treatment of 6.94 months. ICA occlusion was the method used in seven cases. The remaining three cases underwent balloon fistula occlusion. In total, 13 interventions were performed in the ten patients.

The previous evaluation of the patients with dCCF showed the presence of pain in nine of them. Ocular hyperemia, proptosis and oculomotor nerve involvement were present in all patients (Figures 1, 2 and 3). The trochlear nerve had altered function in four, the trigeminal in one and the abducent in seven (Figure 3). After the final therapeutic intervention, all patients presented without pain or ocular proptosis. We observed discrete residual ocular hyperemia in two patients. The function of the oculomotor, trochlear, trigeminal and abducent nerves remained altered in three, one, one and three patients, respectively (Figures 2 and 3).

The endovascular treatment of aneurysms of the cavernous segment of the internal carotid artery was performed in 26 patients. In these patients, the history of previous trauma was observed in three (11.5%) who in fact had a traumatic pseudoaneurysm.

In the group of patients with non-traumatic aneurysms, two were male and 21 female. The mean age of treated patients was 54.35 years (Figure 4). We observed that the 23 patients of this subgroup had giant aneurysms. Only one patient (3.9%) had another aneurysm at the time of diagnosis, which was subjected to microsurgical clipping prior to ICA therapeutic occlusion.

The therapeutic option used in all patients of this subgroup was the ICA endovascular occlusion of with coils. One patient, despite having an ICA occlusion test negative for deficits, evolved with motor deficit contralateral to the occluded side 72 hours after the procedure, being the only complication observed in this group.

In the preoperative evaluation, retro-orbital and periocular pain were present in 21 cases (91.3%). We observed involvement of the oculomotor nerve ipsilateral

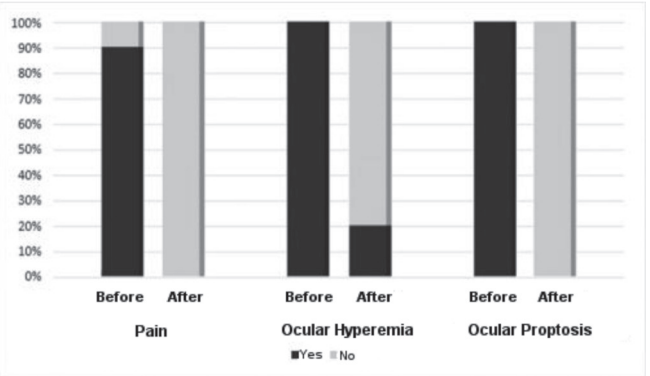

Figure 2. *Clinical manifestations in patients with dCCF before and after endovascular treatment.*

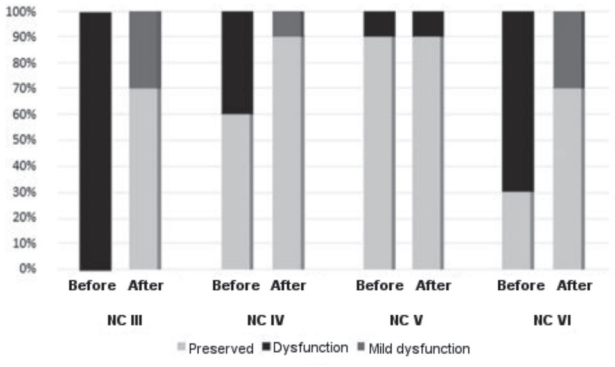

Figure 3. *CN function of in patients with dCCF before and after endovascular treatment.*

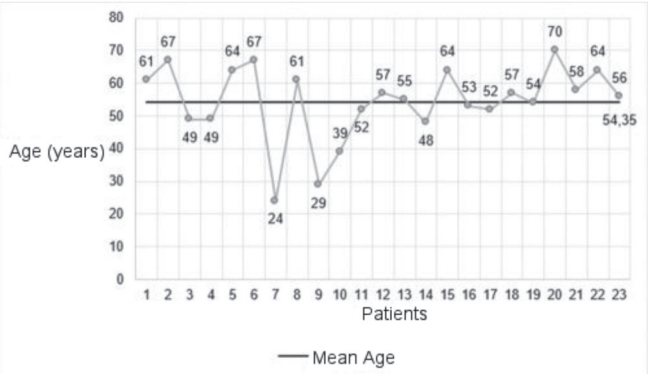

Figure 4. *Distribution of the ages of patients with IcCAA.*

to the aneurysm in 21 patients (Figure 5). Trochlear nerve injury was seen in 47.8% of cases. We found trigeminal nerve involvement in ten patients (43.4%), and abducent nerve commitment in 19 (82.6%) (Figure 6).

In the postoperative evaluation, there was no pain in 15 patients (65.2%). After treatment, retro-orbital pain was present in 34.8%, with lower intensity. The involvement of the oculomotor nerve remained in 11 patients (47.8%). The trochlear nerve was clinically altered in three and the injury of the trigeminal and abducent nerves was evident in less intensity in four and eleven patients, respectively (Figure 6).

Three patients with ICA traumatic pseudoaneurysms were treated with ICA occlusion. Two patients underwent ICA occlusion with balloons, and one, with coils. We observed an iatrogenic etiology in one of these cases, resulting from a previous approach of the Sella region by transsphenoidal endoscopic surgery. This same patient later evolved with the formation of dCCF, being therefore included in two of this work's groups.

In the subgroup of patients with pseudoaneurysms, a single patient was submitted to treatment immediately after the traumatic injury, even during the same anesthetic act, corresponding to the case that suffered injury during a surgical procedure and, therefore, no complaints were recorded regarding CN deficits. Another patient had only a CN VI deficit before treatment. The last patient in this subgroup had a deficit of CN III and VI, in addition to retroocular pain. After treatment, all patients were symptom-free.

DISCUSSION

The dCCF represent high-flow lesions[3] and usually have a traumatic etiology[4-6], as found in 90% of the patients in this study. The only patient with this diagnosis who had no history of trauma supposedly had the fistula due to the rupture of the IcCAA. This situation accounts for up to 25% of dCCF.

The dCCF usually occurs in young male patients[7], as this is the group most frequently affected by traumatic brain injury (TBI). Differently, we found 60% females in this study. The mean age of the treated patients was 35.3 years, corroborating data from the literature[3,7]. One patient, although not correlated with TBI, presented dCCF after inadvertent laceration of the ICA during surgery for resection of a skull base tumor. This etiology is also well documented in the literature[6-10].

The only patient who had no traumatic etiology presented emptying of the balloon used for the selective dCCF occlusion on the second day after treatment, which required a new therapeutic session with the need for ICA occlusion. The emptying of the balloon, often caused by

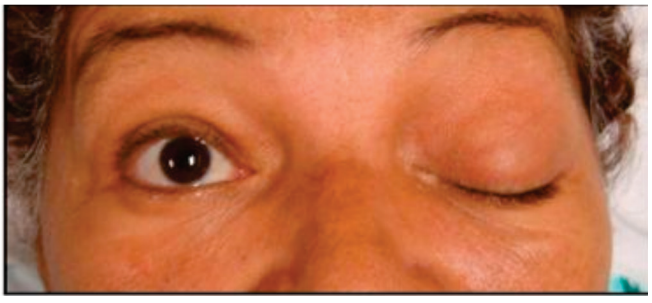

Figure 5. *IcCAA patient presenting left palpebral ptosis due to CN III deficit.*

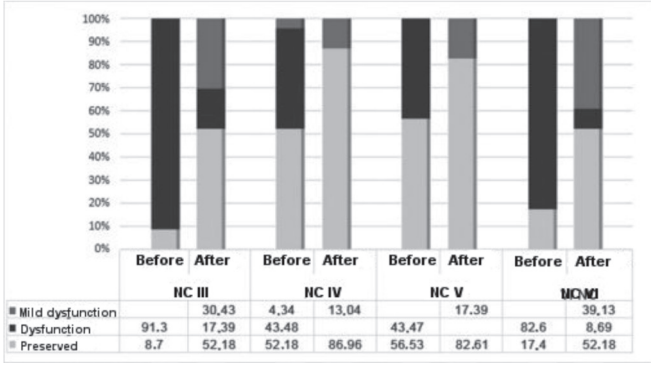

Figure 6. *CN function in IcCAA patients before and after endovascular treatment.*

perforation, is usually described in association with dCCF of traumatic origin, in which bony spicules from fractures at the base of the skull[8,11,12] may cause perforation of the balloon located in CS, especially when it is inflated.

The time elapsed between the beginning of the symptoms and the endovascular treatment was up to 21 months. In this context, we also observed that patients who remained untreated for a longer period had a lower possibility of improvement of the signs and symptoms presented, especially regarding ocular motricity and conjunctival hyperemia, although without significant statistical evidence. This observation reinforces the importance of early diagnosis and treatment[3].

Data from the literature demonstrate clinical exuberance in the presentation of dCCF[13]. The most diverse clinical signs, such as conjunctival hyperemia and ocular proptosis, were present in all patients in the study. In addition, retro-ocular pain was a frequent symptom, present in 90% of patients. The rates of CN impairment found in this study are similar to those reported in publications[2,7], as well as of symptoms improvement after treatment.

Some patients have developed ophthalmoplegia. This is most commonly explained by the involvement of CNs responsible for extrinsic ocular movements[2,7]. However, this condition is facilitated by the appearance of edema of the intraorbital and periocular structures generated by venous engorgement[3].

Diagnostic suspicion of dCCF is based on clinical findings[14]. When one suspects this condition, CT scan of the skull is usually requested as the first imaging examination, which may reveal ocular proptosis and, in contrast phase, venous engorgement and tortuosity of the involved ophthalmic vein, as well as CS[14]. This was the case with this study patients. All were submitted to CT scan of the skull showing the mentioned changes. The diagnostic sequence is based on carotid arteriography (CA), which, in addition to confirming the presence of the fistula and its venous drainage, is of fundamental importance for classification and therapeutic planning[7]. It is also useful in the investigation of other vascular lesions, such as: CS pseudoaneurysms and varicose veins[7], or thrombosis of other venous sinuses.

As to management, once diagnosed, all cases were referred for endovascular treatment. Although there is report of cases of dCCF spontaneous cure[15], there is currently no room for doubt as to whether or not to indicate treatment[3,13]. There is also consensus regarding the indication of endovascular intervention as a treatment[3,6]. Currently, authors differ basically regarding the necessity or not of the treatment immediately after the fistula diagnosis, and the best endovascular technique to be used.

For some authors, such as Halbach *et al*.[16], treatment should be early, especially if there is intracranial hemorrhage, epistaxis, increased intraocular pressure, reduced visual acuity or progressive proptosis. The authors who advocate treatment at a later stage claim that, because of recent trauma, the ICA may present a high reactivity to endovascular navigation, which would lead to an increased risk of endothelial injury. In this study, patients were treated in the late phase.

Once the endovascular approach is indicated, the ideal treatment for dCCF is its exclusion from circulation, with preservation of blood flow by the ICA[3,5,8,11] and this was the goal sought. Thus, we attempted the placement of a latex disposable balloon within the CS for selective fistula occlusion as the initial procedure for all patients. However, the selective occlusion of dCCF with preservation of the flow by the ICA was only definitively achieved in 30% of the patients. The high failure rate (70%) in the preservation of ICA flow differs significantly from that recorded in the literature, which predicts a failure rate of around 10 to 20%[17].

The most common cause of failure of dCCF balloon selective occlusion is the presence of bone spicules within the CS, which would result in the balloon perforation after its positioning in the CS[18]. This usually occurs at the time of balloon insufflation. Balloon perforation at the time of inflation did not occur in this series. One of the cases presented emptying of the balloon in the late phase, corresponding to the only one not having TBI. Another acceptable explanation, which is consistent with the reality found, would be the difficulty of positioning the balloon inside the CS. Such a situation may be related to the small

size of CS, which would make it difficult to inflate the balloon[3], or even to the large dimensions of the fistulous orifice, which may have progressed during the time elapsed until diagnosis and treatment.

Patients submitted to dCCF balloon occlusion displayed no significant complications. There were no residual fistulas or thromboembolic complications that, although rare, are described[3]. However, one patient evolved with intracavernous pseudoaneurysm formation, which remained stable during angiographic follow-up for two years.

In cases of failure of the selective fistula occlusion, patients were candidates for ICA therapeutic occlusion. In most cases, this was accomplished with the placement of detachable balloons occluding the fistular tunnel and the ICA. In these patients, the ICA flow was directed almost exclusively to the fistula, and no occlusion test was required. We observed no complications related to ICA occlusion in this subgroup.

In the group of patients with intracavernous aneurysms, there was a predominance of female gender (84.6%). This situation is in agreement with the existing publications[19,20], although there is no known explanation for this. These lesions usually affect patients in the 5th and 6th decades of life[20], and are commonly manifested by CNs compressive symptoms[19]. In this sample, the mean age at symptoms presentation was 52.2 years[20,21]. If only the group of non-traumatic ICA patients was considered, the mean age was 54.4 years. The increase in the age range of this subgroup is expected, since non-traumatic lesions affect older patients[20].

Intracavernous aneurysms usually have their genesis linked to hemodynamic and atherosclerotic factors[20]. A small proportion of the cases may be associated with TBI or direct ICA lesions[20], in these situations being called traumatic pseudoaneurysms. We observed three patients with diagnosed traumatic pseudoaneurysms, representing 11.5% of the cases. Two of them were caused by closed head trauma and only one due to inadvertent ICA surgical injury.

All cases but the previously mentioned patient who suffered direct ICA injury during the surgical procedure were diagnosed from the compression symptomatology of the CN affected in the CS region. This is the most common presentation[19-21]. Thus, the patients had a clinical picture of retroocular pain, diplopia, ophthalmoparesis and trigeminal neuropathy in different degrees. The same symptoms and signs were found by other authors who investigated aneurysms involving the itracavernous Carotid Artery[19,21]. Although described in the literature[19], none of the intracavernous ansurisms in this study were manifested by spontaneous subarachnoid hemorrhage (SSH).

SSH from an IcCAA is a rare phenomenon[22]. When present, it most often results from the expansion of the aneurysms into the subarachnoid space. This expansion occurs most frequently in aneurysms originating from the C2 segment of the ICA. Another mechanism for its occurrence would be erosion of the lateral wall by the giant aneurysms, or even of the medial wall, causing hemorrhage through the sellar diaphragm[23].

According to Choulakian *et al*.[24], to display CN compressive symptoms, the IcCAA should have diameters greater than 15mm. In our sample, 23 of the 26 aneurysms were considered giant (greater than 25mm), confirming this affirmation. The three remaining aneurysms were, in fact, pseudoaneurysms, with their symptoms associated with cranial trauma.

According to Vasconcellos *et al*.[20], the most commonly encountered IcCAA symptoms were, in decreasing order of frequency: headache, diplopia due to CN IV dysfunction, retro-orbital pain, visual deficit and photophobia. In this study, the most commonly affected CN, in descending order of frequency, were: oculomotor, abducent, trochlear and trigeminal. Still, retro-orbital pain was present in 84.6%. As for pain, this group of patients with severe pain was the most benefited by the treatment, considering that no patient had uncontrollable pain after the endovascular therapy. The improvement in CN symptomatology obtained with endovascular treatment is in agreement with that found in the literature[25,26]. There was improvement in the function of at least one CN in all patients. This high rate of clinical improvement is also justified by the treatment

being instituted at an early stage, when the symptoms had a less than six-month duration.

Regarding the diagnostic sequence employed, the majority of patients with IcCAA came to the service with complaints regarding CN compression, such as diplopia and painful ophthalmoplegia. These patients were initially submitted to head CT, which most of the time showed an intracavernous expansive lesion, adjacent to the ICA, with arterial flow. Magnetic resonance imaging (MRI) of the brain was performed to complement the diagnosis, which was able to better characterize the lesion, as well as to identify the presence of intra-aneurysmal thrombi. In sequence, cerebral angiography was performed with the purpose of diagnostic confirmation and therapeutic planning, often already associated with the ICA occlusion test.

From the conception of the present study, we only included patients who underwent IcCAA endovascular treatment by ICA occlusion. Thus, all treatment candidates were previously submitted to ICA occlusion test. Studies have shown that approximately 25% of the patients undergoing carotid occlusion without having undergone a carotid occlusion test developed cerebral infarctions and about 12% of them died as a result of the occlusion of one of the ICA. After incorporation of the occlusion test, these percentages were drastically reduced[27]. In this sample, 29 ICA occlusion tests were performed and only three patients presented deficits after temporary ICA occlusion. These patients were excluded from the study and referred for surgical treatment through bypass.

However, even patients who adequately tolerate this test may subsequently develop some type of deficit related to the artery occlusion. Only one patient had a late ischemia, with hemiparesis contralateral to the occluded carotid artery. This index is lower than the expected, based on data from the literature, which indicate a rate of up to 22%[28].

It is worth mentioning that the ICA therapeutic occlusion for IcCAA represents a procedure with low morbidity and mortality, taking into account that the alternatives, especially the microsurgical clipping or vascular bypass, have morbidity rates of around 5-10% and mortality rates of 3-10%[29].

The treatment of IcCAA with ICA occlusion, although not the ideal option, is considered by many authors as the choice for this type of lesion[21], with up to 90% improvement in the CNs compressive symptoms[21]. All The patients in the study showed improvement of at least one affected CN.

The efficacy of carotid occlusion to induce thrombosis of the aneurysm is inversely proportional to the degree of existing collateral circulation. Thus, the more proximal the ICA aneurysm, the lower the potential influence of an eventual collateral flow, and therefore the greater the expectation of treatment success[29]. Therefore, carotid occlusion tends to be more effective for aneurysms of the petrous and cavernous segment because of the small number and caliber of the arterial branches. Aneurysms of the ophthalmic segment (paraclinoid) can also be treated by ICA occlusion, but the chances of thrombosis are smaller, especially due to the presence of the retrograde flow through the ophthalmic artery[29].

ICA occlusion is believed to be more effective than the common carotid artery occlusion for IcCAA treatment[28], although occlusion at one or other location is associated with similar incidences of aneurysmal thrombosis, reduced aneurysm volume and reduction of bleeding rates[28]. In the present study, all patients underwent selective ICA occlusion, considering that the preservation of the external carotid flow may be important for the maintenance of adequate cerebral flow.

Although not performed in the study patients, there are other options for the endovascular treatment of IcCAA. The use of flow diversion stent has emerged as an alternative in the search for the ideal treatment model of such lesions, since it aims to exclude the aneurysm from the circulation, preserving the ICA blood flow[29]. Although it may represent the standard IcCAA treatment, even the use of these stents can be followed by ischemic or hemorrhagic complications, often fatal. Other options, such as IcCAA endoscopic embolization, while attempting to preserve the ICA flow, showed no significant benefit in relation to CN compression symptomatology[21].

Another aspect related to the ICA therapeutic occlusion in the treatment of IcCAA is the potential

hemodynamic overload of the intracranial circulation, which may lead to the appearance of *de novo* aneurysms. It is believed that 1-10% of patients undergoing carotid occlusion will develop *de novo* aneurysms, which represents a rate higher than the expected for the general population[29,30]. In addition, the presence of multiple aneurysms is associated with the appearance of new aneurysmal lesions, contributing to the theory of the concomitant occurrence of structural weakness of the vessel wall. Notably, the only patient in the series who developed a *de novo* aneurysm during the study was the one with multiple aneurysms.

Based on the analysis of the results obtained under the conditions of the present study, we conclude that the dCCF endovascular treatment provided an improvement in retroocular pain, proptosis and hyperemia, and of the symptoms related to the involvement of CN III, IV and VI. In patients with IcCAA, endovascular treatment showed improvement of the pain and of the symptoms related to CN IV, V and, mainly, III and VI. Thus, endovascular treatment of direct carotid-cavernous fistulas and aneurysms of the intracavernous portion of the internal carotid artery has been shown to be a safe method, with low complication rates.

R E S U M O

Objetivo: avaliar o tratamento endovascular de lesões vasculares da artéria carótida interna (ACI), segmento cavernoso, realizado na Santa Casa de São Paulo. **Métodos:** estudo descritivo, retrospectivo e prospectivo, de pacientes com aneurisma da porção cavernosa da ACI ou com fístulas carótido-cavernosas diretas (FCCd) submetidos a tratamento endovascular. **Resultados:** foram incluídos 26 pacientes com aneurismas intracavernosos e dez com FCCd. Todos os aneurismas foram tratados com oclusão da ACI. Os com FCCd foram tratados com oclusão, em sete casos, e com oclusão seletiva da fístula nos outros três. Houve melhora da dor e proptose ocular em todos os pacientes com FCCd. Nos pacientes com aneurisma intracavernoso, a incidência de dor retro-orbitária caiu de 84,6% para 30,8% após o tratamento. Após o tratamento endovascular houve uma melhora importante da disfunção de nervos cranianos afetados em ambos os grupos, sobretudo no nervo oculomotor. **Conclusão:** o tratamento endovascular trouxe melhora para os pacientes deste estudo, especialmente nos critérios dor e acometimento do nervo oculomotor.

Descritores: Fístula Carotidocavernosa. Embolização Terapêutica. Lesões das Artérias Carótidas.

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Impact of using a local protocol in preoperative testing: blind randomized clinical trial.

Impacto do uso de um protocolo local na solicitação de exames pré-operatórios: ensaio clínico randomizado cego.

Mônica Loureiro Santos[1]; Antônio Carlos Iglesias[1,2].

ABSTRACT

Objective: *to evaluate the impact of the use of a local protocol of preoperative test requests in reducing the number of exams requested and in the occurrence of changes in surgical anesthetic management and perioperative complications.* **Methods:** *we conducted a randomized, blinded clinical trial at the Gaffrée and Guinle University Hospital with 405 patients candidates for elective surgery randomly divided into two groups, according to the practice of requesting preoperative exams: a group with non-selectively requested exams and a protocol group with exams requested according to the study protocol. Studied exams: complete blood count, coagulogram, glycemia, electrolytes, urea and creatinine, ECG and chest X-ray. Primary outcomes: changes in surgical anesthetic management caused by abnormal exams, reduction of the number of exams requested after the use of the protocol and perioperative complications.* **Results:** *there was a significant difference (p<0.001) in the number of exams with altered results between the two groups (14.9% vs. 29.1%) and a reduction of 57.3% in the number of exams requested between the two groups (p<0.001), which was more pronounced in patients of lower age groups, ASA I, without associated diseases and submitted to smaller procedures. There was no significant difference in the frequency of conduct changes motivated by the results of exams or complications between the two groups. In the multivariate analysis, complete blood count and coagulogram were the only exams capable of modifying the anesthetic-surgical management.* **Conclusion:** *the proposed protocol was effective in eliminating a significant number of complementary exams without clinical indication, without an increase in perioperative morbidity and mortality.*

Keywords: *Preoperative Care. Practice Guidelines as Topic. Laboratory Test. Postoperative Complications.*

INTRODUCTION

The preoperative evaluation (POE) seeks to promote safety in surgery and anesthesia, to ensure a better quality of care, as well as the rational use of resources in the perioperative period. Thus, history and physical examination should be considered the main components of the POE, with the complementary exams remaining under specific clinical conditions[1-3].

In general, patients who are candidates for elective operations have requested preoperative complementary exams (POCE) routinely and indifferently to the clinical findings of the POE. This is based on several factors, such as: ability to identify diseases not diagnosed by anamnesis and physical examination, safety assurance to the professionals involved in the process to make decisions regarding the resolution of intercurrences, as well as safeguarding possible legal responsibilities[4]. However, the medical literature has indicated that abnormalities found in POCEs are not usually clinically important, are generally ignored, do not contribute to changes in the anesthetic-surgical management and are not related to perioperative complications. In addition, there is a risk that non-clinically based tests, especially on the occurrence of false positives, may lead to further invasive investigations, leading to postponement of operations as well as inadequate treatment[3,5].

Regarding selected exams, more controlled clinical research is needed[6]. The rationalization of the request for complementary exams in the POE still requires studies, and to this end, emerged evidence-based guidelines[1,2,7-9] and protocols constructed in view of presence of associated diseases and the procedures to be performed[1,2]. Some authors show that the implementation of protocols increases the effectiveness of the requests for exams without affecting patient's safety and the morbidity of the surgical-anesthetic procedure[10,11].

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The objective of this study was to evaluate the use of a local protocol of preoperative examination requests in the POE, including its impact on the number of requested exams, the occurrence of changes in anesthetic-surgical management and the frequency of perioperative complications.

METHODS

This is a blinded, randomized clinical trial conducted at the Gaffrée and Guinle University Hospital (HUGG) of the Federal University of the State of Rio de Janeiro (UNIRIO), between March 2014 and July 2015, and approved by the Ethics in Research Committee under the Number 27505514400005258. All patients signed an Informed Consent Form.

The population comprised patients who were candidates for surgical procedures in General Surgery, Digestive Surgery and Coloproctology (here grouped as General Surgery), Urology, Gynecology, Thoracic Surgery, Vascular Surgery, Otorhinolaryngology, Orthopedics, Neurosurgery, Plastic Surgery and Ophthalmology. The inclusion criteria were age greater than or equal to 18 years, elective operation, and preoperative evaluation conducted at the HUGG Preoperative Evaluation Clinic. Exclusion criteria were age less than 18 years, emergency/urgency operations, ASA IV or V and those whose preoperative evaluation was done in another hospital. The POE consultations were performed at least 15 days before the operation and followed the guidelines of the American Society of Anesthesiologists (ASA)[1].

The study participants were randomly divided by simple randomization into: Routine Group (RG), in which the routine preoperative complementary exams were requested before POE consultation, and Protocol Group (PG), whose request for exams was Based on the POE consultation following the Preoperative Exam Request Protocol (Figure 1), developed by the researcher according to the guidelines of the ASA Task Force[1]. The POCE included in this study were complete blood count (CBC), prothrombin (PT and INR) and activated partial thromboplastin time (aPTT), serum electrolytes concentration (sodium, potassium and chlorine), glucose, urea and creatinine, resting electrocardiogram (ECG) and chest radiography. All data on history, physical examination and test results were recorded on individual preoperative assessment sheets in addition to data from complementary exams that were not part of the protocol, but were deemed necessary and requested by the POE conductor (supplementary examinations).

On the day of the surgical procedure, after discharge from the post anesthetic recovery (PAR) room, all patients underwent an evaluation by anesthesiologists responsible for the anesthetic procedure with observation and recording of the following parameters: alteration in surgical anesthetic management (cancellation of the procedure, change in anesthetic and/or surgical technique or change in postoperative care) due to absence or abnormal results of preoperative exams (outcome 1) and/or complications, during the anesthetic-surgical procedure or in the period between the patient leaving the operating room until discharge from the PAR room (outcome 2). Complications considered were hypotension (systolic blood pressure ≤80mmHg), cardiac arrhythmia in a patient with no previous history or worsening of preexisting disorder requiring treatment, hypertension (systolic blood pressure ≥200mmHg or diastolic BP≥110mmHg) and cardiorespiratory arrest. These last three were grouped, for statistical purposes, as other cardiovascular complications. Respiratory complications were thus grouped: hypoxemia ($SATO_2$ ≤90% or PaO_2 ≤100mmHg), laryngospasm, bronchospasm, thoracic stiffness, residual curarization and difficulty of oro-tracheal intubation (OTI). Shock, regardless of the cause, was also included, and a group of general complications (nausea and vomiting, inadequate pain control, prolonged awakening, agitation on awakening, hypoglycemia, and total or partial block failure).

Other variables studied were the total number of exams requested, the number of exams with abnormal results, the number of exams additional to the protocol, and the difference between the total and individualized number of exams requested between the two groups.

The sample calculation was performed based on the historical average of the last 24 months of the number of patients seen at the POE/HUGG Clinic and considered

Table 1. *Demographic and clinical data.*

Features	Routine Group (n=204) n (%)	Protocol group (n=201) n (%)	p-value
Gender			0.176
Female	127 (62.3)	135 (67.2)	
Male	77 (37.7)	66 (32.8)	
Age group			0.255
18 to 59 years	106 (48.6)	112 (51.4)	
≥ 60 years	98 (52.4)	89 (47.6)	
Associated Diseases			
None	62 (51.2)	59 (48.8)	0.939
HAS	93 (45.6)	107 (53.2)	0.075
Obesity	63 (30.9)	53 (26.4)	0.374
Diabetes	20 (9.8)	22 (10.9)	0.415
Pneumopathy	21 (10.3)	15 (7.5)	0.677
Dyslipidemia	15 (7.4)	12 (6.0)	0.360
Cardiopathy	12 (5.9)	5 (2.5)	0.072
ASA			0.213
(I)	55 (49.5)	56 (50.5)	0.213
II	137 (52.5)	124 (47.5)	
III	12 (36.4)	21 (63.6)	
MET			0.180
MET < 4	22 (10.8)	31 (15.4)	
MET ≥ 4	140 (68.6)	121 (60.2)	
MET ≥ 10	42 (20.6)	49 (24.4)	
Surgery size			0.149
Minor	61 (29.9)	62 (30.8)	
Medium	107 (52.5)	117 (58.2)	
Major	36 (17.6)	22 (10.9)	
Anesthesia			
General	78 (38.2)	87 (43.3)	0.116
Spinal *	68 (33.3)	66 (32.8)	
Regional #	20 (9.8)	23 (11.4)	
General+ Spinal or regional	31 (15.2)	17 (8.5)	
Local + Sedation	5 (2.5)	7 (3.5)	

** spinal or epidural anesthesia; # brachial plexus or peribulbar; SAH: systemic arterial hypertension; ASA: physical status according to the American Society of Anaesthesiologists; Met: metabolic equivalents (activity index of Duke).*

the calculation methodology for finite population samples and sampling procedures without replacement, with probability of occurrence of the selected outcomes in 50%, with 95% confidence interval, and type I error ≤5%; The estimated sample was 329 patients.

We carried out univariate analyzes by means of simple frequencies to describe the evaluated sample and bivariate analyzes to verify the difference in the distribution of the independent variables for each outcome of interest using the chi-square test. We expressed quantitative variables as mean and standard deviation, and qualitative variables, as percentage. To evaluate the association between the variables of interest, were calculated the gross *Odds Ratio* with a 95% confidence interval through non-conditional logistic regression. We performed all statistical analyzes using the statistical package SPSS® 17.0 (Statistic Package for the Social Science, Chicago, IL, 2008).

RESULTS

Of the 500 initially recruited consecutive patients, six refused to participate in the study and three did not meet the research criteria. The remaining 491 were then randomly allocated in the two study groups. The RG initially received 252 patients, however, 48 were ineligible because their operations were canceled for various reasons (change in surgical management, personal reasons, administrative reasons), leaving a total of 204 patients. The PG had initially 239 patients, but ended with 201 patients for the same aforementioned reasons. There was no statistically significant difference between the two groups regarding gender, age, associated diseases, MET, ASA, surgical size and type of anesthesia (Table 1).

There were 1428 POCE in the RG and 601 exams in the PG, of which 14.9% and 29.1% were altered in the

Table 2. *Distribution of results by analysis group.*

Features	Routine Group (n=204) n (%)	Protocol Group (n=201) n (%)	p-value
CBC			0.009
Normal	165 (80.9)	88 (60.8)	
Altered	39 (19.1)	40 (31.3)	
Electrolytes			0.427
Normal	200 (98.0)	48 (100.0)	
Altered	4 (2.0)	0 (0.0)	
Urea/Creatinine			0.005
Normal	197 (96.6)	120 (88.9)	
Altered	7 (3.4)	15 (11.1)	
PT/aPTT			0.008
Normal	198 (97.1)	17 (81.0)	
Altered	6 (2.9)	4 (9.0)	
Blood glucose			0.001
Normal	181 (78.8)	16 (45.7)	
Altered	43 (21.2)	19 (54.3)	
EKG			0.427
Normal	129 (63.2)	88 (61.5)	
Altered	75 (36.8)	55 (38.5)	
Chest x-rays			0.001
Normal	164 (80.4)	49 (53.8)	
Altered	40 (19.6)	42 (43.2)	
Total tests			0.001
Normal	1214 (85.1)	426 (70.1)	
Altered	214 (14.9)	175 (29.1)	

PT/aPTT: prothrombin time/activated thromboplastin time; EKG-electrocardiogram at rest.

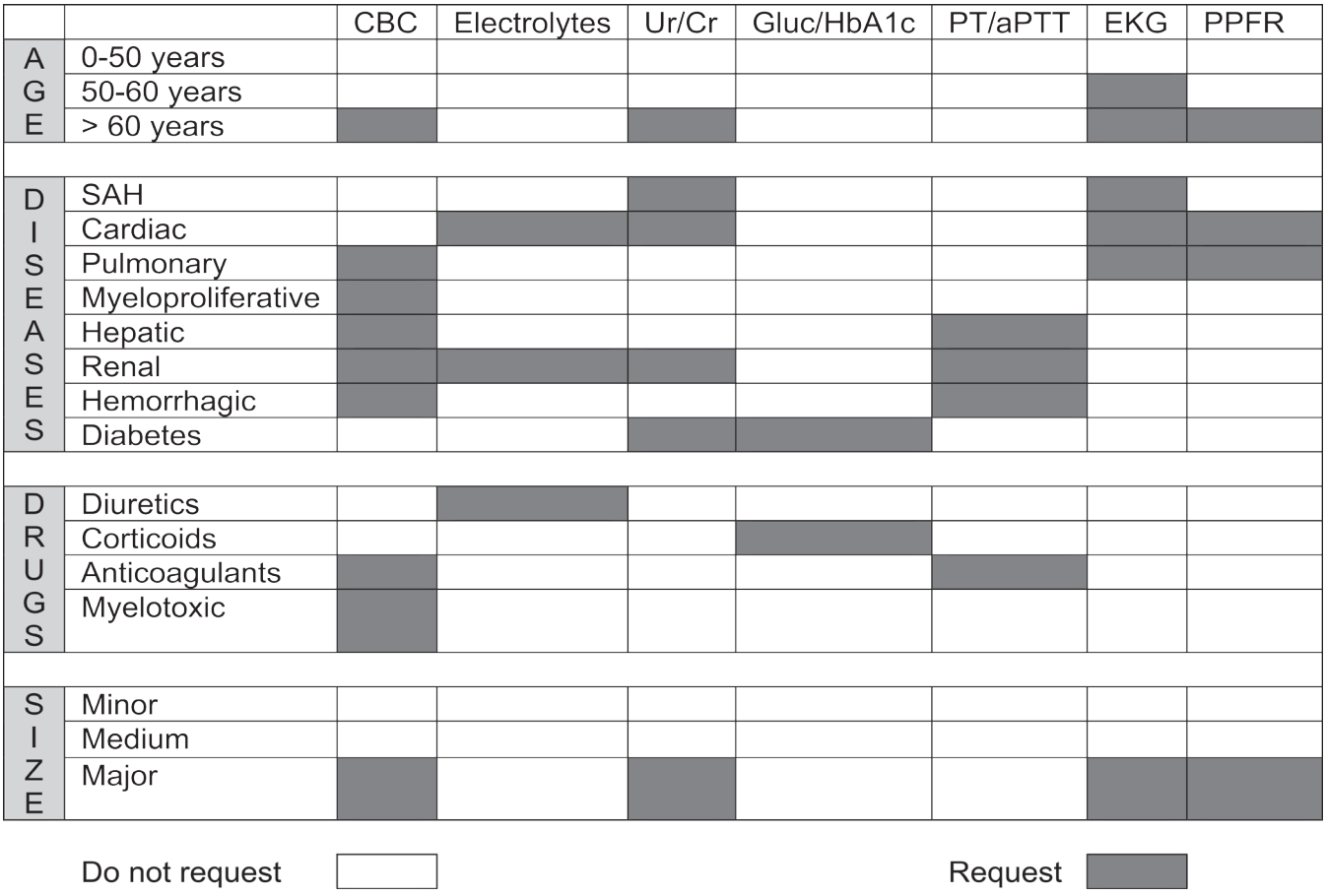
Table 3. *Conduct changes and complications.*

	Routine Group (n=204) n (%)	Protocol group (n=201) n (%)	Total n (%)	p-value
Conduct Alteration				0.231
No	199 (97.5)	199 (99.0)	398 (98.3)	
Yes	5 (2.5)	2 (1.0)	7 (1.7)	
Complications				0.658
No	146 (71.6)	149 (73.2)	295 (72.8)	
Yes	58 (28.4)	52 (26.8)	110 (27.2)	

RG and PG, respectively. The frequency of altered results was higher in the PG for CBC (p=0.009), serum urea and creatinine concentration (p=0.005), PT/aPTT (p=0.008), blood glucose (p<0.001), and chest X-ray (p<0.001). Serum electrolyte concentration and ECG did not reveal statistical significance between the groups (Table 2). The PG underwent less POCE than the RG (p<0.001) for all types of exams except for the category supplementary exams (p=0.158) (Figure 2). The POCE mean of the PG was 2.98±2.04. Fifty additional exams were requested, 29 in the routine group and 21 in the protocol group, with no statistical difference between the groups.

There were conduct changes caused by absence or altered outcome of the exams in seven surgical procedures (1.8% of operations), with five cases (2.5%) in the RG and two cases (1.0%) in the PG (p=0.231) (Table

Figure 1. *Protocol for requesting preoperative exams.*



CBC: Complete Blood Count; U/Cr: urea/creatinine; Gluc/HbA1c: glycemia/glycated hemoglobin; PT/aPTT: prothrombin time and activated partial thromboplastin time; EKG: resting electrocardiogram; PPFR: pleuropulmonary fields radiography.

Table 4. *Influence of exams on surgical-anesthetic conduct and of the sample characteristics on operative complications.*

	Change in conduct		
	No (%)	Yes (%)	Gross OR (95% CI)
CBC			
Normal	251 (77.2)	2 (28.6)	1.00
Altered	74 (22.8)	5 (71.4)	8.48 (1.61-44.60)
PT/aPTT			
Normal	212 (96.8)	3 (50.0)	1.00
Altered	7 (3.2)	3 (50.0)	30.28 (5.17-177.55)
	Hypotension		
	No (%)	Yes (%)	Gross OR (95% CI)
Associated Diseases			
0	108 (31.6)	13 (20.6)	1.00
1	136 (39.8)	24 (38.1)	1.46 (0.71-3.01)
2	72 (21.1)	15 (23.8)	1.73 (0.77-3.85)
3 or more	28 (7.6)	11 (17.5)	3.51 (1.41-8.73)
	Other cardiovascular complications		
	No (%)	Yes (%)	Gross OR (95% CI)
MET			
< 4	44 (11.7)	9 (30.0)	3.13 (1.30-7.53)
≥ 4	245 (65.3)	16 (53.3)	1.00
≥ 10	86 (22.9)	5 (16.7)	0.89 (0.31-2.50)
ASA			
(I)	105 (28.0)	6 (20.0)	1.00
II	242 (64.5)	19 (63.3)	1.37 (0.53-3.54)
III	28 (7.5)	5 (16.7)	3.12 (0.89-10.99)

PT/aPTTÇ prothrombin time and activated partial thromboplastin time; ASA: physical status according to the American Society of Anaesthesiologists; Met: metabolic equivalents (activity index of Duke).

3). Considering the change in conduct and the POCE, we observed statistically significant associations, and the chance of conduct change was 8.48 times higher for the altered blood count when compared to the normal CBC. For the evaluation of the PT/aPTT, this estimate was even higher (OR=30.28, 95% CI= 5.17-177.55). However, one must exercise caution with this finding because of the size of the confidence interval (Table 4).

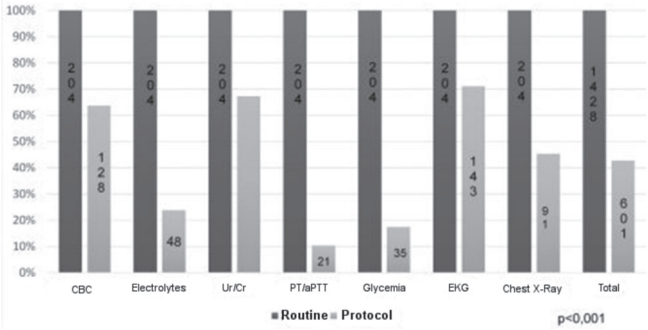
The frequency of complications was 58 cases in the RG (28.43%) and 54 cases in the PG (26.86%), with p=0.658 (Table 3). There was an increase in the risk estimates in the association between the characteristic "associated diseases" and the occurrence of the complication "hypotension", with a cumulative effect according to the increase in the number of associated diseases, with a statistically significant result (OR=3.51, 95% CI= 1.41-8.73) (Table 4). We observed a positive association between the ASA variable and the other cardiovascular complications. Nonetheless, the values found were not statistically significant. When the association between this group of complications and the classification of MET was evaluated, we observed that individuals classified as MET's ≤4 presented a three times greater chance of complications when compared with the group classified with MET's ≥4 (Table 4).

DISCUSSION

Several studies seek to analyze the effectiveness of preoperative examinations in modifying surgical anesthetic management and its impact on the frequency of perioperative complications. One of the pioneer studies was a retrospective study from Kaplan *et al*.[12], which concluded that only 4.3% of the routine exams had abnormal results and of those, 0.17% had some clinical significance. Similarly, Soares *et al*.[5], in a descriptive study, found 2.25% of changes in the results of such exams and only 0.38% were cause for behavior change. Differently from these findings, our study revealed that in the RG group 14.9% of the exams were altered and there was a change in surgical anesthetic management in 2.5% of operations. These data are similar to those found by Guerra *et al*.[13], who conducted a retrospective study and observed 19.8% of abnormalities in routine preoperative exams, which led to a change of conduct in 1.8% of cases. Benarroch-Gampel *et al*.[14], in a retrospective cohort using data from the American National Surgical Quality Improvement Program of patients with a profile similar to that of our sample, found that 61.6% had at least one abnormal test result. Roizen[15] observed that, assuming that the tests are independent of each other, the more tests are requested, the greater the likelihood of finding abnormal results if we take into account issues such as the specificity and sensitivity of such tests and that routine tests are not suitable instruments to identify unknown diseases, are not cost effective, have no impact on surgical anesthetic management, and potentially add risks to the patient and medical-legal problems.

Regardign selective exams, they were altered in 29.1% of our study. Charpak *et al*.[16], in an analysis of surgical patients who underwent a chest X-ray with a clinical indication identified that 52% had abnormalities in the examination, but in only 23% of the cases, these abnormalities were not expected by anamnesis and physical examination. Also in this study, the observed changes modified the anesthetic-surgical management in only 5% of the cases. Chung *et al*.[17], in a randomized clinical trial of patients undergoing outpatient surgical procedures, found 11.5% of selective exams with

Figure 2. *Reduction of the number of exams with the Protocol.*



Ur/Cr: urea/creatinine; PT/aPTT: prothrombin time and activated thromboplastin time; EKG: resting electrocardiogram.

abnormal results and only one change in perioperative care was detected. In these studies, it can be concluded that abnormalities found in selective preoperative exams can often be anticipated by anamnesis and physical examination and/or reflect physiological changes in aging, and have no impact on surgical planning and anesthetic management, such as observed in our study. These findings have implications not only on the direct and indirect financial costs of this practice, but also on the quality of the preoperative evaluation. Thus, we share the opinion of Roizen[18], which says that the real question is not to do or not to do exams, but rather to establish the clinical characteristics of the surgical patient through a careful anamnesis and physical examination and not to replace them by the complementary exams requests.

In the last 20 years several medical societies and health technology institutes[1,2,7-9] have developed protocols with the purpose of reducing the routine of requesting non-selective preoperative exams, a practice that found no evidence support. One of the first studies was that of Fischer *et al*.[19], who compared patients in preoperative elective surgery distributed in two groups: in one group the tests were routinely ordered and in the other they were based on the presence of specific clinical conditions. These authors observed a reduction of 55.14% in the number of exams requested without there being an increase in the procudures' cancellations.

Similarly, the present study found a reduction of 57.3% in the requests for preoperative exams between the study groups. This reduction ranged from 28.8% for ECG to 89.6% for PT/aPTT. When analyzing only the exams done by the PG group, we found that 22.4% of

the patients did not undergo any tests and only 1% had all the examinations contemplated in the protocol.

When testing the association between the mean number of exams and the characteristics of this group, we observed that 68.4% of the patients classified as ASA I did not undergo any tests and 70.8% of the patients classified as ASA III underwent four or more tests (p<0.001). Regarding the associated diseases, we observed that in the set of patients with three or more diseases, 89% underwent four or more exams (p<0.001), and when analyzing the distribution of exams by age group, we found that in patients with 60 years or more, 75.2% had four or more exams (p<0.001). As for the type of anesthesia, 91.2% of patients submitted to peribulbar anesthesia underwent four or more exams (p=0.006), and of the patients submitted to local anesthesia with sedation, 42.9% did not undergo any examination, and 14.3% underwent only one exam (p=0.008).

In a study involving six hospitals in Switzerland, Barazzoni *et al*.[10] investigated the impact and adherence to guidelines for requesting preoperative exams over six time intervals before and after implementation of these guidelines. There was a 81% reduction in coagulogram requests and 43% in ECG requests. The reduction was more significant in the ASA I and II patients, and did not mean an increase in the number of perioperative complications or surgical mortality. In a study investigating the impact after two years of the implementation of guidelines for requesting preoperative exams in outpatient orthopedic operations, Mancuso[9] found a reduction, varying from 23 to 44%, in the mean number of exams requested without an increase in the frequency of complications or hospital readmissions. When analyzing, by group of patients and type of anesthesia, the group with a greater number of associated diseases and those who underwent general anesthesia did not present a reduction in the number of exams. In contrast, Finegan *et al*.[11] performed a prospective cohort study in a hospital with a similar profile to ours and compared a group of patients who had their exams requested in an established preoperative evaluation practice with a group of patients whose preoperative exams were requested by different health professionals who received prior guidance on evidence-based guidelines. In this study, there was no reduction in the average number of exams found, complications were higher in the group of exams selected, but these were not related to the exams' results or to their absence. In the present study, when submitting a group of patients to the proposed protocol, we observed a reduction in the mean number of exams requested, similar to the findings of Mancuso[9] and Barazzoni[10], that is, a more pronounced reduction of exams requests for those younger patients, without associated diseases, classified as ASA I and undergoing small operations (procedures with local anesthesia and sedation). This significant reduction in the number of requested exams was not accompanied by increase in the incidence of perioperative complications or in the request for exams complementary to the protocol.

On the other hand, Chung *et al*.[17] tested a local protocol for preoperative exams versus a group of patients who did not undergo any preoperative exams and found no difference in the frequencies of complications or hospital readmissions. In a multicenter, randomized trial, Schein *et al*.[20] tested the complete elimination of preoperative exams in cataract surgery and found the same incidence of intra- and postoperative complications in the group without exams compared with the group with exams, concluding that preoperative exams do not contribute to surgical safety. It should be emphasized that the patients' profile in these studies is different from ours, since the analyzed only small, outpatient operations, whereas in our sample predominated mid-size surgeries, requiring hospitalization.

We found seven cases of conduct change in this study: in four surgical procedures, there was a change in the anesthetic technique (replacement of the combined epidural/general technique with general anesthesia) caused by thrombocytopenia in two cases and by changes in PT/aPTT in the others. Two surgical procedures were postponed due to lack of an additional protocol exam (echocardiogram) and one procedure was postponed by an altered exam (hyperglycemia). When analyzing the association between the cases of altered conduct and the abnormal results of exams, we found that the only exams capable of influencing surgical anesthetic management were CBC and PT/aPTT, a result similar to that found by Guerra[13].

In the present study, the frequency of complications was 28.4% and 26.8%, respectively, in the Routine and Protocol groups, with no statistical significance. This result presents rates higher than those observed by several authors[9,11,17,20], which ranged from 0.8% to 6% for the routine group and 1.4% to 6.0% for the selective exams group or no exam. We believe that this difference is due to the fact that, for the most part, these studies were carried out on samples from patients undergoing small and outpatient surgeries, with the exception of the Finegan[10] study. In our study, hypotension was the most common complication, with 63 cases, followed by other cardiovascular complications, with 30 events. When analyzing the association of complications with the sample's characteristics, we found a statistically significant association with the presence and number of associated diseases and functional classification (MET's). Such associations were not observed in the study by Schein *et al*.[20], nor in the one by Chung *et al*.[17]. However, there are studies in the medical literature associating surgical morbidity and mortality with preoperative conditions of the physical state, clinical compensation of associated diseases, besides the type and nature of the executed procedure[21,22]. Studies on perioperative complications are difficult to perform. Although this discussion fits the objectives of this study, it is important to note that perioperative morbidity does not have any association with the number of exams requested, nor with altered results of such exams, a fact observed both by us and by other authors[9,11,17,19,20].

We conclude that the protocol we used was effective in eliminating a significant number of complementary exams requested without clinical indication, without, however, causing an increase in perioperative morbidity and mortality.

R E S U M O

Objetivos: avaliar o impacto do uso de um protocolo local de solicitações de exames pré-operatórios na redução do número de exames solicitados e na ocorrência de alterações na conduta anestésico-cirúrgica e de complicações perioperatórias**. Métodos**: ensaio clínico randomizado, cego, realizado no Hospital Universitário Gaffrée e Guinle com 405 pacientes candidatos à operação eletiva divididos randomicamente em dois grupos segundo a prática de solicitação de exames pré-operatórios: grupo Rotina com exames solicitados de maneira não seletiva e grupo Protocolo com exames solicitados de acordo com o protocolo em estudo. Exames em estudo: hemograma, coagulograma, glicemia, eletrólitos, ureia e creatinina, ECG e radiografia de tórax. Desfechos primários: alterações na conduta anestésico-cirúrgica motivadas por exames anormais, redução do número de exames solicitados após o uso do protocolo e complicações perioperatórias. **Resultados:** foi observada diferença significativa (p<0,001) no número de exames com resultados alterados entre os dois grupos (14,9% x 29,1%) e redução de 57,3% no número de exames pedidos entre os dois grupos (p<0,001), mais acentuada nos pacientes de menor faixa etária, ASA I, sem doenças associadas e submetidos a procedimentos de menor porte. Não houve diferença significativa na frequência de alterações de conduta motivada por resultado de exames, nem de complicações entre os dois grupos. Na análise multivariada hemograma e coagulograma foram os únicos exames capazes de modificar a conduta anestésico-cirúrgica. **Conclusão:** o protocolo proposto foi efetivo em eliminar um quantitativo significativo de exames complementares sem indicação clínica, sem que houvesse aumento na morbidade e mortalidades perioperatórias.

Descritores: Cuidados Pré-Operatórios. Testes Diagnósticos de Rotina. Guia de Prática Clínica. Complicações Pós-Operatórias.

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Effects of heparin and hyperbaric oxygenation on necrosis reduction in an animal model for degloving injuries

Efeitos da heparina e da oxigenação hiperbárica na redução de necrose de modelo animal para desluvamentos

Douglas Neumar Menon[1]; Letícia Teixeira[1]; Natalha Bristot Paurosi[1]; Marcio Eduardo Barros[1].

ABSTRACT

Objective: *to evaluate the efficacy of the treatment with hyperbaric oxygen therapy or with topical and intralesional heparin in an animal model of degloving lesions.* **Methods**: *we conducted an experimental study with adult, male Wistar rats submitted to degloving of the left hind limb and divided into four groups according to the treatment: Group 1 (control) - without treatment; Group 2 (Heparin) - intralesional application at the time of surgery and topically, in the postoperative period, with heparin spray 10,000IU/mL; Group 3 (hyperbaric oxygenation) - daily sessions of 30 minutes in a hyperbaric chamber with 100% oxygen and 2 ATA pressure; Group 4 (positive control) - administration of a single dose of 45 mg/kg of intraperitoneal allopurinol. On the seventh day, we killed the animals, removed the cutaneous flaps and measured the total and necrotic areas, as well as computed the percentage of necrotic area.* **Results**: *the mean percentage of necrosis in the control group was 56.03%; in the positive control group it was 51.36% (p<0.45); in the heparin group, 42.10% (p<0.07); and in the hyperbaric oxygen therapy group, 31.58% (p<0.01).* **Conclusion**: *both hyperbaric oxygen and heparin therapies were effective in reducing the percentage of necrosis in the model studied, although only the hyperbaric oxygenation showed statistical significance.*

Keywords: *Surgery, Plastic. Wounds and Injuries. Traumatology.*

INTRODUCTION

Deglovings are injuries in which there is detachment of the integument from the underlying tissues[1]. The most common cleavage plane is between the fascia and the subcutaneous tissue, but there may be detachment in the muscular, periosteal, subperiosteal planes or even in multiple planes, the latter cases being of high complexity, morbidity and mortality. The most common sites of degloving are the limbs, especially the lower ones, but it may occur in other regions of the body, such as the trunk[2] and cephalic region[3]. Deglovings of the limbs are usually accompanied by musculoskeletal trauma and not infrequently are also associated with polytrauma of other segments of the body, such as traumatic brain injury, abdominal and chest trauma.

There are several degloving causes reported in the literature, the most frequent being the traffic accidents with mechanisms of grip and rotation[4], but other causes have been described, such as industrial accidents and accidents with agricultural machines[5].

Some authors have proposed classification systems for degloving: Hidalgo[6] classified these wounds into three groups, the first group being typical lesions, with a skin continuity solution associated with the detaching wound. The second group consists of the closed detaching lesions, while the third group is cutaneous avulsions, or wounds with loss of substance.

Another classification system was proposed by Arnez[7], that considered four patterns of degloving: pattern 1- limited degloving with abrasion or avulsion. In this pattern, injuries result from abrasion forces, with a slight detachment of the skin. Pattern 2- refers to non-circumferential deglovings, where normally the detached skin is preserved or there is little loss of substance. Usually these lesions have a well-defined cleavage plane, usually between the deep fascia and the subcutaneous tissue. Pattern 3- comprises circumferential deglovings in a single plane, which, just as the type-2 lesions, usually have their cleavage plane between the deep fascia and the subcutaneous tissue, there being open or closed lesions (with or without skin continuity solution). Pattern 4- refers

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to circumferential deglovings in multiple planes, in which, in addition to cutaneous avulsions, detachments occur between muscle structures or in the musculo-periostal plane. Of course, this latter pattern represents the trauma with the greatest amount of energy applied.

There is a specific category of closed deglovings, in which the skin is detached from the fascia due to liquid collections, such as bruises, seromas, or steatonecrosis material, and receives the eponym of Morel-Lavallée Syndrome or Injury. This usually results from high-energy tangential trauma over richly vascularized tissues, but may also be due to distant lesions with serous and / or blood leakage leading to tissue detachment[8].

Various treatment modalities are mentioned in the literature, such as, for example, primary closure, removal of the detached skin and its use as a cutaneous graft, use of dermal matrices[9], vacuum dressings[10], local or remote flaps, microsurgical flaps, and even conservative treatment, indicated mainly in cases of closed deglovings. However, the most commonly performed treatment for this type of injury is the immediate removal of the detached skin, followed by removal of the subcutaneous tissue and repositioning of the treated skin as a cutaneous graft. Cryopreservation of the skin may also be performed for use after the trauma, after better stabilization of the patient's clinical condition[11]. The choice of the best form of treatment depends on the characteristics of the lesion and requires an accurate judgment of the surgeon.

Most of the work with deglovings in humans is composed of cross-sectional, descriptive studies or even case reports. The limitation to the emergenge of more elaborate studies on the subject probably resides in the diversity of presentation of this type of injury, causing difficulty in conducts' standardization[12]. In view of this, Milcheski *et al*.[13] developed an experimental model in rats for studies of this type of injury, in which they promoted a detaching injury of the entire right lower limb of rats, giving rise to a distal flap, susceptible to ischemia and, therefore, useful in the evaluation of aproaches for deglovings. Also in this study the authors tested the protective effect of pentoxifylline and allopurinol on these injuries. The use of pentoxifylline was justified because of its hemorheological effect, increasing the plasticity of the erythrocyte membrane and consequently improving perfusion by possibly damaged capillaries, whereas allopurinol was used for antioxidant purposes. After injury induction, rats received a single intraperitoneal dose of these drugs and the necrosis area relative to the total flap area was compared to the control group on the seventh postoperative day. Both agents showed a relative decrease in the necrosis area, demonstrating a protective effect, with better performance for the allopurinol.

Heparin has been used clinically in Plastic Surgery in the treatment of partial thickness burns through topical application. In addition, due to its possible anti-inflammatory effect, it is also used for the treatment of pathological scars, especially those with fibroproliferative disorders such as keloids and hypertrophic scars[14]. Studies have also shown an angiogenic effect with the use of topical heparin applied in random flaps in rats[15] and improvement in the healing of chronic venous ulcers[16]. The association of these angiogenic, anti-inflammatory and healing properties makes heparin a potentially useful compound in deglovings.

Another therapeutic modality normally applied in the treatment of complicated wounds is hyperbaric oxygenation[17], which consists of exposing the patient to an environment with 100% oxygen concentration under pressure of 2 ATA (absolute atmosphere)[18]. In clinical practice, hyperbaric oxygenation is normally used in the management of chronic wounds and/or wounds complicated by infection or necrosis[19], although research has studied the application of this therapeutic modality in other situations where an increase in tissue oxygen concentration is desirable, as in muscle trauma[20], fractures[21], nerve injuries[22], anemia[23] and spinal cord injuries[24]. The effect of hyperbaric oxygenation in animal models of degloving (on rats' tails) was tested by Demirtas *et al*.[25], with positive results. There are descriptions of hyperbaric chamber models for specific use in research on animals[26].

Thus, we propose to evaluate the effect of several therapeutic modalities in an animal model of degloving wounds, to seek new treatment options for this type of lesion.

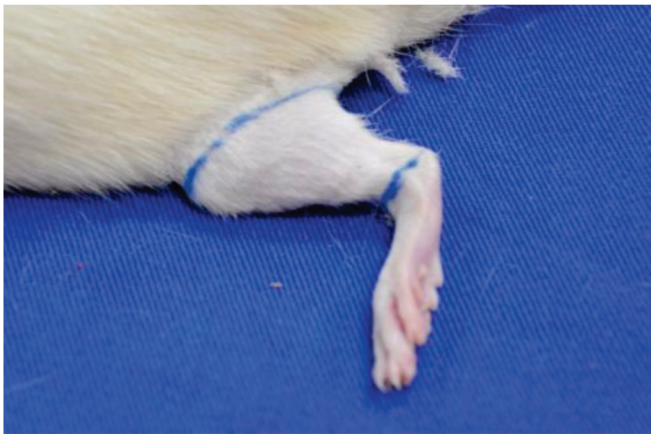

Figure 1. *Marking of the flap detachment area.*

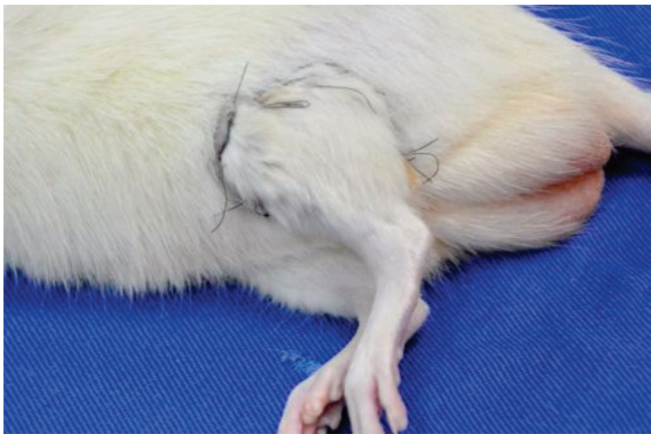

Figure 2. *Surgical site on the 7th postoperative day.*

METHODS

The present study was approved by the Ethics Committee with the Use of Animals of the Federal University of Grande Dourados (UFGD) under protocol number 025/2014.

We used adult, male rats from the UFGD vivarium, housed before the procedures in appropriate cages, in groups of six animals, with chow and water *ad libitum*, kept until the day of surgery. We randomized the animals by draw and divided them into the following groups: Group 1- Control, formed by animals submitted to surgery alone, without additional treatment; Group 2- Heparin, formed by animals treated with spray of topical and intralesional heparin; Group 3- Hyperbaric Oxygen Therapy; and Group 4- Positive Control, submitted to treatment with intraperitoneal injection of allopurinol, in a single dose of 45mg/kg. Group 1 (control) comprised 12 animals, while the other groups were composed of six animals each.

The animals received general anesthesia with ketamine 60mg/kg associated with xylazine10mg/kg, applied intramuscularly to the right animal'sthigh, and the surgical procedure was started after confirmation of the anesthetic plane through the absence of the corneal eyelid reflex. After performing a tricotomy at the base of the left hind limb, we inflicted the wound through a circular incision in the left thigh root and dissection of the skin in the subcutaneous plane. We applied traction at the edge of the flap with Backauss clampsin the craniocaudal direction, from the root of the thigh to the ankle joint (Figure 1), with later repositioning of the flap and skin suture in the incision area with continuous mononylon 5.0 (Figure 2).

All animals received antibiotic prophylaxis through the intramuscular application of benzathine penicillin at a dose of 40,000IU/kg in the lower limb contralateral to the surgery limb, in addition to analgesia by the addition of dipyrone to the drinking water at a dose of 2mg/ml. After the surgeries, we placed the animals in individual cages in order to avoid aggression or cross autophagy.

The animals of the heparin group received intralesional application of the medication through a specific spraying device. We applied two jets, one anterior and one posterior, before the repositioning and suturing of the wound. This preparation is equivalent to a concentration of 10,000IU/ml. During the first six days

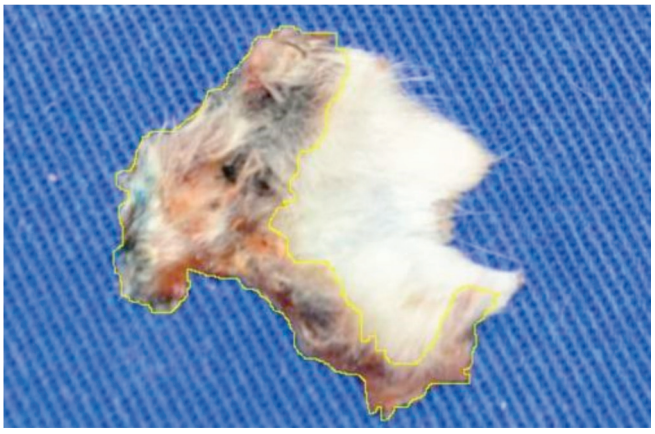

Figure 3. *Demarcation of the flap necrotic area.*

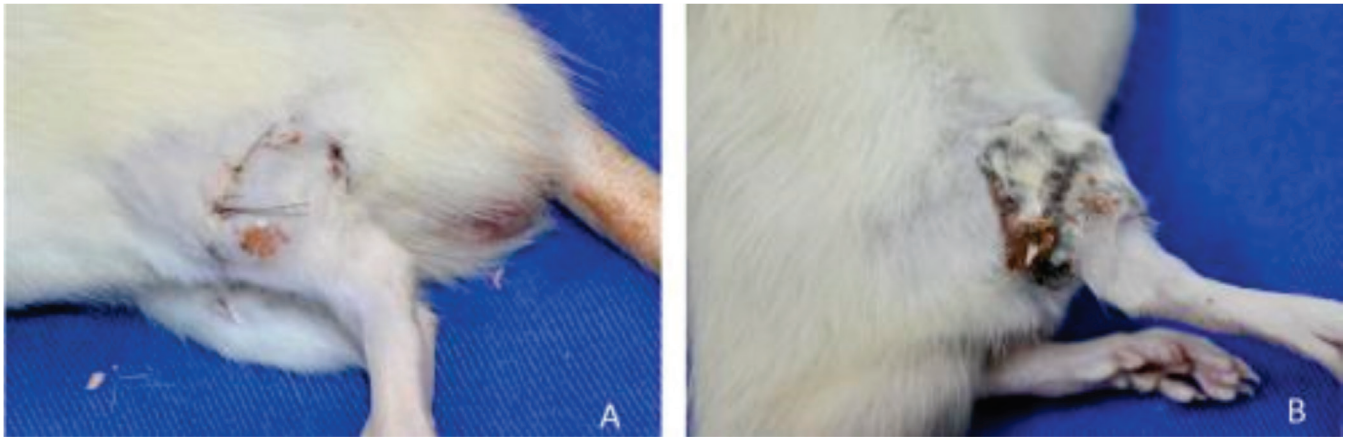

Figure 4. *Comparison of examples of healing in an animal treated with (A) hyperbaric oxygen therapy and (B) control group.*

of postoperative observation, we performed daily topical applications of the same dose of spray heparin (one anteriorjet and one posterior) on the flap, and euthanized the animals on the seventh postoperative day.

We submitted the animals of the Hyperbaric Oxygen Therapy group to therapy in a hyperbaric chamber specific for animal use of the UFGD Laboratory of Surgical Technique, filled with 100% oxygen under pressure of two atmospheres with daily sessions of 30 minutes, initiated immediately after surgery. During each session, the animals were housed in individual boxes and placed inside the chamber. A flush was performed for five minutes with oxygen in order to remove all the air present inside the chamber, maintaining the oxygen concentration at 100%.

The Positive Control group animals received a single dose of 45mg/kg intraperitoneal allopurinol after the standard surgical procedure.

We monitored the animals daily for changes that could interfere with the study, as well as medication application when applicable. After seven postoperative days, all animals were submitted to euthanasia through intramuscular administration of ketamine 100mg/kg associated with xylazine 10mg/kg, followed by cardiac puncture exsanguination. We performed no application of heparin or hyperbaric oxygenation session on animals on the day of euthanasia.

We then proceeded to the complete removal of the cutaneous flaps by removing the stitches and bluntly dissecting the suture line and the fasciocutaneous cleavage plane. We sectioned the flaps longitudinally in the craniocaudal direction on the lateral anatomical side to form a flat specimen, allowing the measurement of total and necrosis areas. We duly identified the specimens according to the animal and group (control or intervention) and photographed them. We analyzed the images using the ImageJ® software (Wayne Rasband, National Institutes of Health, USA, 1997). We measured the total area and the necrotic area of the flap, respectively, and calculated the percentage of necrotic area in each specimen and the mean percentage of necrotic area in each group (Figure 3). We performed the statistical analysis through analysis of variance – ANOVA – for comparison between groups, followed by the Student's T test for comparison of each group with the control one.

RESULTS

We observed cutaneous necrosis in all animals of all groups. In the control group, the percentage of necrotic area ranged from 18.07 to 81.08%, with a mean of 56.04% ± 5.42 and a median of 60.16. There was one death in this group due to anesthetic complications. The mean total flap area was 5.22cm^2 ± 0.65, and the mean necroticarea was 2.77cm^2 ± 0.37.

The allopurinol group, used as a positive control, had a mean necrosis area of 51.36% ± 1.99 and a median of 51.57 (p=0.45), ranging from 44.69 to 57.37%, the mean of the total area being 5.50cm^2 ± 0.26

and the mean of the necrotic area, 2.85cm² ± 0.22.

In the group of animals treated with both topical and intralesional heparin, necrosis ranged from 32.41 to 49.95%, with a mean of 42.10% ± 3.56 (p≤0.07) and a mean of 43.02. The mean total area of the flaps was 6.25 cm² ± 0.12, while the mean necrotic area was 2.60 cm² ± 0.24. In this group, two deaths occurred due to anesthetic complications and was observed hemorrhage in the wounds of all the animals after the application of heparin, although not measured. There was hematoma formation in one of the subjects.

In the Hyperbaric Oxygen Therapy group, there was necrosis ranged from 8.25 to 47.21%, with a mean of 31.58% ± 5.49 (p≤0.01) and a median of 33.49, with a mean total area of 5.15cm² ± 0.29 and mean necrotic area of 1.88cm² ± 0.45. We also empirically observed improved healing in the animals submitted to hyperbaric therapy, with improvement in both scar appearance and flap adhesion to the bed compared with control animals (Figure 4). Table 1 shows the means of the necrotic areas in the four groups.

Table 1 - *Comparison between the mean percentages of necrosis in the groups studied.*

Group	Meanpercentage of necrosis	
Control	56.04 ± 5.42	
Allopurinol	51.36 ± 1.99	p ≤ 0.45
Heparin	42.10 ± 3.56	p ≤ 0.07
Hyperbaric Oxygenation	31.58 ± 5.49	p ≤ 0.01

DISCUSSION

The great doubt in the treatment of patients with deglovings remains whether to remove or preserve the detachedskin. In cases where it is possible to perform a more conservative treatment, with only the primary suture, a more efficient skin coverage is obtained, both from aesthetic and functional points of view. However, keeping an ischemic flap will cause skin necrosis and consequently the loss of an important graft donor area, generating the need for skin capture in other areas, adding morbidity to an already severely compromised patient. On the other hand, an aggressive approach, with early debridement, when ill indicated, imposes unnecessary sequelae to the patient[3]. In addition, it is very difficult to precisely define which areas are devascularized and which are viable. Hence, optimal treatment is hardly achieved[4,27].

Therapies that improve the blood supply to peripheral tissues may favor more conservative treatments in degloving cases and may have broad application in Plastic Surgery. In addition to the specific degloving wound cases, their use may be considered in any situation in which an improvement in the vascularization of the involved tissues is desired, as in cases of random skin flaps, skin grafts, chronic wounds, venous or ischemic ulcers and pressure ulcers[28].

Regarding the control group, our results were similar to those of Milcheski *et al*.[13], who found 63.34% of necrotic area, while in our study this rate was 56.04%. However, the group chosen as positive control (allopurinol) presented results discordant from these authors', who observed 34.85% of necrosis, with an important reduction in ischemia, whereas we found 51.36%, showing a much more modest improvement despite the use of the same dosage and route of administration.

We observed a decrease in the percentage of necrotic area in the other two groups tested, with rates of 42.10% for the heparin group and 31.58% for the hyperbaric oxygenation one, although only the hyperbaric oxygenation group showed statistical significance.

In a review article, Berner *et al*.[29] cites several positive effects of hyperbaric oxygenation that would justify the positive results found in our study, such as neoangiogenesis, increased collagen synthesis, increased stem cell migration and improved local immune response, as well as overall improvement in healing. Another study, produced by Yan *et al*.[30], showed several effects of this therapy, such as increased blood oxygen concentration and partial pressure, improved blood dispersion of oxygen and its diffusion in tissues, formation of collateral

circulation, reduction of cellular apoptosis, reduction of inflammation, balanced oxygen free radicals and stem cell activation. Evidently, these effects also contributed to the reduction of necrosis in our model.

We also empirically observed that the quality of the scar in the animals of this group, both the suture line and the adherence of the flap to the deep tissues being better, since the flaps presented greater tensile strength in both the cutaneous fascial cleavage plane and in the suture line. Although we did not objectively measure these parameters, they are interesting options for future testing. Zhang *et al*.[31] tested the effects of hyperbaric therapy in an animal healing model and observed improved healing. The authors evidenced a reduction in healing time and a decrease in the incidence of hypertrophic scars, corroborating our observation.

In the heparin group, the improvement in the necrosis area is due to reduced inflammation and vasodilatation caused by heparin, which are already known and beneficial in the treatment of superficial burns, especially of the face, the usual use of this type of product[32]. All animals treated with this method showed a visible increase in bleeding in the immediate postoperative period, although we did not measure it. In one of the heparin treated animals, we observed the formation of a small laminar hematoma after the flap withdrawal, which we believe did not influence the results of this study due to the small volume of the collection. However, these complications (hemorrhage and hematoma) seem sufficient to discourage heparin studies in humans with degloving injuries, since the occurrence of any adverse events in severely compromised patients, as they are, would significantly increase morbidity and mortality.

Cebesoy *et al*.[33] carried out a study with the use of intraperitoneal heparin in the a rat tail degloving model. They analyzed the cutaneous necrosis depth according to the National Pressure Ulcer Advisory Panel (NPUAP), and demonstrated a reduction in the skin necrosis thickness with the use of both unfractionated and low molecular weight heparin compared with the use of saline solution, as seen in our study. The authors attributed this improvement to the prevention of microthrombus formation during the flaps neovascularization process, but this hypothesis was not objectively studied.

A similar study analyzed the effects of subcutaneous enoxaparin and rivaroxaban, an oral antithrombotic agent, compared with the subcutaneous application of saline using the same animal model. Both agents showed clinical healing improvement, decrease in the necrotic area and decrease in the histopathological necrosis stage[34].

Studies involving human beings present great conduction difficulty, since in large deglovings the treatment should not be delayed, under risk of important sequelae, both of the affected area and of possible tissue donor areas for reconstruction, since even in the best of the hypothesis, large areas of necrosis still occur[35]. However, the modalities studied in this study are good options for studies of minor lesions, with a lower possibility of limiting sequelae, such as small degloving wounds or local flaps.

The model used in this study should be understood not only as a model of degloving, but as a model of cutaneous flaps of dubious or deficient vascularity, suggesting the possibility of further studies of these therapeutic modalities in various Plastic Surgery situations, Skin flaps, remote flaps, breast reconstruction and even cosmetic surgery. Because of the distinct mechanisms of action, we believe that it would be interesting to conduct a study with the association of these therapeutic methods to evaluate possible benefits synergism.

The proposed model was successfully reproduced, as the percentages of necrotic areas were similar to those in the literature and our studies showed a decrease in the area of ischemia in the flaps treated with the two methods studied, with advantage for hyperbaric oxygen therapy, although only the latter Presented statistical significance.

The results obtained in this study are insufficient to encourage studies in humans with large degloving wounds, the best option being the study of small lesions of doubtful vascularization or random skin flaps, situations that do not offer great risks of incapacitating sequelae. The intralesional use of heparin in topical preparation should be viewed with caution due to the possibility of

complications such as bleeding and bruising. We believe that new studies, capable of measuring inflammatory activity, partial oxygen pressure in tissues, histological changes, tensile strength in the suture line and in the flap cleavage plane are interesting alternatives to the sequence of this work.

R E S U M O

Objetivos: avaliar a eficácia do tratamento com oxigenoterapia hiperbárica ou com heparina tópica e intralesional em modelo animal de desluvamentos. **Métodos**: estudo experimental, com ratos adultos machos *Wistar*, submetidos a desluvamento do membro posterior esquerdo e divididos em quatro grupos, de acordo com o tratamento: Grupo 1 (controle) – sem tratamento; Grupo 2 (Heparina) – aplicação intralesional no momento da cirurgia e tópica, no pós operatório, com spray de heparina 10.000UI/mL; Grupo 3 (oxigenação hiperbárica) – sessões diárias de 30 minutos em câmara hiperbárica com 100% de oxigênio e 2 ATA de pressão; Grupo 4 (controle positivo) – administração de dose única de 45mg/kg de alopurionol intraperitoneal. No sétimo dia os animais foram mortos e os retalhos cutâneos foram retirados e realizadas medidas das áreas total e necrótica, bem como cálculo da porcentagem da área de necrose. **Resultados**: a média da porcentagem de necrose do grupo controle foi 56,03%; no grupo controle positivo, 51,36% (p≤0,45); no grupo da heparina, 42,10% (p≤0,07) e no grupo da oxigenoterapia hiperbárica, 31,58% (p≤0,01). **Conclusão**: tanto a oxigenoterapia hiperbárica quanto a terapia com heparina mostraram-se eficazes na redução do percentual de necrose no modelo estudado, embora neste trabalho apenas a oxigenação hiperbárica tenha demonstrado significância estatística.

Descritores: Cirurgia Plástica. Ferimentos e Lesões. Traumatologia.

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Efficacy of bacterial cellulose membrane for the treatment of lower limbs chronic varicose ulcers: a randomized and controlled trial

Eficácia da membrana de celulose bacteriana no tratamento de úlceras venosas de membros inferiores: estudo randomizado e controlado

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A B S T R A C T

Objective: *to evaluate the efficacy of Bacterial Cellulose (BC) membrane dressings in the treatment of lower limb venous ulcers.* **Methods:** *we carried out a prospective, randomized, controlled study of 25 patients with chronic venous ulcer disease in the lower limbs from the Angiology and Vascular Surgery Service of the Federal University of Pernambuco Hospital and from the Salgado Polyclinic of the County Health Department, Caruaru, Pernambuco. We randomly assigned patients to two groups: control group, receiving dressings with triglyceride oil (11 patients) and experimental group, treated with BC membrane (14 patients). We followed the patients for a period of 120 days.* **Results:** *There was a reduction in the wound area in both groups. There were no infections or reactions to the product in any of the groups. Patients in the BC group showed decreased pain and earlier discontinuation of analgesic use.* **Conclusion:** *BC membrane can be used as a dressing for the treatment of varicose ulcers of the lower limbs.*

Keywords: *Varicose Ulcer. Cellulose. Saccharum. Wound Healing.*

INTRODUCTION

Chronic venous disease (CVD) of the lower limbs (LL) is common and occurs due to abnormal venous system function caused by valvular insufficiency, which may be associated with obstruction of blood flow[1,2]. Its incidence is higher in women and only 30% of men are affected, which represents 3% to 5% of the population over 65 years old[1,3-6]. It causes significant social impact, is prone to complications, such as infection and hemorrhage, limits quality of life and causes psychological changes.

The severity of LL CVD can be determined based on an international classification that considers clinical manifestation, etiological factors, anatomical distribution of the disease and pathophysiological findings (CEAP). By means of a score, the lesions can be divided into seven classes (0 to 6), the most severe clinical manifestation being the open ulcer (CEAP 6)[7].

Currently, numerous materials are used as dressings for the treatment of chronic venous ulcers (CVU), most of them expensive and, therefore, not available in the Brazilian Unified Health System (SUS)[8,9]. The bacterial cellulose (BC) membrane, a biopolymer made from sugarcane molasses, has been developed at the Experimental Station of Sugar Cane in Carpina (EECC), Federal University of Pernambuco, Brazil (UFRPE)[10]. Several studies, Including experimental analyzes and clinical trials have shown that BC is non-toxic, biocompatible and effective for tissue remodeling[11-14].

The aim of this study was to evaluate the efficacy of BC membrane dressing in the treatment of chronic varicose ulcers of the lower limbs.

METHODS

It is a prospective, randomized, controlled intervention study in which we evaluated 25 patients with CVD ulcers (CEAP 6)[7] located in the lower limbs. These patients were treated at the Angiology and Vascular Surgery Service of the Clinics Hospital of the Federal

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University of Pernambuco (HC/UFPE) and at the Salgado Polyclinic, of the County Health Department in Caruaru, Pernambuco (PS / Caruaru / PE).

We randomly divided the participants in two groups: an experimental group that used BC membrane dressings (14 patients) and a control group that received conventional treatment with triglyceride oil (11 patients), a reference for the treatment of varicose ulcers in HC/UFPE and PS/Caruaru/PE. We performed the random selection with the software Randomizer (Urbaniak, G. C., & Plous, S. 2013, Version 4.0).

The sample was calculated based on the expected frequency of active or cured ulcers (3.6%) in the population with CVD[5], considering the acceptable margin of error (5%), the confidence level (95%) and the level of heterogeneity (50%). The calculation was based on a normal distribution.

Research participants were submitted to anamnesis, including questions about previous treatments and clinical examinations. The study included adults, regardless of age and gender, with diagnosis of varicose ulcers of the lower limbs, CEAP 6, infected or not. The presence of peripheral pulses was the decisive criterion for inclusion.

We excluded children and adolescents, as well as patients with the following conditions: neuropathy, arterial, lymphatic or malignant ulcers, and anemia.

The BC membrane

The BC membrane is an exopolysaride obtained from sugarcane molasses, composed of stable polymerized sugars. Its size ranged from 2x2 to 6x60 cm and thickness, from 0.01 to 0.02 mm. It was perforated and packaged separately in surgical grade-type envelopes[13]. BC dressings were previously sterilized with 25kGy gamma irradiation and were donated by POLISA® Biopolymers for Health, and incubated at the EECC/UFRPE.

Dressing technique

We performed the clinical evaluation of the lesion based on the MEASURE[15] methodology and applied the dressing according to the standard operating procedures (SOP) of the HC/UFPE and PS/Caruaru/PE. We carried out the following steps: debridement; cleaning with saline solution (0.9%); wound swab for evaluation of contaminating bacteria; application of BC membrane or oils with essential fatty acids (EFA) or containing medium chain triglycerides (MCT).

After applying the coverage, we placed a secondary dressing (gauze) and elastic cotton bandage on the wounds of all patients. We performed weekly follow-up visits and instructed the patients to remain for 48 hours without changing the dressing. They were also instructed to remove the secondary bandage (gauze and bandages) prior to initiating personal hygiene and, during the bath, moisten the BC dressing by washing the area normally without removing it. BC membrane change was done weekly under medical supervision.

Evaluated outcomes

We considered the healing process within 120 days as the primary outcome. We collected sociodemographic information, medical history, primary diagnosis and comorbidities, as well as drug use, at the first clinical visit. We based the lesions clinical evaluation on the MEASURE[15] acronym, evaluating the following parameters: M (measure, E (exudate), A (appearance), S (suffering), U (undermining), R (reevaluate) and E (edge).

We assessed the wound healing process by direct measurement of the lesion with a millimeter ruler and through the analysis of the images captured with a digital camera in all dressings exchanges during clinical consultation. We captured the lesion areas from the photographs with the software Image-Pro®, version 6.0 for Windows™.

We classified treatment efficacy according to: the degree of healing and size of the wound area; the characteristics of the tissue during the healing process; and the number of wounds completely healed.

We monitored confounding variables (presence of comorbidities and chronic and recurrent lesions) to limit variations in interpretation of the primary outcome. Comorbidities, represented by advanced diseases, can

interfere directly in the healing process. In addition, the presence of chronic and recurrent lesions may indicate resistance to other treatment protocols.

We performed a descriptive analysis for the sociodemographic data and statistical inference for the clinical data (MEASURE). We evaluated all data with the software GraphPad Prism®, version 3.0. We expressed the frequencies as percentages, using the Fisher exact test or the chi-square test. We presented continuous data as mean and standard deviation, studied by means of difference tests. We chosen the nominal level of 0.05 to reject the null hypothesis.

The study followed the ethical recommendations of the National Health Council, the Helsinki Declaration and the Nuremberg Code for studies with human beings and was approved by the Institutional Ethics in Research Committee (№ 1.117.265, CEP/CCS/UFPE). We formally informed participants about the study and invited them to attend. All patients enrolled in the study signed an informed consent form (ICF).

RESULTS

Male participants constituted 54.5% of the control group and 50.0% of the experimental group, the majority with low level of schooling and retirees. The mean age of participants was 60 ± 17 years in the control group, compared with 61 ± 14 years in the experimental one. On the degree of functional independence, that is, the ability to walk without help, in the control group this corresponded to 72.7%, and in the experimental group, to 78.6%.

Regarding previous disease history, 18.2% had diabetes mellitus (DM), 18.2% had systemic arterial hypertension (SAH) and 9.1% had malignant neoplasms. In the BC group there were 35.7% with SAH, 28.6% with DM and 7.14% with malignant neoplasia. The mean body mass index (BMI) was 29.0 ± 8.0 kg/m^2 in the control group and 32.0 ± 8.0kg/m^2 in the experimental group.

The swab culture was positive in 90.1% of the cases in the control group and in 100% in the experimental group (Table 1). The mean hemoglobin count was 13.0g/100ml in both groups.

Table 1. *Bacteria found in secretion cultures (initial assessment).*

Bacterial Profile (%)	Control	BC
Pseudomonasaeruginosa	30	42.9
Providencia rettgeri	20	0.0
Acinetobacter	10	0.0
Proteus	10	7.1
Escherichia coli	10	7.1
Citrobacter	10	7.1
Providencia stuartii	10	0.0
Staphylococcusequorum	0	7.1
Gram negative bacilli	0	14.4
Staphylococcus aureus	0	7.1
Enterobacter	0	7.1

Most ulcers were located in the right lower limb, seven (63.6%) in the control group and eight (57.1%) in the BC group. The most frequently affected site was the medial malleolus, five (45.4%) in the control and seven (50.0%) in the BC one. The wound area, measured during the initial clinical evaluation, was 50.0 ± 59.0cm^2 in the control group and 54.0 ± 57.0cm^2 in the BC. After 30 days (first reevaluation), the area was 31.0 ± 26.0cm^2 in the control group and 55.0 ± 54.0cm^2 in the BC group. After 120 days (second reevaluation), the wound area in the control group was 36.0 ± 27.0cm^2 and 54.0 ± 49.0cm^2 in the BC. There was no statistically significant difference between groups (p=0.5748). There was also no significant difference between the groups (p=0.7120) when the wounds were grouped by the mean area size at any of the evaluation times (initial, 1st or 2nd reevaluations).

The number of clinically healed wounds was similar in both groups, three (27.27%) in the control group and two (14.28%) in the BC membrane one. The analysis of the healing process by the Image-Pro Plus software revealed a statistically significant difference between the groups in the initial evaluation (p=0.0096), as well as in the first (p=0.0096) and in the second

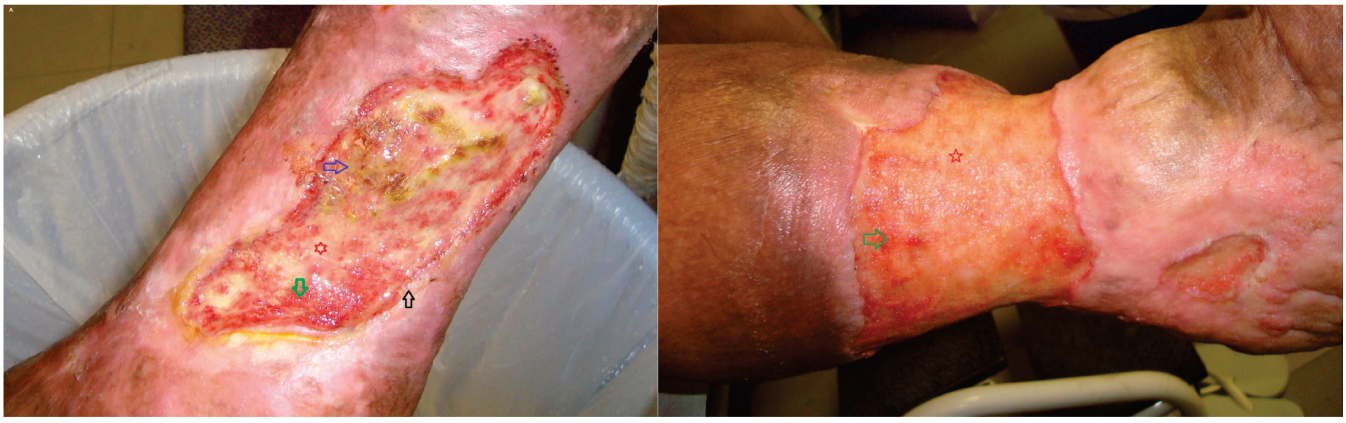

Figure 1. *Varicose ulcer, initial evaluation: A) Bacterial Cellulose Group; B) Control Group. Bright yellow fibrous tissue (red star), scarce granulation tissue (green arrow), macerated borders (black arrow) and signs of infection (redness and swelling) (purple arrow).*

(p=0, 0156) reevaluations. The amount (p=0.9928) and the quality (p=0.9921) of exudates was not significant between the groups, although in the BC group the absence of exudates was more evident.

Pain intensity, measured by the analogue scale for pain, was lower in the BC group compared with controls (p=0.0357) in the second reevaluation, with earlier interruption of analgesic use by these patients. There was no difference in the other follow-up times (initial and first reevaluation).

In the control group, 63.6% of the patients had loss of subcutaneous tissue (deeper) in the initial evaluation. After 120 days, loss of epidermis (superficial wound) was more frequent (62.5%). In the BC group at baseline, participants with subcutaneous loss were also more common (57.14%) and, after 120 days, loss of epidermis was present in 83.33% of the cases. There was a significant difference between groups (p<0.0001). After 120 days of evaluation, patients with granulation tissue were 25% in the control group and 41.7% in the BC group. Epithelial tissue was present in 37.5% of the control group and 25.0% in the BC group. We also observed wounds with both types of tissue (granulation + epithelial) in the second reassessment in the control group, in 12.5% and in the BC group, in 25%, without statistical significance (p=0.6946).

All baseline and reevaluation measurement parameters (30 or 120 days after initial assessment) can be seen in Table 2 and are shown in Figures 1 and 2.

DISCUSSION

The assessment of the sociodemographic profile showed that the majority of patients with varicose ulcers of the lower limbs were, on average, 60 years old. They had a low level of education, evidenced by a high illiteracy rate, observed both in the control and in the experimental group (36% and 50%, respectively). These results are similar to those described in the literature[16,17]. CVD of the lower limbs is insidious and progressive, and is usually aggravated by the difficulty presented by patients in taking proper care of their health, which determines the evolution to the disease's most severe forms[16,18,19]. Low educational level is also related to the lack of access to medical care, since most of these patients depend exclusively on the Unified Health System (SUS) and therefore are often evaluated only when they present ulcers in advanced stages (CEAP 6).

In this study, most patients were male, contrary to the literature[16,20]. Most were married, which may have contributed to adherence to treatment in both groups[16,19]. A high percentage of patients, more than 60% in both groups, was unemployed and this data has also been widely described in the literature[2,5,16,19].

On the functional level, most participants were classified as independent, but almost all presented some degree of difficulty in walking, similar to what was found in the literature[16,21,22]. Advanced CVD (CEAP 6) usually evolves with venous claudication (pain in walking), which,

Table 2. *Evaluation of ulcers by MEASURE, initial assessment, after 30 and 120 days.*

Parameters	Control			BC		
	Initial Assessment	1ª Reassessment	2ª Reassessment	Initial Assessment	1ª Reassessment	2ª Reassessment
Lesion area[1] (mean ± SD, cm²)	50 ± 59	31 ± 26	36 ± 27	54 ± 57	55 ± 54	54 ± 49
Classification of area (mean±SD)						
up to 30cm2	7.1 ± 5.7	12.8 ± 9.3	14.4 ± 8.7	8.6 ± 7.5	12.5 ± 7.5	12 ± 4.3
31 to 60cm2	43.7 ± 4.7	43.8 ± 7.4	39.8 ± 3.2	44.1 ± 15.5	36 ± 0	37.3 ± 1.8
61 to 90cm2	78 ± 0	71 ± 1.4	74 ± 5.7	96 ± 0	80.3 ± 0.4	77 ± 15.6
above 100cm2	150 ± 70.7	0	0	145.3 ± 30.8	134.3 ± 36.3	119.7 ± 34.9
Nº of clinically healed wounds	0	01	02	0	01	01
Healing process[2] (%, pixel)						
healing[3]	36.4	34.5	27.1	51.1 *	42.6 *	50.1 *
nothealed	63.6	56.4	61.7	48.9 *	40.9 *	38.6 *
completelyhealed	0	9.1	11.2	0	16.5 *	11.3
Exudate quantity (%)						
none	0	0	0	21.4	15.4	25.0
little	54.5	70	75	42.9	53.8	66.7
moderate	18.2	30	25	28.6	30.8	8.3
large	27.3	0	0	7.1	0	0
Exudate quality (%)						
none	0	0	0	0	15.4	25.0
serous	81.8	80.0	75.0	100	76.9	58.3
seropurulento	18.2	20.0	25.0	0	7.7	16.7
Pain intensity (analogue scale) (%)						
0	0	0	0	0	0	41.7 *
2	36.4	20.00	50.00	35.7	46.2	50.00 *
4	54.5	80.00	50.00	57.1	53.8	8.3 *
6	9.1	0	0	7.1	0	0
Appearance of wound (%)						
loss of epidermis	36.4	70.00	62.5	42.9	76.9	83.3 *
loss of subcutaneous tissue	63.6	30.00	37.5	57.1	23.1	16.7 *
Edge type						
epithelialized	9.1	60.0	50.0	14.3	15.4	16.7
bounded	45.5	10.0	37.5	57.1	30.8	33.3
irregular	45.5	30.0	12.5	28.6	53.8	50.0
Type of tissue						
integrity	0	0	0	0	7.7	0
Destroyed	18.2	0	12.5	14.3	15.4	0
Granulation	18.2	30.0	25.0	28.6	30.8	41.7
Epithelial	18.2	30.0	37.5	21.4	7.7	25.0
destroyed + granulation	27.3	20.0	0	0	0	0
Epithelial + granulation	9.1	10.0	12.5	7.1	7.7	25.0
Destroyed + epithelial	9.1	0	0	28.6	23.1	8.3
Destroyed + granulation + necrotic	0	10.0	12.5	0	7.7	0
Tissue color						
Red	36.4	40.0	75.0	50.0	46.2	50.0
Yellow	0	0	0	0	0	0
Mixed	63.6	60.0	25.0	50.0	53.8	50.0

The values are percentages (%) or average followed by the standard deviation (mean ± SD). Statistically significant if p<0.05. [1] Manual evaluation of wound area, conducted by clinical evaluation. [2]Evaluation of the healing process by Image-Pro Plus. [3]Evaluation on the amount of granulation tissue present in injury.*

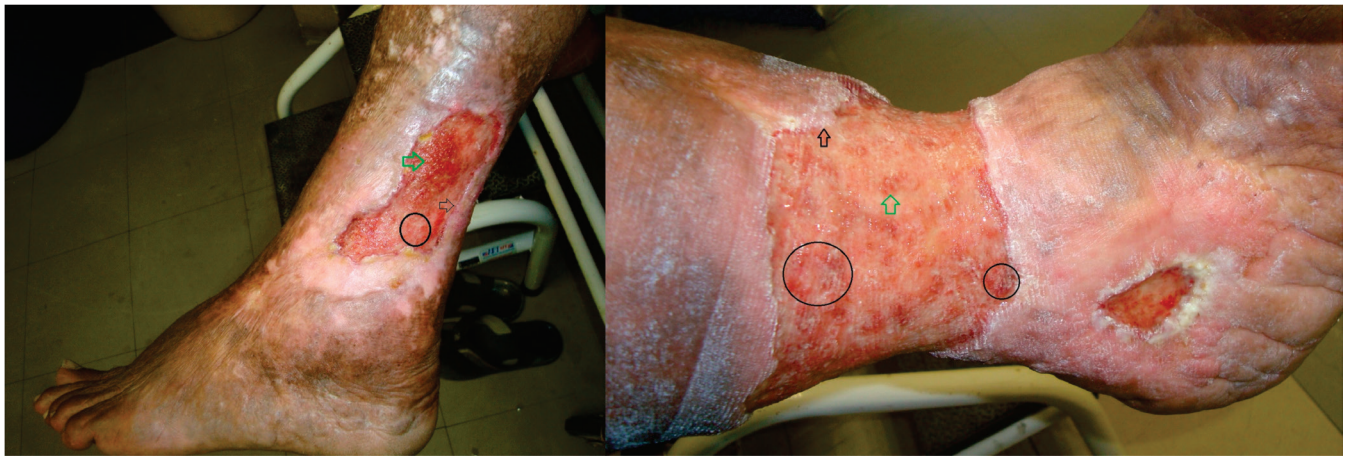

Figure 2. *Varicose ulcer after 120 days: A) Bacterial Cellulose Group; B) Control Group. Granulation tissue more present in A than in B (green arrow), epithelial tissue lighter than surrounding tissue (that is, pink color) (black circle) and epitelilized borders (black arrow).*

although not preventing ambulation, makes it difficult and slow.

As for comorbidities, the main ones were diabetes mellitus and arterial hypertension, common in the predominant age group of the studied patients[20]. Although these diseases are not the cause of CVD, when present, they can aggravate the patient's condition and interfere with the ulcer healing process. Diseases that may interfere with wound healing have also been observed, such as rheumatoid arthritis and uterine cancer, in which therapy requires the use of steroidal anti-inflammatory agents and antineoplastic drugs[23,24].

Another factor that interferes with the healing process is obesity. In the control group, most participants had pre-obesity, whereas in the BC group, most were classified as grade-1 BMI[25]. Several studies have shown that high BMI contributes to the prolongation of wound healing time[26]. In a study that evaluated 50 patients with lower limb venous ulcers, the authors identified obesity in 46% of the patients[27].

The majority of the participants, in both groups (control: 90%, BC: 100%), had positive cultures for the wounds' secretion swabs. The microorganism most frequently found in both groups was *Pseudomonas aeruginosa*. This finding is expected and confirms the high rate of lower limbs CVU contamination[27,28]. The longer the ulcer is active or the more frequent the relapses, the greater the chances of contamination, increasing the risk of infection, which in turn slows down the healing process. The knowledge of the CVU's bacteriological profile can guide early empirical antibiotic therapy in cases where there is a clinical diagnosis of wound infection[29].

In the control group, the wounds were treated with substances based on essential fatty acids (EFA) or containing medium chain triglycerides (MCT), and then covered with gauze and bandages (foot and leg). Although this type of dressing may not be the gold standard for CVU treatment, it has been routinely used in other clinics in the SUS due to its low cost. Its use and advantages have been described in the literature[5,8,18,22].

The use of BC for the treatment of LL CVD is promising, since it is non-toxic[11], biocompatible[12] and promotes tissue remodeling. In addition, the BC membrane is made from a renewable source, whose raw material is the sugar cane, of low cost[10], allowing its use in the SUS. There were no cases of cutaneous hypersensitivity reactions and BC-induced dermatitis. There have been reports of dermatitis and pain due to the use of MCT[30]. There was no evidence of MCT dermatitis in this study.

Follow-up of with the MEASURE[15] methodology occurred for 120 days. The healing process of this type of injury occurs slowly and, in many cases, complete wound healing is only obtained after a long period of time, sometimes more than 12 months[5,27], especially in cases of large ulcers[6], similar to those presented by the majority of the participants of this study.

The 120 day period was chosen as sufficient to evaluate the CVU response to BC dressings. At the end of

the observation period, there was a reduction in the wound area in both groups. This difference was not statistically significant because several patients had extensive lesions and of different sizes in the first evaluation, which may justify the high standard deviation in relation to the mean area, which, therefore, compromises the results of the evaluation. To correct this potential error, wounds were classified according to their mean area or percentage (30cm^2, 31-60 cm^2, 61-90 cm^2 and above 100cm^2) in each group, and then the comparison was made by group classification.

In the BC group, ulcers were more superficial at the end of the observation period in more than 80% of the patients (versus 60% in the control group). This may indicate that BC dressings acted as an inducer of tissue remodeling, stimulating the granulation process[14]. This is important because the ulcer healing depends not only on the epidermal proliferation at the margins of the lesion but also on the growth of the granulation tissue from the central area. Other studies have evaluated the application of BC membrane in animals and humans. The authors also observed an increase in granulation tissue, infection control and reduction of healing time[12,13,31-35].

All participants in the two groups reported decreased pain and discontinuation of analgesics. The participants who used BC dressing reported feeling more comfort and less pain than those in the control group. The BC membrane promoted self-care, including the possibility of bathing, without having to worry about the dressing. There was no restriction on wetting the dressing, though were recorded some reports of dressing loss. The BC membrane is a wet dressing that favors hygiene, adheres well to the wound bed and spontaneously detaches once the wound is healed[13]. BC studies demonstrate that this is an innovative, effective, safe and low cost material[13,31].

This study is pioneer in the use of the BC membrane in the treatment of wounds resulting from peripheral vascular diseases in humans. It establishes the scientific basis for further research in the field of vascular surgery, including the use of BC for the treatment of other types of wounds caused by vascular diseases, such as ulcers, or even as dressings for other skin wounds, such as neuropathic ulcers and those caused by burns.

In addition, various structural modifications can be made to the BC membrane to optimize its properties as a dressing, increasing its water absorption capacity and antimicrobial activity or associating it with a controlled release system of antibiotics or other active principles.

Our study allowed us to observe that the Bacterial Cellulose membrane has the ideal properties as a dressing, for maintaining the humidity in the bed of the wound, absorbing excess exudates, limiting infectious processes and protecting the lesion against mechanical trauma. It is an effective alternative to the dressings used for the treatment of chronic varicose ulcers of the lower limbs.

R E S U M O

Objetivo: avaliar a eficácia de curativos com membrana de Celulose Bacteriana (CB) no tratamento de úlceras venosas de membros inferiores. **Métodos:** estudo prospectivo, randomizado e controlado de 25 pacientes com úlceras decorrentes de doença venosa crônica nos membros inferiores provenientes do Serviço de Angiologia e Cirurgia Vascular do Hospital de Clínicas da Universidade Federal de Pernambuco e da Policlínica do Salgado da Secretaria Municipal de Saúde, Caruaru, Pernambuco. Os pacientes foram distribuídos aleatoriamente em dois grupos: grupo controle, que recebeu curativos com óleo de triglicerídeos (11 pacientes) e grupo experimental, tratado com membrana de CB (14 pacientes). Os pacientes foram acompanhados por um período de 120 dias. **Resultados:** houve uma redução na área de ferida em ambos os grupos. Não houve infecção ou reações ao produto em nenhum dos grupos. Pacientes do grupo CB mostraram diminuição da dor e interrupção mais precoce do uso de analgésicos. **Conclusão:** a membrana de CB pode ser usada como curativo para o tratamento de úlceras varicosas dos membros inferiores.

Descritores: Úlcera Varicosa. Celulose. Saccharum. Cicatrização.

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Efficacy of bacterial cellulose membrane for the treatment of lower limbs chronic varicose ulcers: a randomized and controlled trial

Eficácia da membrana de celulose bacteriana no tratamento de úlceras venosas de membros inferiores: estudo randomizado e controlado

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A B S T R A C T

Objective: *to evaluate the efficacy of Bacterial Cellulose (BC) membrane dressings in the treatment of lower limb venous ulcers.* **Methods:** *we carried out a prospective, randomized, controlled study of 25 patients with chronic venous ulcer disease in the lower limbs from the Angiology and Vascular Surgery Service of the Federal University of Pernambuco Hospital and from the Salgado Polyclinic of the County Health Department, Caruaru, Pernambuco. We randomly assigned patients to two groups: control group, receiving dressings with triglyceride oil (11 patients) and experimental group, treated with BC membrane (14 patients). We followed the patients for a period of 120 days.* **Results:** *There was a reduction in the wound area in both groups. There were no infections or reactions to the product in any of the groups. Patients in the BC group showed decreased pain and earlier discontinuation of analgesic use.* **Conclusion:** *BC membrane can be used as a dressing for the treatment of varicose ulcers of the lower limbs.*

Keywords: *Varicose Ulcer. Cellulose. Saccharum. Wound Healing.*

INTRODUCTION

Chronic venous disease (CVD) of the lower limbs (LL) is common and occurs due to abnormal venous system function caused by valvular insufficiency, which may be associated with obstruction of blood flow[1,2]. Its incidence is higher in women and only 30% of men are affected, which represents 3% to 5% of the population over 65 years old[1,3-6]. It causes significant social impact, is prone to complications, such as infection and hemorrhage, limits quality of life and causes psychological changes.

The severity of LL CVD can be determined based on an international classification that considers clinical manifestation, etiological factors, anatomical distribution of the disease and pathophysiological findings (CEAP). By means of a score, the lesions can be divided into seven classes (0 to 6), the most severe clinical manifestation being the open ulcer (CEAP 6)[7].

Currently, numerous materials are used as dressings for the treatment of chronic venous ulcers (CVU), most of them expensive and, therefore, not available in the Brazilian Unified Health System (SUS)[8,9]. The bacterial cellulose (BC) membrane, a biopolymer made from sugarcane molasses, has been developed at the Experimental Station of Sugar Cane in Carpina (EECC), Federal University of Pernambuco, Brazil (UFRPE)[10]. Several studies, Including experimental analyzes and clinical trials have shown that BC is non-toxic, biocompatible and effective for tissue remodeling[11-14].

The aim of this study was to evaluate the efficacy of BC membrane dressing in the treatment of chronic varicose ulcers of the lower limbs.

METHODS

It is a prospective, randomized, controlled intervention study in which we evaluated 25 patients with CVD ulcers (CEAP 6)[7] located in the lower limbs. These patients were treated at the Angiology and Vascular Surgery Service of the Clinics Hospital of the Federal

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University of Pernambuco (HC/UFPE) and at the Salgado Polyclinic, of the County Health Department in Caruaru, Pernambuco (PS / Caruaru / PE).

We randomly divided the participants in two groups: an experimental group that used BC membrane dressings (14 patients) and a control group that received conventional treatment with triglyceride oil (11 patients), a reference for the treatment of varicose ulcers in HC/UFPE and PS/Caruaru/PE. We performed the random selection with the software Randomizer (Urbaniak, G. C., & Plous, S. 2013, Version 4.0).

The sample was calculated based on the expected frequency of active or cured ulcers (3.6%) in the population with CVD[5], considering the acceptable margin of error (5%), the confidence level (95%) and the level of heterogeneity (50%). The calculation was based on a normal distribution.

Research participants were submitted to anamnesis, including questions about previous treatments and clinical examinations. The study included adults, regardless of age and gender, with diagnosis of varicose ulcers of the lower limbs, CEAP 6, infected or not. The presence of peripheral pulses was the decisive criterion for inclusion.

We excluded children and adolescents, as well as patients with the following conditions: neuropathy, arterial, lymphatic or malignant ulcers, and anemia.

The BC membrane

The BC membrane is an exopolysaride obtained from sugarcane molasses, composed of stable polymerized sugars. Its size ranged from 2x2 to 6x60 cm and thickness, from 0.01 to 0.02 mm. It was perforated and packaged separately in surgical grade-type envelopes[13]. BC dressings were previously sterilized with 25kGy gamma irradiation and were donated by POLISA® Biopolymers for Health, and incubated at the EECC/UFRPE.

Dressing technique

We performed the clinical evaluation of the lesion based on the MEASURE[15] methodology and applied the dressing according to the standard operating procedures (SOP) of the HC/UFPE and PS/Caruaru/PE. We carried out the following steps: debridement; cleaning with saline solution (0.9%); wound swab for evaluation of contaminating bacteria; application of BC membrane or oils with essential fatty acids (EFA) or containing medium chain triglycerides (MCT).

After applying the coverage, we placed a secondary dressing (gauze) and elastic cotton bandage on the wounds of all patients. We performed weekly follow-up visits and instructed the patients to remain for 48 hours without changing the dressing. They were also instructed to remove the secondary bandage (gauze and bandages) prior to initiating personal hygiene and, during the bath, moisten the BC dressing by washing the area normally without removing it. BC membrane change was done weekly under medical supervision.

Evaluated outcomes

We considered the healing process within 120 days as the primary outcome. We collected sociodemographic information, medical history, primary diagnosis and comorbidities, as well as drug use, at the first clinical visit. We based the lesions clinical evaluation on the MEASURE[15] acronym, evaluating the following parameters: M (measure, E (exudate), A (appearance), S (suffering), U (undermining), R (reevaluate) and E (edge).

We assessed the wound healing process by direct measurement of the lesion with a millimeter ruler and through the analysis of the images captured with a digital camera in all dressings exchanges during clinical consultation. We captured the lesion areas from the photographs with the software Image-Pro®, version 6.0 for Windows™.

We classified treatment efficacy according to: the degree of healing and size of the wound area; the characteristics of the tissue during the healing process; and the number of wounds completely healed.

We monitored confounding variables (presence of comorbidities and chronic and recurrent lesions) to limit variations in interpretation of the primary outcome. Comorbidities, represented by advanced diseases, can

interfere directly in the healing process. In addition, the presence of chronic and recurrent lesions may indicate resistance to other treatment protocols.

We performed a descriptive analysis for the sociodemographic data and statistical inference for the clinical data (MEASURE). We evaluated all data with the software GraphPad Prism®, version 3.0. We expressed the frequencies as percentages, using the Fisher exact test or the chi-square test. We presented continuous data as mean and standard deviation, studied by means of difference tests. We chosen the nominal level of 0.05 to reject the null hypothesis.

The study followed the ethical recommendations of the National Health Council, the Helsinki Declaration and the Nuremberg Code for studies with human beings and was approved by the Institutional Ethics in Research Committee (№ 1.117.265, CEP/CCS/UFPE). We formally informed participants about the study and invited them to attend. All patients enrolled in the study signed an informed consent form (ICF).

RESULTS

Male participants constituted 54.5% of the control group and 50.0% of the experimental group, the majority with low level of schooling and retirees. The mean age of participants was 60 ± 17 years in the control group, compared with 61 ± 14 years in the experimental one. On the degree of functional independence, that is, the ability to walk without help, in the control group this corresponded to 72.7%, and in the experimental group, to 78.6%.

Regarding previous disease history, 18.2% had diabetes mellitus (DM), 18.2% had systemic arterial hypertension (SAH) and 9.1% had malignant neoplasms. In the BC group there were 35.7% with SAH, 28.6% with DM and 7.14% with malignant neoplasia. The mean body mass index (BMI) was 29.0 ± 8.0 kg/m^2 in the control group and 32.0 ± 8.0kg/m^2 in the experimental group.

The swab culture was positive in 90.1% of the cases in the control group and in 100% in the experimental group (Table 1). The mean hemoglobin count was 13.0g/100ml in both groups.

Table 1. *Bacteria found in secretion cultures (initial assessment).*

Bacterial Profile (%)	Control	BC
Pseudomonasaeruginosa	30	42.9
Providencia rettgeri	20	0.0
Acinetobacter	10	0.0
Proteus	10	7.1
Escherichia coli	10	7.1
Citrobacter	10	7.1
Providencia stuartii	10	0.0
Staphylococcusequorum	0	7.1
Gram negative bacilli	0	14.4
Staphylococcus aureus	0	7.1
Enterobacter	0	7.1

Most ulcers were located in the right lower limb, seven (63.6%) in the control group and eight (57.1%) in the BC group. The most frequently affected site was the medial malleolus, five (45.4%) in the control and seven (50.0%) in the BC one. The wound area, measured during the initial clinical evaluation, was 50.0 ± 59.0cm^2 in the control group and 54.0 ± 57.0cm^2 in the BC. After 30 days (first reevaluation), the area was 31.0 ± 26.0cm^2 in the control group and 55.0 ± 54.0cm^2 in the BC group. After 120 days (second reevaluation), the wound area in the control group was 36.0 ± 27.0cm^2 and 54.0 ± 49.0cm^2 in the BC. There was no statistically significant difference between groups (p=0.5748). There was also no significant difference between the groups (p=0.7120) when the wounds were grouped by the mean area size at any of the evaluation times (initial, 1st or 2nd reevaluations).

The number of clinically healed wounds was similar in both groups, three (27.27%) in the control group and two (14.28%) in the BC membrane one. The analysis of the healing process by the Image-Pro Plus software revealed a statistically significant difference between the groups in the initial evaluation (p=0.0096), as well as in the first (p=0.0096) and in the second

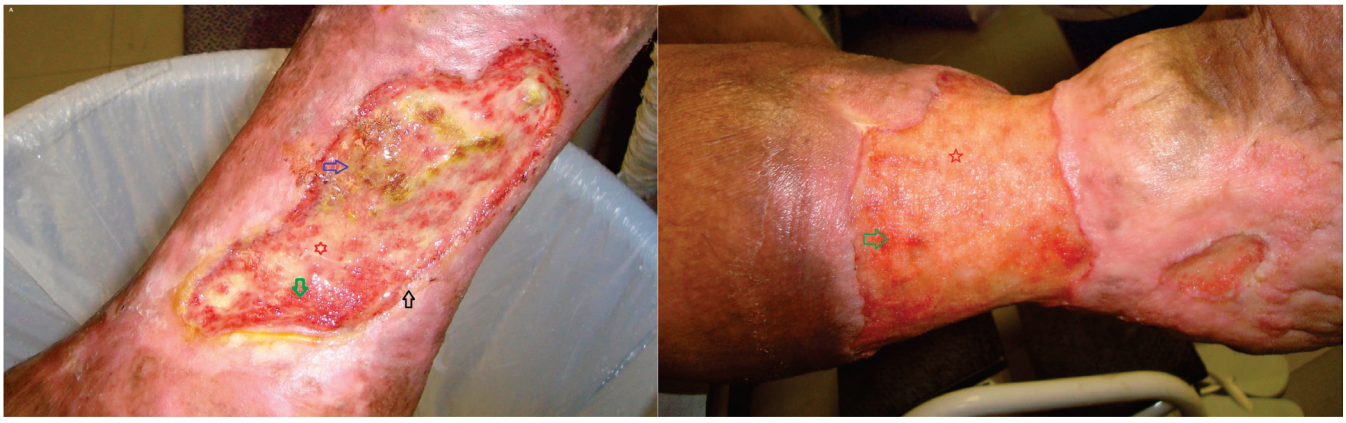

Figure 1. *Varicose ulcer, initial evaluation: A) Bacterial Cellulose Group; B) Control Group. Bright yellow fibrous tissue (red star), scarce granulation tissue (green arrow), macerated borders (black arrow) and signs of infection (redness and swelling) (purple arrow).*

(p=0, 0156) reevaluations. The amount (p=0.9928) and the quality (p=0.9921) of exudates was not significant between the groups, although in the BC group the absence of exudates was more evident.

Pain intensity, measured by the analogue scale for pain, was lower in the BC group compared with controls (p=0.0357) in the second reevaluation, with earlier interruption of analgesic use by these patients. There was no difference in the other follow-up times (initial and first reevaluation).

In the control group, 63.6% of the patients had loss of subcutaneous tissue (deeper) in the initial evaluation. After 120 days, loss of epidermis (superficial wound) was more frequent (62.5%). In the BC group at baseline, participants with subcutaneous loss were also more common (57.14%) and, after 120 days, loss of epidermis was present in 83.33% of the cases. There was a significant difference between groups (p<0.0001). After 120 days of evaluation, patients with granulation tissue were 25% in the control group and 41.7% in the BC group. Epithelial tissue was present in 37.5% of the control group and 25.0% in the BC group. We also observed wounds with both types of tissue (granulation + epithelial) in the second reassessment in the control group, in 12.5% and in the BC group, in 25%, without statistical significance (p=0.6946).

All baseline and reevaluation measurement parameters (30 or 120 days after initial assessment) can be seen in Table 2 and are shown in Figures 1 and 2.

DISCUSSION

The assessment of the sociodemographic profile showed that the majority of patients with varicose ulcers of the lower limbs were, on average, 60 years old. They had a low level of education, evidenced by a high illiteracy rate, observed both in the control and in the experimental group (36% and 50%, respectively). These results are similar to those described in the literature[16,17]. CVD of the lower limbs is insidious and progressive, and is usually aggravated by the difficulty presented by patients in taking proper care of their health, which determines the evolution to the disease's most severe forms[16,18,19]. Low educational level is also related to the lack of access to medical care, since most of these patients depend exclusively on the Unified Health System (SUS) and therefore are often evaluated only when they present ulcers in advanced stages (CEAP 6).

In this study, most patients were male, contrary to the literature[16,20]. Most were married, which may have contributed to adherence to treatment in both groups[16,19]. A high percentage of patients, more than 60% in both groups, was unemployed and this data has also been widely described in the literature[2,5,16,19].

On the functional level, most participants were classified as independent, but almost all presented some degree of difficulty in walking, similar to what was found in the literature[16,21,22]. Advanced CVD (CEAP 6) usually evolves with venous claudication (pain in walking), which,

Table 2. *Evaluation of ulcers by MEASURE, initial assessment, after 30 and 120 days.*

Parameters	Control			BC		
	Initial Assessment	1ª Reassessment	2ª Reassessment	Initial Assessment	1ª Reassessment	2ª Reassessment
Lesion area[1] (mean ± SD, cm²)	50 ± 59	31 ± 26	36 ± 27	54 ± 57	55 ± 54	54 ± 49
Classification of area (mean±SD)						
up to 30cm2	7.1 ± 5.7	12.8 ± 9.3	14.4 ± 8.7	8.6 ± 7.5	12.5 ± 7.5	12 ± 4.3
31 to 60cm2	43.7 ± 4.7	43.8 ± 7.4	39.8 ± 3.2	44.1 ± 15.5	36 ± 0	37.3 ± 1.8
61 to 90cm2	78 ± 0	71 ± 1.4	74 ± 5.7	96 ± 0	80.3 ± 0.4	77 ± 15.6
above 100cm2	150 ± 70.7	0	0	145.3 ± 30.8	134.3 ± 36.3	119.7 ± 34.9
Nº of clinically healed wounds	0	01	02	0	01	01
Healing process[2] (%, pixel)						
healing[3]	36.4	34.5	27.1	51.1 *	42.6 *	50.1 *
nothealed	63.6	56.4	61.7	48.9 *	40.9 *	38.6 *
completelyhealed	0	9.1	11.2	0	16.5 *	11.3
Exudate quantity (%)						
none	0	0	0	21.4	15.4	25.0
little	54.5	70	75	42.9	53.8	66.7
moderate	18.2	30	25	28.6	30.8	8.3
large	27.3	0	0	7.1	0	0
Exudate quality (%)						
none	0	0	0	0	15.4	25.0
serous	81.8	80.0	75.0	100	76.9	58.3
seropurulento	18.2	20.0	25.0	0	7.7	16.7
Pain intensity (analogue scale) (%)						
0	0	0	0	0	0	41.7 *
2	36.4	20.00	50.00	35.7	46.2	50.00 *
4	54.5	80.00	50.00	57.1	53.8	8.3 *
6	9.1	0	0	7.1	0	0
Appearance of wound (%)						
loss of epidermis	36.4	70.00	62.5	42.9	76.9	83.3 *
loss of subcutaneous tissue	63.6	30.00	37.5	57.1	23.1	16.7 *
Edge type						
epithelialized	9.1	60.0	50.0	14.3	15.4	16.7
bounded	45.5	10.0	37.5	57.1	30.8	33.3
irregular	45.5	30.0	12.5	28.6	53.8	50.0
Type of tissue						
integrity	0	0	0	0	7.7	0
Destroyed	18.2	0	12.5	14.3	15.4	0
Granulation	18.2	30.0	25.0	28.6	30.8	41.7
Epithelial	18.2	30.0	37.5	21.4	7.7	25.0
destroyed + granulation	27.3	20.0	0	0	0	0
Epithelial + granulation	9.1	10.0	12.5	7.1	7.7	25.0
Destroyed + epithelial	9.1	0	0	28.6	23.1	8.3
Destroyed + granulation + necrotic	0	10.0	12.5	0	7.7	0
Tissue color						
Red	36.4	40.0	75.0	50.0	46.2	50.0
Yellow	0	0	0	0	0	0
Mixed	63.6	60.0	25.0	50.0	53.8	50.0

The values are percentages (%) or average followed by the standard deviation (mean ± SD). Statistically significant if p<0.05. [1] Manual evaluation of wound area, conducted by clinical evaluation. [2]Evaluation of the healing process by Image-Pro Plus. [3]Evaluation on the amount of granulation tissue present in injury.*

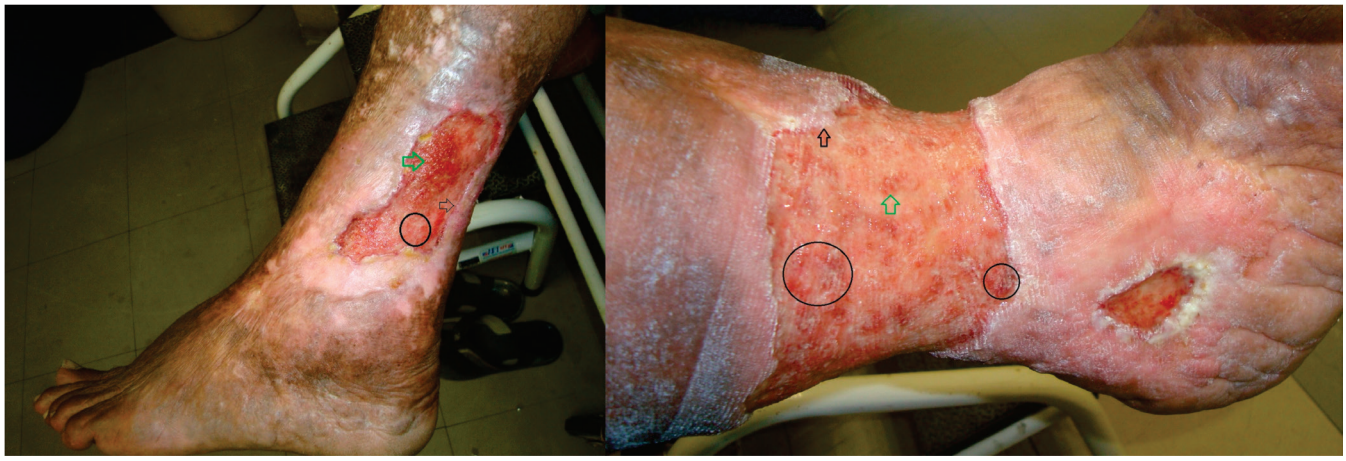

Figure 2. *Varicose ulcer after 120 days: A) Bacterial Cellulose Group; B) Control Group. Granulation tissue more present in A than in B (green arrow), epithelial tissue lighter than surrounding tissue (that is, pink color) (black circle) and epitelilized borders (black arrow).*

although not preventing ambulation, makes it difficult and slow.

As for comorbidities, the main ones were diabetes mellitus and arterial hypertension, common in the predominant age group of the studied patients[20]. Although these diseases are not the cause of CVD, when present, they can aggravate the patient's condition and interfere with the ulcer healing process. Diseases that may interfere with wound healing have also been observed, such as rheumatoid arthritis and uterine cancer, in which therapy requires the use of steroidal anti-inflammatory agents and antineoplastic drugs[23,24].

Another factor that interferes with the healing process is obesity. In the control group, most participants had pre-obesity, whereas in the BC group, most were classified as grade-1 BMI[25]. Several studies have shown that high BMI contributes to the prolongation of wound healing time[26]. In a study that evaluated 50 patients with lower limb venous ulcers, the authors identified obesity in 46% of the patients[27].

The majority of the participants, in both groups (control: 90%, BC: 100%), had positive cultures for the wounds' secretion swabs. The microorganism most frequently found in both groups was *Pseudomonas aeruginosa*. This finding is expected and confirms the high rate of lower limbs CVU contamination[27,28]. The longer the ulcer is active or the more frequent the relapses, the greater the chances of contamination, increasing the risk of infection, which in turn slows down the healing process. The knowledge of the CVU's bacteriological profile can guide early empirical antibiotic therapy in cases where there is a clinical diagnosis of wound infection[29].

In the control group, the wounds were treated with substances based on essential fatty acids (EFA) or containing medium chain triglycerides (MCT), and then covered with gauze and bandages (foot and leg). Although this type of dressing may not be the gold standard for CVU treatment, it has been routinely used in other clinics in the SUS due to its low cost. Its use and advantages have been described in the literature[5,8,18,22].

The use of BC for the treatment of LL CVD is promising, since it is non-toxic[11], biocompatible[12] and promotes tissue remodeling. In addition, the BC membrane is made from a renewable source, whose raw material is the sugar cane, of low cost[10], allowing its use in the SUS. There were no cases of cutaneous hypersensitivity reactions and BC-induced dermatitis. There have been reports of dermatitis and pain due to the use of MCT[30]. There was no evidence of MCT dermatitis in this study.

Follow-up of with the MEASURE[15] methodology occurred for 120 days. The healing process of this type of injury occurs slowly and, in many cases, complete wound healing is only obtained after a long period of time, sometimes more than 12 months[5,27], especially in cases of large ulcers[6], similar to those presented by the majority of the participants of this study.

The 120 day period was chosen as sufficient to evaluate the CVU response to BC dressings. At the end of

the observation period, there was a reduction in the wound area in both groups. This difference was not statistically significant because several patients had extensive lesions and of different sizes in the first evaluation, which may justify the high standard deviation in relation to the mean area, which, therefore, compromises the results of the evaluation. To correct this potential error, wounds were classified according to their mean area or percentage (30cm^2, 31-60 cm^2, 61-90 cm^2 and above 100cm^2) in each group, and then the comparison was made by group classification.

In the BC group, ulcers were more superficial at the end of the observation period in more than 80% of the patients (versus 60% in the control group). This may indicate that BC dressings acted as an inducer of tissue remodeling, stimulating the granulation process[14]. This is important because the ulcer healing depends not only on the epidermal proliferation at the margins of the lesion but also on the growth of the granulation tissue from the central area. Other studies have evaluated the application of BC membrane in animals and humans. The authors also observed an increase in granulation tissue, infection control and reduction of healing time[12,13,31-35].

All participants in the two groups reported decreased pain and discontinuation of analgesics. The participants who used BC dressing reported feeling more comfort and less pain than those in the control group. The BC membrane promoted self-care, including the possibility of bathing, without having to worry about the dressing. There was no restriction on wetting the dressing, though were recorded some reports of dressing loss. The BC membrane is a wet dressing that favors hygiene, adheres well to the wound bed and spontaneously detaches once the wound is healed[13]. BC studies demonstrate that this is an innovative, effective, safe and low cost material[13,31].

This study is pioneer in the use of the BC membrane in the treatment of wounds resulting from peripheral vascular diseases in humans. It establishes the scientific basis for further research in the field of vascular surgery, including the use of BC for the treatment of other types of wounds caused by vascular diseases, such as ulcers, or even as dressings for other skin wounds, such as neuropathic ulcers and those caused by burns.

In addition, various structural modifications can be made to the BC membrane to optimize its properties as a dressing, increasing its water absorption capacity and antimicrobial activity or associating it with a controlled release system of antibiotics or other active principles.

Our study allowed us to observe that the Bacterial Cellulose membrane has the ideal properties as a dressing, for maintaining the humidity in the bed of the wound, absorbing excess exudates, limiting infectious processes and protecting the lesion against mechanical trauma. It is an effective alternative to the dressings used for the treatment of chronic varicose ulcers of the lower limbs.

R E S U M O

Objetivo: avaliar a eficácia de curativos com membrana de Celulose Bacteriana (CB) no tratamento de úlceras venosas de membros inferiores. **Métodos:** estudo prospectivo, randomizado e controlado de 25 pacientes com úlceras decorrentes de doença venosa crônica nos membros inferiores provenientes do Serviço de Angiologia e Cirurgia Vascular do Hospital de Clínicas da Universidade Federal de Pernambuco e da Policlínica do Salgado da Secretaria Municipal de Saúde, Caruaru, Pernambuco. Os pacientes foram distribuídos aleatoriamente em dois grupos: grupo controle, que recebeu curativos com óleo de triglicerídeos (11 pacientes) e grupo experimental, tratado com membrana de CB (14 pacientes). Os pacientes foram acompanhados por um período de 120 dias. **Resultados:** houve uma redução na área de ferida em ambos os grupos. Não houve infecção ou reações ao produto em nenhum dos grupos. Pacientes do grupo CB mostraram diminuição da dor e interrupção mais precoce do uso de analgésicos. **Conclusão:** a membrana de CB pode ser usada como curativo para o tratamento de úlceras varicosas dos membros inferiores.

Descritores: Úlcera Varicosa. Celulose. Saccharum. Cicatrização.

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Negative pressure therapy for the treatment of complex wounds

Terapia por pressão negativa no tratamento de feridas complexas

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A B S T R A C T

The objective of this study is to evaluate the effectiveness of negative pressure therapy (NPT) in the treatment of complex wounds, with emphasis on its mechanisms of action and main therapeutic indications. We searched the Pubmed / Medline database for articles published from 1997 to 2016, and selected the most relevant ones. The mechanisms of action of NPT involveboth physical effects, such as increased perfusion, control of edema and exudate, reduction of wound dimensions and bacterial clearance, and biological ones, such as the stimulation of granulation tissue formation, microdeformations and reduction of Inflammatory response. The main indications of NPT are complex wounds, such as pressure ulcers, traumatic wounds, operative wound dehiscences, burns, necrotizing wounds, venous ulcers, diabetic wounds, skin grafts, open abdomen, prevention of complications in closed incisions and in the association with instillation of solutions in infected wounds.

Keywords: *Negative-Pressure Wound Therapy. Wounds and Injuries. Wound Closure Techniques. Pressure Ulcer. Surgical Wound Dehiscence.*

INTRODUCTION

Studied since antiquity, wounds still represent a challenge to health professionals. Of diverse etiology and clinical presentations, this pathological entity has always been prevalent in the different cultures, receiving varied treatments in light of the knowledge available in each period.

At present, wounds considered to be difficult to treat, the so-called complex wounds[1], have received increasing attention from physicians and nurses (directly involved in the care, treatment and use of new technologies), as well as from health managers (concerned with the impact that wound treatment generates on institutional costs). The increase in the prevalence of such wounds is mainly due to aging of the population and to trauma in large urban centers.

The onset of a complex wound raises morbidity and mortality rates, increases overall treatment costs (material and human resources), and leads to longer hospital stays. In this context, it is mandatory for the surgeon to know alternatives that can accelerate the wound's repair process, allowing the patient to be discharged earlier and to return to daily activities.

To this end, negative pressure therapy (NPT) or subatmospheric pressure therapy, introduced commercially after the studies of Argenta and Morykwas in 1997[2], is an important adjuvant method in the treatment of wounds - with the main proposal of accelerating the repair process and preparating the wound bed for its definitive coverage through the various methods of tissue reconstruction.

The aim of this study is to review the literature on NPT in the treatment of complex wounds, with emphasis on its mechanisms of action and main therapeutic indications.

METHODS

We reviewed the literature in the Pubmed/ Medline database, including original articles and systematic reviews, published between 1997 and 2016. The descriptors used were "negative pressure therapy", isolated or associated with "wound", "ulcer", "pressure sore", "trauma", "dehiscence", "burn", "venous ulcer", "diabetic wound", "open abdomen", "skin graft", "prevention" and "instillation". We selected the most relevant articles and grouped the evidence to summarize their recommendations.

NPT PRINCIPLES AND EQUIPMENT

NPT is a type of active wound treatment that promotes healing in a humid environment by means of controlled and locally applied subatmospheric pressure.

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The NPT is composed of an interface material (foam or gauze), through which subatmospheric pressure is applied and the exudate is removed. This material is in contact with the wound bed in order to cover its entire length, including tunnels and cavities. The interface material is covered by a transparent adhesive film, which wholly isolates the wound from the external medium. A suction tube is connected to that system and the exudate reservoir, which is adapted to a computerized device. This device may allow the programming of parameters to provide a subatmospheric pressure in the wound bed, has an audible alarm which indicates possible leakage of air from the dressing, and may indicate the need to exchange the reservoir.

Currently, in Brazil, there are several models and brands of commercial dressings and NPT-based devices. Such brands have differences between them, like the type of therapy available, the interface material, the reservoir, the computerized device (therapy programming, audible alarms, etc.), type of installation (hospital or home), among others.

Regarding the type of therapy, subatmospheric pressure can be administered continuously (without interruption), intermittently (with programmed interruption cycles interspersed with therapy), or associated with instillation of solutions (with scheduled instillation cycles interspersed with cycles of removal of the solution and cycles of therapy). Intermittent therapy aims to accelerate the formation of granulation tissue, and instillation therapy is indicated for the treatment of infected wounds[3,4].

The interface material may be composed of foam or gauze. There is evidence that both provide the NTP's benefits, with some particularities[3,5-8]. The vast majority of the foams are composed of polyurethane, with pores with diameters ranging from 400 to 600 microns (which facilitate the transmission of suction forces to the tissue and drainage of the exudate). The foams have a greater elasticity, which favors their fitting to the wound bed, and allows greater contraction of the wound, optimizing the approximation of its edges. However, the granulation tissue may grow into the pores of the foam, which may cause minor trauma and pain during withdrawal, especially if held for more than three days in the wound bed.

The gauze is composed of cotton fibers arranged in multiple layers. Granulation tissue generally does not grow into gauze fibers, deeming removal less painful. It can also be impregnated with antimicrobial solution. However, the porosity of the different tissue layers is not coincidental (which may hinder the transmission of suction forces to the tissue and exudate drainage). Because it has less elasticity, it leads to less contraction of the wound and the approximation of the edges is more limited.

Regarding the histological and morphological characteristics, there is evidence that foam and gauze healings are similar[3,6-8]. In clinical practice, some authors claim that foamed NPT is associated with faster tissue granulation formation and greater contraction of wound edges compared to NPT with gauze[6,7], but further clinical studies are required to confirm such characteristics.

The foams have different sizes and forms of presentation, some having particularities related to their main indication. The conventional foam is composed of polyurethane, but there are polyurethane foams impregnated with silver for use on infected wounds. There are also foams composed of polyvinyl alcohol that have the advantage of having less adherence to the bed, being indicated for use on skin grafts and in cavitations or tunnelled wounds, since their removal is facilitated. For use in the abdominal cavity, in contact with viscera, there are foams that have extensions with multipierced plastic protection associated with pre-cut foams. Instillation therapy of solutions for treatment and cleaning of infected wounds may be associated with NPT. In addition, other conformations of the foam may facilitate its use, such as those that already come pre-cut and those that allow the application of NPT in more difficult places of the body as in plantar wounds, since it allows the adaptation of the connector far from the lesion, allowing patients to walk.

INSTALLATION OF NPT

Regarding the type of NPT installation, there are devices that require patient hospitalization and

others that allow the application of NPT at home regimen. The recommendation of the manufacturers is that dressing changes should be made every 48 to 72 hours, since uses for longer periods result in saturation of the foam or the gauze, with a decrease in adequate exudate drainage capacity, reducing treatment efficacy. The exchange of the reservoir, in some brands, is independent of the change of dressing, allowing rationalization of resources. The end of treatment is determined by the finding of favorable local conditions, i.e., when the wound bed is adequately prepared for subsequent skin coverage (by tissue reconstruction methods such as grafts and flaps) or when there is complete healing and wound closure.

The outpatient installation can be performed in the office room itself, and is indicated for superficial and non-painful wounds. The dressing is coupled to a portable, battery-operated device that is responsible for maintaining subatmospheric pressure.

The hospital installation can be done in the patient's bed or in the operating room, with anesthesia, the latter indicated for deeper and more painful wounds, or when there is a need for association with other procedures, such as debridement of devitalized tissues.

NPT MECHANISMS OF ACTION

The application of NPT provides uniform subatmospheric pressure in the wound bed and its mechanisms of action involve both biological and physical effects.

Biological Effects

a) Change in cytoskeletal conformation

The application of NPT on a wound causes a deformation of the cellular cytoskeleton (microdeformations), responsible for triggering potent stimulation of cell proliferation and angiogenesis[5]. This is the principle associated with the mechanism of action of tissue expanders and bone elongation through osteogenic distraction. This stimulation to the cell proliferation associated with the tension on the cells was proven in vitro in a study realized by Huang *et al*., in 1998[9].

b) Stimulation of granulation tissue formation

After application of NPT, there is an increase in the number of capillaries in the wound bed, in addition to the deposition of connective tissue and extracellular matrix, which together form the granulation tissue. Chen *et al*. carried out an experimental study comparing the presence of new vessels in biopsies of wounds treated with NPT and with conservatively. In the determined periods (six and 24 hours, three and six days), the density of capillaries in the group submitted to NPT was significantly higher when compared to the control group ($p<0.01$)[10].

c) Reduction of local inflammatory response

It is believed that the use of NPT results in a control of the acute inflammatory response by the clearance of pro-inflammatory cytokines and proteolytic enzymes (membrane metalloproteinases) present in the wound exudate, which are responsible for the degradation of the extracellular matrix and apoptosis. An experimental study by Norbury *et al*., with a porcine model, evaluated the serum and wound bed dosage of inflammatory cytokines. The authors found lower serum gamma interferon levels (INF-gamma) 12 and 36 hours after injury in animals submitted to NPT than in the control animals ($p<0.05$). In the wound bed, levels of interleukin 8 (IL-8) were also lower after 12 hours in the experimental group ($p<0.05$). Other cytokines such as transforming growth factor beta (TGF-ß) and tumor necrosis factor alpha (TNF alpha) also showed reduction in the wound bed[11].

Physical Effects

a) Increased blood flow to the wound

The application of NPT increases the blood flow to the wound, consequently stimulating the formation of granulation tissue. Through Doppler ultrasound studies[2], Argenta *et al*. demonstrated that blood flow increases in the tissues adjacent to the wound with NPT, the highest flow velocity being observed with subatmospheric pressure of 125mmHg. On the other hand, some experimental studies[12,13] have shown that the application of excessive subatmospheric

pressure has an opposite effect, and may even reduce local blood flow.

b) Reduction of edema and control of exudate

The exudate present in the wound bed can macerate the edges of the wound, interfering with the healing process, besides being a medium conducive to the proliferation of microorganisms. Similarly, edema is detrimental because it impairs the perfusion of nutrients and oxygen from the capillaries to the wound bed. NPT removes variable amounts of wound exudate, reducing tissue edema and promoting the restoration of vascular and lymphatic flow, a factor that explains the increase in local blood perfusion and the improvement of the nutrients and oxygen supply[2].

c) Reduction of wound dimensions

The application of NPT approaches the edges of the wound by means of a centripetal force, leading to the diminution of its dimensions by tissue contraction[3,14]. In 2004, Moues *et al*. conducted a controlled, randomized clinical study and verified a significant reduction in wound size of 3.8% per day for patients using NPT and 1.7% per day for patients wearing gauze soaked with saline ($p<0.05$)[15].

d) Cleansing of bacterial load

The bacteria present in the wound compete for the nutrients and oxygen that would be destined to tissue repair, hampering the healing process[2]. The clearance of the wound's bacterial load, however, is a controversial subject in the literature. While some studies[2] demonstrated a reduction in the number of bacteria with the use of NPT, other[15,16] did not show significant alterations in the bacterial load of wounds treated by this method.

NPT INDICATIONS

In the literature, it is possible to find several indications for the application of NTP, with good results reported both in randomized, controlled clinical studies, prospective and retrospective cohorts, and in studies with less strength of evidence (clinical series and case reports). The main indications comprise: a) complex wounds: pressure ulcers, traumatic wounds, surgical wounds (dehiscences), burns, necrotizing wounds, diabetic wounds, venous ulcers, inflammatory wounds, radiation wounds, and others; b) skin grafts: to optimize graft integration to the bed; c) open abdomen; d) prevention of complications in closed incisions; e) instillation of solutions in contaminated or infected wounds.

NPT has become an important adjuvant method for the treatment of complex wounds[17]. In a retrospective study, Coltro *et al*. analyzed 1926 patients with complex wounds evaluated by the Plastic Surgery team of the Clinics Hospital, Faculty of Medicine, USP. Of these, 907 patients (47%) were submitted to NPT as part of their treatment[18].

NPT should applied on a clean wound, without devitalized tissue or after adequate debridement. It is also necessary to observe the contraindications to its use, reported later. Next, we present the main indications of NPT.

Pressure ulcers

Pressure ulcers (PU) are caused by the pressure maintained between a bone prominence and the patient's bed, leading to ischemia and necrosis of the involved tissues. They are common in patients with some mobility restriction, such as spinal cord injuries (paraplegic and quadriplegic) and patients under prolonged sedation. The most frequent sites of their development are the sacral, sciatic, trochanteric, calcaneal and occipital regions, among others (Figure 1).

The application of NPT in these wounds has the main objective of improving the local conditions for a later repairing surgery to obtain definitive cutaneous cover. This sequence is valid mainly in the cases of PU stages III and IV of the National Pressure Ulcer Advisory Panel (NPUAP), represented by deeper wounds, with muscular or bone exposure. Clinical reports such as that performed by Batra and Asseja[19], however, show that even more complex wounds, when acute, could be treated only with NPT.

In 2002, Ford et al conducted a randomized, controlled study with 41 patients with deep PU,

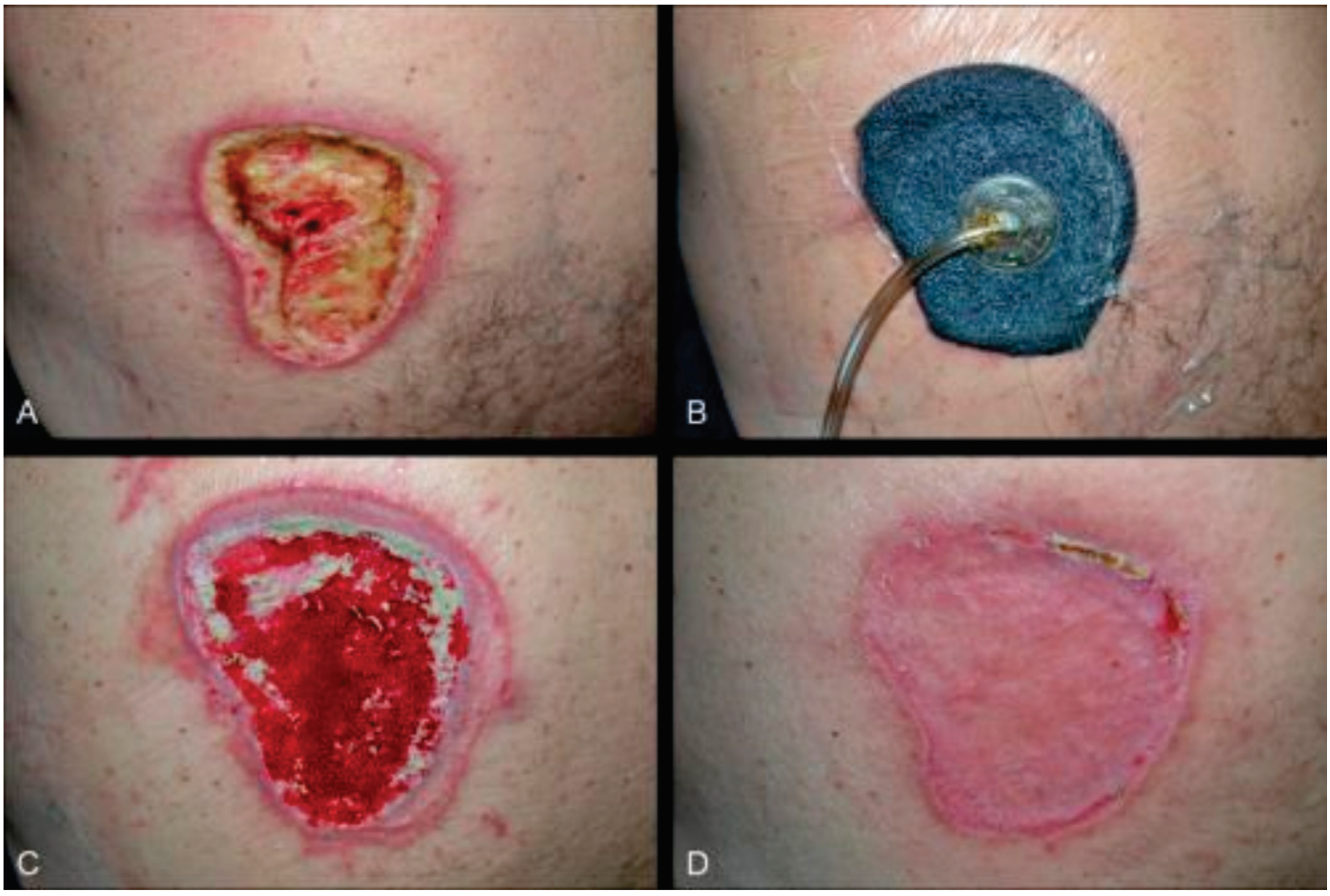

Figure 1. *Male patient, 58 years old, paraplegic. A) Pressure ulcer in the left lumbar region, with wound bed filled with devitalized tissues; B) Application of NPT after surgical debridement; C) Appearance after NPT, with improvement of granulation tissue in the wound bed, before skin grafting; D) Postoperative aspect, with cutaneous cover of the wound, after satisfactory integration of the skin graft.*

comparing NPT with topical healing promoter gels. The mean percentage reduction in ulcer volume was higher in the NPT group (51.8% vs. 42.1%, p=0.46). The mean number of capillaries per wound bed field was also higher in the NPT group (p=0.75). The authors stated that NPT promotes healing and neovascularization when compared to topical gel treatment[20].

Ashby *et al*., in 2012, conducted a randomized controlled trial in patients with PU grades III and IV, showing superior benefits of NTP in comparison with moist dressing[4].

Traumatic wounds

Traumatic wounds include a group of acute, generally extensive, wounds with loss of cutaneous lining, associated or not with fractures. They are represented by degloving wounds (Figure 2), exposed fractures, wounds associated with muscular crushing, and others, affecting predominantly patients of economically active age.

The stimulation to the formation of granulation tissue in these wounds may be responsible for the reduction in the complexity of the reconstruction option. For example, NPT can promote the coverage of exposed bones and tendons by granulation tissue, allowing wound closure by means of skin grafting, rendering unnecessary the use flaps, with and without concomitant use dermal matrices[21].

In 2012, Blum *et al*. evaluated the effect of NPT on the rate of infection in 220 patients with exposed tibial fractures, through a multicenter retrospective cohort study. The infection rate of the NTP group was lower (8.4% x 20.6%, p=0.01) compared with the group receiving conventional moist dressing[22]. In 2006, Yang *et al*. evaluated the efficacy of NPT in the Treatment of 34 patients with fasciotomy

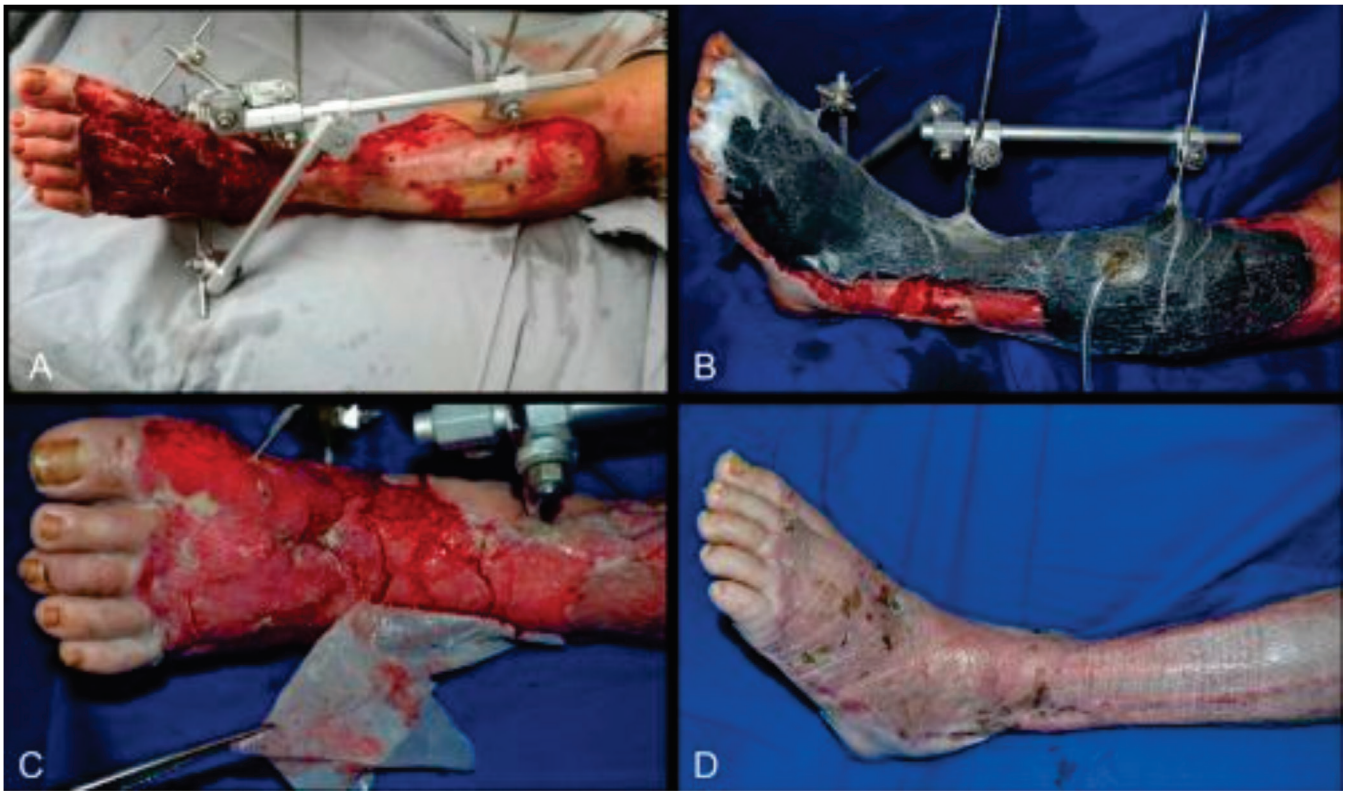

Figure 2. *A 30-year-old male patient, victim of an automobile accident. A) Degloving (detachment injury) of the left leg; B) Application of NPT, allowing growth of granulation tissue on initially exposed bones and tendons; C) Aspect after maturation of the dermal matrix applied on the wound bed, demonstrating the removal of the silicone film to receive the skin graft; D) Postoperative aspect, with cutaneous cover of the wound, after satisfactory integration of the skin graft.*

wounds after traumatic compartment syndrome. The mean time to final wound closure was 6.7 days for the NPT group and 16.1 days for the conventional moist dressing group ($p<0.05$)[23].

In 2013, Milcheski *et al*. studied 178 patients with traumatic lower limb wounds, most of them represented by degloving wounds. NPT significantly reduced the morbidity and healing time when compared with the previously used conventional dressings. According to the authors, NPT is useful in the treatment of acute traumatic wounds, acting as a bridge between emergency treatment and definitive cutaneous coverage[24].

Surgical wounds (dehiscences)

Dehiscences are the rupture or opening of a previously closed surgical incision that occur in 1% to 5% of surgeries and are associated with obesity, infection and tension in the suture line. In 2010, Petzina *et al*., retrospectively, analyzed 118 patients with mediastinitis and sternotomy dehiscence after cardiac surgery treated with NPT (n=69) or with conventional therapy (n=49). The group treated with NPT had a reduction in the mortality rate ($p=0.005$) and in the rate of sternal reinfection ($p=0.008$), in addition to a tendency of lower hospital stay ($p=0.08$), reinforcing the idea of NTP as a first-line treatment for sternal wound infection[25].

In 2016, Morisaki *et al*. evaluated 73 patients who developed deep sternal wound infection after cardiac surgery. The authors stated that preparation of the wound bed with NTP followed by flap reconstruction was associated with improved prognosis and reduced mortality due to infection associated with sternotomy dehiscence[26].

A precaution to be taken is the interposition of a fenestrated and non-adherent film between the surface of the sternal cleft wound and the foam, minimizing the possibility of injury to organs such as the heart or lungs.

Burns

Third degree burns, after adequate debridement, may benefit from NPT, which may be applied as an adjuvant in bed preparation for subsequent skin grafting, or as a method of optimizing the integration of skin grafts[27]. Patients with electrical trauma, which generally cause deep burns with extensive tissue destruction and progressive tissue damage, are also NPT candidates. The increase in blood perfusion secondary to NPT use is beneficial to burn injury. Kamolz *et al*. observed this in 2003, in a prospective study comparing the blood perfusion of burned hands that underwent conservative therapy and NPT. In the conservatively treated group, the authors observed reduced limb blood perfusion, which did not occur in the NPT-treated group[28].

Necrotizing wounds

Necrotizing wounds are characterized by aggressive infection of deep tissues, usually of acute onset and rapid evolution, as occurs in cases of necrotizing fasciitis (called Fournier's gangrene when beginning in the perineum). The diagnosis should be early and treatment should be instituted as soon as possible, since such wounds are associated with a high mortality rate. The pillars of its treatment are based on extensive debridement and systemic antibiotic therapy. In 2011, Assenza *et al*. reviewed the literature and evaluated six patients with Fournier's gangrene treated with NPT. The authors affirmed that NPT accelerated the preparation of the wound, which allowed an earlier reconstruction, reduced the days of hospitalization, the discomfort of the patients and the number of medications, collaborating to improve their quality of life[29].

Wounds associated with infection may benefit from specific dressings in which the polyurethane foam is impregnated with silver, which is released in a sustained fashion over the days of therapy and has bactericidal and bacteriostatic effects. In addition, such wounds may be treated with NPT associated with instillation of solutions, as discussed below.

Diabetic wounds

Wounds in diabetic patients are more common in the lower limbs, especially in the feet, and can be triggered by neuropathy, macroangiopathy and microangiopathy that are present in the pathophysiology of diabetes *mellitus*. In many cases, such wounds may evolve with deep tissue infection and gangrene, leading to amputation of the lower extremity. In 2005, Armstrong *et al*. carried out a multicenter, randomized, controlled clinical study (in 18 US hospitals), which included 162 diabetic patients after partial amputation of the foot, comparing NPT with conventional moist dressing. The authors verified that more patients healed in the NPT group in relation to the control group (56% x 39%, p=0.04). The wound healing rate (time until complete closure) was faster in the NTP group (p=0.005), as well as the rate of granulation tissue formation (p=0.002)[30].

In 2008, Blume *et al*. evaluated 342 diabetic patients with foot wounds in a randomized, multicenter, controlled clinical study comparing a group that used NPT with one that used moist dressing. The authors demonstrated a higher proportion of complete wound closure in patients who used NPT (43.2% x 28.9%, p=0.007) and lower a amputation rate in the same group (4.1% vs. 10.2%, p=0.035)[31].

In 2015, Sajid *et al*. conducted a randomized, controlled trial with 278 patients with diabetic foot wounds comparing NPT with conventional moist dressing. After two weeks of treatment, the reduction of wound size was significantly greater in the group using NPT (p<0.001)[32].

Venous ulcers

Venous ulcers are a complication of chronic venous hypertension of the lower limbs of patients with varicose veins. These wounds can be large, often circumferential, and have low closure rates with conventional compressive therapy. They may remain for years or decades, causing a significant impact on patients' quality of life and on treatment costs[33]. In 2006, Vuerstaek *et al*. evaluated 60 patients with lower limb venous ulcers, comparing wound treatment with NPT or moist dressings in a randomized, controlled clinical study. Patients in the NPT group healed faster (29 days x 45 days, p=0.0001), also reaching more quickly the time of wound bed preparation (7 days x 17 days, p=0.005)[34].

In 2012, Egemen *et al*. applied NPT in 20 patients with venous ulcers and found a rapid preparation of the bed, as well as an optimization of the subsequent integration of the skin graft[35]. Yang *et al*., in 2015, also compared the treatment of venous ulcers and demonstrated that NPT followed by partial skin grafting was more effective for the closure of these ulcers than conventional compressive therapy, with similar costs between the two treatments[33].

Skin grafts

NPT is indicated over skin grafts to improve their adherence to the bed, to guarantee their immobility and to reduce the formation of seroma or hematoma, to optimize the integration of the skin graft to the wound bed. In such cases, NPT must always be administered in continuous mode. Polyvinyl alcohol foam is especially recommended in these cases because it has less adherence to the bed, facilitating its removal at the end of therapy, without interference with the integrated graft.

In 2010, Blume *et al*. performed a retrospective review of 142 patients treated with partial thickness skin grafts in reconstructive surgeries of the foot and ankle. Comparing NPT with conventional dressing, patients who used NPT presented greater graft integration (97% x 84%, p=0.009) and less need for graft repetition due to integration failure (5% x 16%, p=0.006)[36].

A randomized, controlled trial conducted by Moisidis *et al*. in 2004 evaluated the effects of NPT in comparison with conventional dressing in 22 patients undergoing partial thickness skin grafts. The results showed that graft integration was significantly better with NPT compared ($p<0.05$)[37].

In 2002, Scherer *et al*. performed a retrospective study including 61 patients submitted to partial thickness skin grafting. The results demonstrated that skin grafts that needed to be repeated due to losses were 3% in the NPT group and 19% in the conventional dressing group (p=0.04)[38].

Open abdomen

The open abdomen and the temporary abdominal closure are valuable techniques in the surgeon's arsenal and are indicated in the strategy of damage control, management of abdominal sepsis and prevention and treatment of abdominal compartment syndrome. In recent years, there has been an increase in NPT application in the abdominal wall closure of patients maintained in peritonostomy. As the foam cannot be in direct contact with the viscera, an interposed protective film is necessary. There are specific dressings for the application of NPT in open abdomen, such as the V.A.C. system. In this, the foam has extensions to reach the parietal and pelvic recesses (for drainage of the exudate), coupled with double protection with multipierced non-adherent film (to allow it to be positioned over the viscera), in addition to pre-cut foams, which are positioned on the first (to perform the medial approximation of the aponeurosis). The advantages of the NPT use in the open abdomen are the maintenance of the integrity of the abdominal wall, the prevention of the abdomen dominance loss over its visceral content, and peritoneal fluid removal.

In 2013, a prospective, multicenter study by Cheatham *et al*. included 168 patients with open abdomen who were treated with specific NPT or NPT made with packs and using the available vacuum system in the patient's bed (Barker's vacuum). The authors demonstrated that the V.A.C. system was associated with a lower 30-day mortality rate (14% x 30%, p=0.01) and a higher rate of primary abdominal wall closure (69% x 51%, p=0.03) when compared with the Barker's vacuum[39].

Kirkpatrick *et al*., in 2015, conducted a randomized, controlled study in 45 patients with open abdomen, comparing the use of V.A.C. system with Barker's vacuum. After 90 days, the authors verified that mortality was significantly lower in the group that used V.A.C. (p=0.04), but the aponeurosis primary closure rate was similar in the two groups (p=0.17)[40].

Prevention of dehiscence and surgical wound infection

NPT can be used on closed surgical incisions to avoid dehiscence or infection of the operative wound. It is particularly indicated for patients at high

risk of dehiscence or infection, such as obese, diabetic, smokers, and those whose wounds' edges have been under tension. In 2012, Stannard *et al*. conducted a randomized, prospective, multicenter clinical trial to evaluate the prevention of dehiscence and infection in 249 high-risk patients with extremity fractures. The authors compared NPT with conventional postoperative dressing. There was less dehiscence in the NTP group (8.6% x 16.5%, p=0.044), as well as a lower infection rate (10% x 19%, p=0.049)[41].

Solutions insulation

The instillation of solutions in the wound bed can be associated with the NPT benefits. Instillation may be performed with isotonic solutions such as saline or lactated Ringer's or with solutions containing topical antimicrobials such as polyhexyl methylene biguanide (PHMB) or polyexanide, silver nitrate, hypochlorite and others. The main indications of NPT with instillation are contaminated or infected wounds. The time and frequency of the solution application in the wound bed can be controlled by the device parameters.

In 2011, Lehner *et al*. carried out a prospective, multicentric study associating NPT with instillation of PHMB in the treatment of wounds with infected orthopedic implants. After a four to six-month follow-up period, 86% of patients with acute infections and 80% with chronic infections kept their implants. The results suggest that NPT with instillation of PHMB can be effective as an adjuvant therapy in the treatment of these wounds, aiming at implant preservation, both in acute and chronic wounds[42].

In 2016, Anghel *et al*. reviewed the evidence for the use of NTP with instillation, indicating a role for this therapy in helping to reduce hospital stay, number of debridements and treatment costs in patients with complex infected wounds[43].

Other indications

NPT can also be used in inflammatory wounds (present in sickle cell anemia and in rheumatological diseases such as rheumatoid arthritis and scleroderma), radiation wounds (radiodermitis and radionecrosis), other vascular (artery, ischemic and neuropathic) ulcers, tunneled or cavitary wounds (to reduce dead space), as well as over the acellular dermal matrix (allowing its earlier integration into the wound bed).

NPT CONTRAINDICATIONS

The application of NPT may be harmful to the patient if contraindications are not observed. Huang *et al*. cite the main contraindications of NPT[44], which may be absolute or relative: presence of necrosis on the wound bed; presence of tissue with malignancy; untreated osteomyelitis; non-enteric or non-explanted fistulas; exposure of vessels, nerves, organs or sites of anastomoses.

Despite these contraindications, there are reports of the application of NPT to exposed viscera, however with protection of these structures from direct contact with the polyurethane foam[45]. This protection may be performed by a non-adherent dressing or by a multipierced film. In addition, there are reports of NPT use as an adjuvant in the closure of bronchial fistula[46].

DIFFICULTIES AND INTERCORRENCES WITH NPT

The application of NPT may be related to some difficulties or intercurrences, such as in the presence of external fixator, anticoagulated patients, sacral or excessively exudative wounds, and patients with pain during outpatient exchanges or in the hospital bed.

Patient with external fixator

Trauma patients who undergo orthopedic treatments may have the external fixator positioned near or in the wound bed (Figure 2). Although difficult to apply, this does not prevent the indication of NTP. An effective way of overcoming this difficulty is to cut the adhesive film into smaller fragments to accommodate between the fastener rods, seeking to completely seal the air intake. After installation of the dressing and with the device in operation, if there are still areas where there is air in the system and loss of vacuum, new reinforcing films can be applied, often guided by hearing the air escape points. There are devices that visually indicate in

their panels if there is air intake, in addition to accusing air leak by an audible alarm.

Patient under anticoagulation regimen

Although it is not an absolute contraindication to NPT, its use in anticoagulated patients should be judicious. Increased blood flow in the treated area can result in bleeding, which is noted only by the rapid accumulation of blood in the reservoir. When it is indicated, it is imperative that NPT be done with the patient in a hospital stay and with broad clinical and surgical support for the diagnosis and early treatment of possible bleeding.

Excessively Exudative Wounds

NPT used in patients with excessively exudative wounds is associated with more frequent reservoir changes, increased risk of adhesive film detachment and air leakage, with loss of vacuum. In these cases, hospital admission may be more comfortable for the patient and the team due to the need for frequent exchange of the reservoir.

Sacral wounds

This location poses difficulty to NPT adjustment, since the displacement of the adhesive film from the region of the intergluteal groove is common, leading to air escape and loss of vacuum. The local humidity of the region is also a complicating factor to obtain complete seal of the dressing. To reduce this difficulty, one can apply a paste of hydrocolloid to fill and regularize folded areas, such as the intergluteal groove. After this paste dries, the adhesive film is placed more easily, reducing the risk of air entering the system.

Intermittent therapy

NPT in intermittent mode is generally set at 5:2, that is, five minutes running at subatmospheric pressure and two minutes at rest. Although experimental studies have shown a greater formation of granulation tissue and greater retraction of the wound edges with intermittent therapy[3], its application presents some difficulties. When the negative pressure is not in place', there is a risk of accumulation of exudate in the wound bed, leading to detachment of the adhesive film. After the resumption of NPT, there is air leakage in the dressing and loss of vacuum. This situation, especially in patients treated in an outpatient setting, causes great harm by making continuity of therapy impossible. In addition, the application of intermittent NTP may be painful and intolerable for some patients, especially in the periods when therapy is resumed, at the end of rest cycles.

Pain during the exchanges

Patients may experience pain during dressing changes performed outside the operating room and without anesthesia. It is common for the foam to be closely adhered to the wound bed, leading to pain and bleeding during withdrawal. To reduce this effect, NPT can be switched off a few hours before the dressing is removed. In addition, the foam may be soaked with saline after removal of the adhesive film, or even by the plastic connector prior to removal of the film. Such techniques facilitate the removal of foam, with less trauma and less pain.

Another alternative is the interposition of a fenestrated and non-adherent film between the surface of the wound and the foam, minimizing the possibility of pain during the exchanges. However, there is evidence that interposition of any material between the foam and the wound bed can reduce the intensity of the negative pressure applied by the system.

CONCLUSION

Since its introduction, NPT has become a well-established adjuvant method in the treatment of complex wounds. Despite the accumulation of evidence in recent years, NPT still raises doubts for many surgeons. Although its application is not complex, adequate knowledge of its mechanism of action and its main indications can optimize and rationalize its use, leading to more effectively wound resolution. NPT must compose the therapeutic arsenal of surgeons for the treatment of the most varied complex wounds.

R E S U M O

O objetivo desse estudo é avaliar a eficácia da terapia por pressão negativa (TPN) no tratamento de feridas complexas, com ênfase em seus mecanismos de ação e principais indicações terapêuticas. Foi realizada revisão na base de dados *Pubmed* / *Medline*, em artigos publicados de 1997 a 2016, e selecionados os mais relevantes. O mecanismo de ação da TPN envolve efeitos físicos, como o aumento da perfusão, controle do edema e do exsudato, redução das dimensões da ferida e depuração bacteriana, e biológicos, como o estímulo à formação de tecido de granulação, microdeformações e redução da resposta inflamatória local. As principais indicações da TPN são as feridas complexas como úlceras por pressão, feridas traumáticas, deiscências de ferida operatória, queimaduras, feridas necrotizantes, úlceras venosas, feridas diabéticas, os enxertos de pele, o abdome aberto, na prevenção de complicações em incisões fechadas e na associação com instilação de soluções em feridas infectadas.

Descritores: Tratamento de Ferimentos com Pressão Negativa. Ferimentos e Lesões. Técnicas de Fechamento de Ferimentos. Úlcera por Pressão. Deiscência da Ferida Operatória.

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The role of surgery in the management of women with gestational trophoblastic disease

Papel da cirurgia no manejo de mulheres com doença trofoblástica gestacional

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ABSTRACT

The Gestational Trophoblastic Disease includes an interrelated group of diseases originating from placental tissue, with distinct behaviors concerning local invasion and metastasis. The high sensitivity of the serial dosages of human chorionic gonadotrophin, combined with advances in chemotherapy treatment, have made gestational trophoblastic neoplasia curable, most often through chemotherapy. However, surgery remains of major importance in the management of patients with gestational trophoblastic disease, improving their prognosis. Surgery is necessary in the control of the disease's complications, such as hemorrhage, and in cases of resistant/relapsed neoplasia. This review discusses the indications and the role of surgical interventions in the management of women with molar pregnancy and gestational trophoblastic neoplasia.

Keywords: *Gestational Trophoblastic Disease. General Surgery. Hysterectomy. Thoracotomy. Craniotomy.*

INTRODUCTION

Gestational trophoblastic disease (GDT) comprises a group of tumors derived from placental tissue, including benign lesions, represented by the complete and partial hydatidiform mole, and a group of lesions with different degrees of invasion and dissemination, called gestational trophoblastic neoplasia (GTN): Invasive molar disease, choriocarcinoma, placental trophoblastic tumor and epithelioid trophoblastic tumor[1].

GTD has a variable global incidence, being five to ten times more frequent in Latin America and Asia than in North America and Europe[2,3]. In the United States, about 120 cases are reported per 100,000 pregnancies, while in Brazil, about 460 cases occur in 100,000 gestations[4,5].

As a result of the introduction of effective and individualized chemotherapy from prognostic factors, and thanks to the ability to monitor treatment response by monitoring human chorionic gonadotrophin (hCG) levels – a tumor marker –, GTN became a highly curable disease[1]. However, even with advances in the treatment of GTD, there are still surgical indications for the patients affected by this disease, ranging from techniques of uterine evacuation to the management of chemoresistant or relapsed neoplasia and its complications. Discussing them, emphasizing operative tactics, is the purpose of this review.

METHODS

We performed a search on three databases (Medline, Scielo and Lilacs) using the following keywords: gestational trophoblastic disease, surgery, hysterectomy, thoracotomy, and craniotomy. We limited the search to human studies published in English, Portuguese, Spanish and French from 1966 to 2015. We also used the bibliographic references of articles selected for reading.

Surgical indications for patients with molar pregnancy

Uterine evacuation

All patients with suspected molar gestation, confirmed by ultrasonography, should be sent to centers of reference in the treatment of this disease, where they

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will be submitted to uterine emptying of the hydatidiform mole. Studies have shown that there is greater survival and absence of sequelae in patients treated by specialized services[4].

Preoperative care

Blood and Rh factor, hematocrit/hemoglobin and platelet levels, plasma hCG titration, liver function (AST, ALT, total bilirubin and fractions) and renal functiontests (Urea, creatinine and uric acid) should be requested in the preoperative period of uterine evacuation of patients with molar pregnancy[5]. In patients with a uterine fundus greater than 16cm, TSH, free T4, and electrocardiogram dosages should also be ordered. Reserve of red blood cell concentrates is prudent in all cases[5].

Pelvic-transvaginal ultrasonography should be performed for uterine evaluation (confirmation of diagnostic suspicion) and adnexal evaluation (search for any tea- luteinic cysts). This exam should be complemented with Doppler of the uterine arteries, a prognostic marker of the disease evolution. Chest radiography should be requested not only to serve as a base exam, since the lungs are the main site of metastasis, but also to evaluate cases of trophoblast embolization[5].

Uterine evacuation techniques

The use of medications such as oxytocics and prostaglandin analogues produce contractions of the uterine musculature, which, by raising the intracavitary pressure, may cause embolization of trophoblastic tissue and should not be used[6]. In the specific cases of partial hydatidiform mole with fetal presence, cautious use of drug agents becomes necessary for tissue expulsion[7]. Since hysterotomy renders important morbidity, due both to allowing the passage of trophoblastic tissue into the circulation, raising the risk of post-molar GTN, and to compromising the reproductive future, it is a proscribed technique[8].

Uterine vacuum aspiration is the procedure of choice for the uterine evacuation of patients with molar pregnancy, because it is safe, fast and effective (Figure 1). It can be performed by electrical aspiration or by intrauterine manual aspiration. For this, the cervical

Figure 1. *Uterine aspiration (electric).*

dilation is performed with dilators, with later introduction of the cannula into the uterine cavity. Large amounts of molar material are aspirated with rotational movements of the instrument. The aspirate is completed with discrete movements with the cannula, simulating the classic curettage movements[6]. One should avoid the use of oxytocin, restricted to the end of the procedure or in cases of copious hemorrhage, due to the imminent risk of trophoblastic embolization. Intraoperative ultrasonography is very useful because it allows the location of the cannula, minimizing the risk of uterine perforation, and confirming complete emptying[9].

It is known that the uterine volume shows direct correlation with the risk of complications, among them perforation, hemorrhage, infection and pulmonary complications. In uterine volumes less than 16cm, the occurrence of such complications is rare[10]. Mungan *et al*.[11] found a 0.6% uterine perforation rate in 310 patients. If a perforation occurs, the procedure must be interrupted and the lesion site can be identified by laparoscopy (or

Table 1. *FIGO 2000 risk score system.*

FIGO Score	0	1	2	4
Previous pregnancies	Mole	Abortion	Term	-
Gestation interval (months)	< 4	4-6	7-12	> 12
Pre-treatment ß-hCG (mIU/mL)	$< 10^3$	10^3-10^4	10^4-10^5	$>^5$
Greatest extent of tumor including uterus (cm)	> 3	3-5	> 5	-
Site of metastasis	Lung	Spleen/Kidney	GIS*	Liver/Brain
Number of metastasis	0	1-4	5-8	> 8
Previous chemotherapy	-	-	1 drug	≥ 2 drugs

The total score is obtained by summing the individual points for each prognostic factor. Low risk, 0-6; high risk ≥7. The Placental Trophoblastic tumor and Epithelioid Trophoblastic Tumor should not be evaluated by this method.
GIS – gastrointestinal system.
Source: FIGO Oncology Commitee (2003).

by laparotomy if this technique is not available). In the absence of damage to other structures, uterine emptying is finished under direct vision, with subsequent synthesis of the perforation[9]. In cases of hemostatic difficulty, management should be individualized and hysterectomy may become a therapeutic option.

Pulmonary complications are also likely to occur when emptying large uteri. Twiggs *et al*.[12] found 27% of complications among patients with uterine volumes greater than 16cm. Trophoblastic embolization, preeclampsia, anemia, water intoxication and hyperthyroidism are cited as responsible for the majority of cases of pulmonary involvement[9].

Prophylactic hysterectomy may be an option to uterine evacuation for patients with established offspring and advanced maternal age. It reduces the risk of progression to GTN from 20% to 3.5% when compared with vacuum aspiration[13]. Elias *et al*.[14] did not find any case of evolution to neoplasia in patients treated with prophylactic hysterectomy over 40 years. However, although the prophylactic hysterectomy eliminates the risk of local invasion, it does not exclude the possibility of metastatic GTN. For this reason, it is important that all patients perform post-molar follow-up with serial hCG.

Second uterine emptying

The efficacy of the second uterine evacuation is unclear. Studies have shown that only a limited number of patients with low-risk GTN (Table 1)[15] benefit from this approach[10]. Van Trommel *et al*.[16] reported that only eight (9.4%) out of 85 patients who underwent a second emptying did not need chemotherapy compared with none in the control group (209 patients). They also identified an effect of tumor load reduction in this study, with the intervention group requiring on average one chemotherapy cycle less than the control group. In the United Kingdom, the second uterine evacuation is considered only in cases where ultrasound suggests disease confined to the uterine cavity and hCG levels below 5000IU/L[17].

Surgical indications for patients with GTN

Hysterectomy as primary GTN treatment

Chemotherapy is considered the first-line treatment for patients with GTN who wish to maintain fertility. The remission rate in patients with non-metastatic or low-risk GTN is nearly 100%. However, the adjuvant surgical procedure has the power to reduce the length of hospital stay and the number of chemotherapy cycles and, therefore, is reported as an option in cases of disease confined to the uterus and absence of reproductive desire (Figure 2). It is usually associated with exploration of the entire abdominal cavity. However, the vaginal route can also be performed without major complications[18]. Cagayan and Magallanes[19] found a 98.4% survival rate among 129 hysterectomized patients during GTN management. Indications for the procedure were uterine rupture, vaginal bleeding, resistance

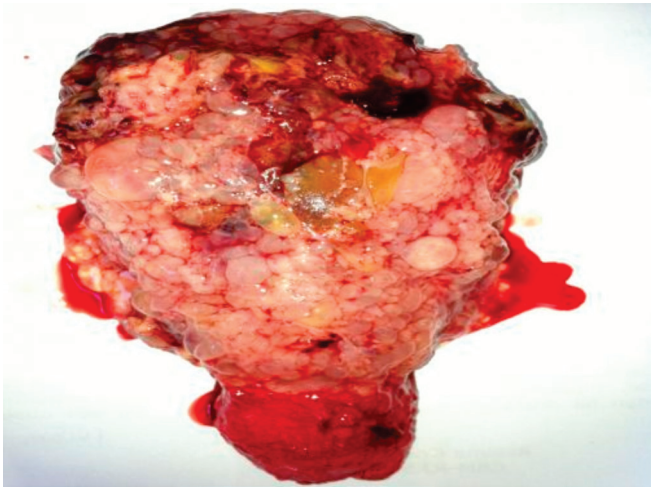

Figure 2. *Prophylactic hysterectomy specimen.*

to chemotherapy, and adjuvant initial therapy when there was no reproductive desire. In cases of advanced metastatic disease, its indication is controversial, as besides not presenting a curative role, it may increase morbidity. An exception to this is the presence of bulky and hemorrhagic tumor[20].

Surgery in patients with chemoresistant/relapsing GTN

Before indicating surgical resection, imaging examinations are performed to document the presence of neoplasia in the uterus or in other localities. They are chest tomography and magnetic nuclear resonance of the skull and pelvis[7,9]. Most surgical procedures are performed during chemotherapy to minimize the possibility of metastatic induction by tissue manipulation. Studies do not show an increase in morbidity with this therapeutic combination[1].

Hysterectomy/Robotics/Local uterine resection by minimally invasive surgery

Hysterectomy is an option for patients who did not respond to the chemotherapy regimen of first and second lines (usually methotrexate and actinomycin-D), especially in those with no reproductive desire. Ghaemmaghami *et al*.[21] reported an incidence of 17.6% of hysterectomies in patients with chemoresistant GTN. Several studies have shown that uterine excision is effective in producing remission in most patients and those who did not benefit probably had occult metastatic neoplasia[1].

Most hysterectomies are performed by the abdominal route. The vaginal route can be considered in women without metastatic neoplasia, with small volume uteri and low hCG levels, but the evaluation of the upper abdomen in search of hidden metastasis becomes impossible[1]. The laparoscopic route has well documented advantages, including less complications and shorter hospital stay. Riley *et al*.[22] documented the first robotic-assisted hysterectomy in a patient with GTN in 2015. After surgery, she received five cycles of mono-chemotherapy with actinomycin D. The patient achieved normalization of hCG levels at the fourth postoperative week.

Resection of local uterine lesion with reconstruction may be considered an option in patients without metastatic disease and with a desire to maintain fertility. There is a report of a patient with chemotherapy-resistant GTN treated with uterine segmental resection followed by hysteroplasty. She had two successful pregnancies after treatment[23]. The lesion should be carefully located by a combination of imaging tests: magnetic resonance imaging, Doppler ultrasonography and/or hysteroscopy. Lesions smaller than 2cm in diameter associated with low hCG levels are more likely to be completely resected[20].

Pulmonary resection

It is the most performed procedure to eliminate extrauterine metastatic neoplasia. Pulmonary metastasis occurs in up to 70% of patients with GTN, and 90% of these are cured with chemotherapy. Treatment failure has been attributed to an ineffective concentration of the drug that reaches the lesion, due to central necrosis or tumor incarceration by fibrin[1]. There are several cases of GTN detection only after the histopathological result of a resected lung lesion without previous diagnosis[9].

Several reference centers have published satisfactory results with nodulectomy and lobectomy in the management of patients at high risk for GTN (Table 1)[15]. A single, unilateral lesion associated with low levels of hCG has encouraging results[9].

Tomada *et al*.[24] proposed five criteria to obtain therapeutic success with surgery: patient with good surgical status; controlled primary uterine tumor; absence

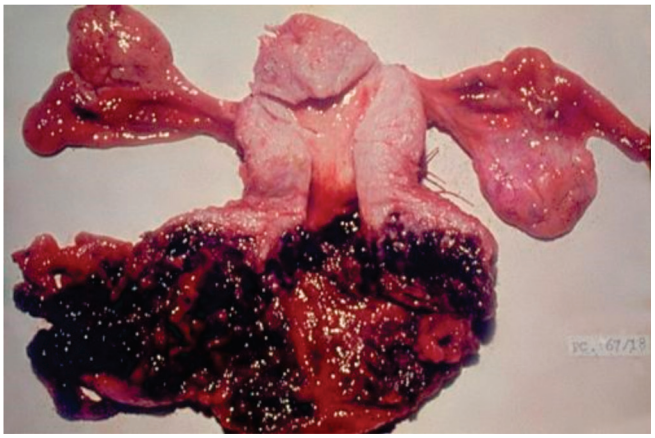

Figure 3. *PTT with extensive vaginal metastasis.*

of other sites of metastasis; solitary lung injury; and hCG level <1000mIU/mL. They also reported that 14 out of 15 patients who fulfilled all the criteria were cured with the procedure, compared with no case among patients with a score greater than or equal to 1. Eoh *et al*.[25], in 2015, reported complete remission in the three cases that underwent pulmonary resection due to persistent disease.

Several research centers have demonstrated that the occurrence of expressive regression of hCG levels within one to two weeks of surgical resection predicts a favorable outcome[20].

Craniotomy

Brain metastases occur in 8-15% of patients with GTN and the treatment is based initially on the association of radiation therapy with chemotherapy, to prevent hemorrhage, neurological deterioration and death. In cases of increased intracranial pressure, craniotomy is indicated for CNS decompression and stabilization[9]. Another indication is the excision, in rare cases, of isolated nodules resistant to drug treatment. This therapeutic regimen results in rates of 65% to 80% of primary remission and up to 90% cure[20].

The timing of perioperative chemotherapy is likely to play a role in the prevention of late metastases. Patients who underwent chemotherapy within one week of craniotomy became less likely to present recurrence compared with those who received chemotherapy more than one week after surgery[25].

Clinical predictors of surgical response in patients with chemoresistant GTN

The identification of surgical response predictors in patients with persistent GTN is a field that remains under investigation. Feng *et al*.[26] showed that several preoperative factors were significantly different between the group with therapeutic success and the group that presented failure. These factors included age greater than 35 years, history of non-molar gestation, metastases in locations beyond the uterus and lungs, and pre-surgical levels of hCG. Patients older than 35 years or pre-surgical levels of hCG greater than 10mIU/mL have a near 50% chance of treatment failure. No patient with two or more unfavorable factors evolved for cure.

Several studies have shown that the level of hCG before surgery is an important predictor of the therapeutic response and should be maintained low. Tomada *et al*.[24] found survival improvement in patients with levels below 1000mIU/mL.

There is a correlation between metastatic sites and surgical response. The presence of other foci other than the uterine and pulmonary ones is a poor prognostic factor. However, Wang *et al*.[27] reported the survival of five out of seven patients who had more than one metastatic site and underwent pulmonary resection.

The FIGO prognostic score did not prove to be a good predictor of surgical treatment and was considered inadequate for the evaluation of chemoresistant patients[26].

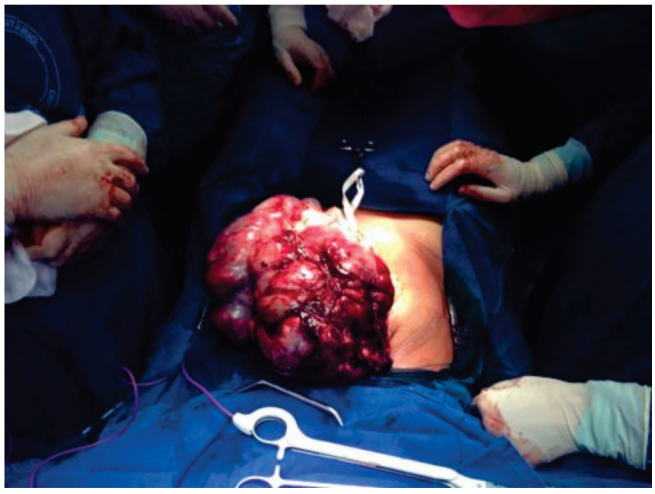

Figure 4. *ETT in patient with large abdomino-pelvic mass.*

Table 2. *Staging system for GTN– FIGO 2000.*

Stage I	Disease confined to the uterus.
Stage II	GTN spread out of the womb, but limited to the genital system.
Stage III	GTN spread to the lungs, with or without involvement of the genital system.
Stage IV	All other sites of metastasis.

Source: FIGO Oncology Commitee (2003)

Treatment of special forms of GTN

The placental trophoblastic tumor (PTT) and the epithelioid trophoblastic tumor (ETT) are the rarest forms of GTN, with biological behavior different from the others. They present with low levels of hCG, slow growth, metastases months or years after the gestation, and are resistant to polychemotherapy[28].

Placental trophoblastic tumor (PTT)

Its incidence is 1:100,000 pregnancies, accounting for 1% to 2% of GTN cases[28]. The primary treatment for this group of tumors is total hysterectomy, with pelvic and retroperitoneal lymph node sampling, especially for women with localized disease and complete offspring (Figure 3). In patients with reproductive desire, there are reports of good results with non-sterilizing procedures. Saso *et al*.[29] published a case of PTT treated with free-margin resection of the uterine lesion and organ reconstruction (modified Strassman's surgery). After the procedure, the patient had two miscarriages and one term gestation with a healthy fetus. The prognosis is favorable when the disease is limited to the uterus. In the presence of metastatic disease, the mortality rate may reach 25%. Schmid *et al*.[28] showed that the combination of surgery with chemotherapy in stages II, III, IV (Table 2)[15] improves outcomes.

Epithelioid trophoblastic tumor (ETT)

ETT accounts for less than 2% of all GTN cases (Figure 4). They are present in women with full term gestation with one to 18 years interval after pregnancy[30]. Metastatic neoplasm associated with an interval greater than four years from the previous gestation is considered a worse prognostic factor[28,30]. Surgical resection is the pillar of the treatment. Hysterectomy should be indicated in patients with disease confined to the uterus to maximize the cure opportunity. Davis *et al*.[30] reported that several surgical procedures are frequently required in patients with ETT, particularly in those with extrauterine disease.

CONCLUSION

Molar gestation should be treated with uterine vacuum aspiration, avoiding techniques such as hysterotomy and drug inductions. Although chemotherapy continues as the central point of management of patients with GTN, surgery, when correctly indicated, plays a significant role in increasing cure rates. Approximately half of patients with high-risk GTN require surgery during treatment, both to achieve remission and to treat complications. Although the literature shows improved therapeutic success rates, the management of chemoresistant patients is still a challenge. Higher cure rates are expected when patients are treated at referral centers.

RESUMO

Doença trofoblástica gestacional inclui um grupo interrelacionado de doenças originadas do tecido placentário, com tendências distintas de invasão local e metástase. A alta sensibilidade das dosagens seriadas de gonadotrofina coriônica humana aliada aos avanços do tratamento quimioterápico tornou a neoplasia trofoblástica gestacional, curável, na maioria das vezes, através da quimioterapia. No entanto, a cirurgia permanece ainda, da maior importância na condução de pacientes com doença trofoblástica gestacional, melhorando seu prognóstico. A cirurgia é necessária no controle de complicações da doença, tais como hemorragia, e em casos de neoplasia resistente/recidivada. Esta revisão discute as indicações e o papel das intervenções cirúrgicas durante o manejo de mulheres com gravidez molar e neoplasia trofoblástica gestacional.

Descritores: Doença Trofoblástica Gestacional. Cirurgia Geral. Histerectomia. Toracotomia. Craniotomia.

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Intra-aortic balloon pump in cardiogenic shock: state of the art

Balão intra-aórtico no choque cardiogênico: o estado da arte

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ABSTRACT

The clinical definition of cardiogenic shock is that of a low cardiac output and evidence of tissue hypoxia in the presence of adequate blood volume. Cardiogenic shock is the main cause of death related to acute myocardial infarction (AMI), with a mortality rate of 45-70% in the absence of aggressive and highly specialized technical care. The intra-aortic balloon pump (IABP) is one of the most widely used mechanical assisting devices. During the last two decades, about 42% of patients with AMI who evolved with cardiogenic shock received mechanical circulatory assistance with IABP. Its clinical indication has been based on non-randomized studies and registry data. Recent studies have shown that the use of IABP did not reduce 30-day mortality in patients with AMI and cardiogenic shock treated with the strategy of early myocardial revascularization as the planned primary objective. The guidelines of the American Heart Association and of the European Society of Cardiology have reassessed their recommendations based on the results of meta-analyzes, including the IABP-SCHOCK II Trial study, which did not evidence an increase in survival of patients who received mechanical support with IABP. This review article addresses the clinical impact of IABP use in the cardiogenic shock caused by AMI.

Keywords: *Intra-Aortic Balloon Pumping. Shock, Cardiogenic. Myocardial Infarction.*

INTRODUCTION

The first description of the counter pulsation principle in experimental animals was made by Adrian Kantrowitz in 1952[1].

This author used the hemidiaphragm wrapped around the thoracic aorta of dogs, electrically stimulated via the phrenic nerve during the animal's diastole, producing the effect of aortic counter pulsation. In 1962, Moulopoulos *et al*.[2], using the counter pulsation principle, developed the modern intra-aortic balloon pump (IABP), which consisted of a flask mounted on a flexible two-lumen catheter that was able to inflate and deflate in the descending thoracic aorta during each cardiac cycle. In 1968, Kantrowitz *et al*.[3] described the hemodynamic effects of IABP use in a patient with cardiogenic shock. Cardiogenic shock is the main factor related to the mortality of acute myocardial infarction (AMI). Despite the great advances in the treatment of patients with AMI with the invasive percutaneous intervention or myocardial revascularization surgery, the mortality of cardiogenic shock remains high, with rates varying from 45% to 70%[4]. Similarly, there is little decline in the incidence of cardiogenic shock, remaining in values from 5% to 10% of AMI patients[5]. For more than two decades, IABP has been used in association with the inotropic support with vasoactive drugs, as mechanical support in cases of AMI complicated with cardiogenic shock. In this long period, the treatment of infarction has undergone considerable changes. This text will focus on the evidence for the use of IABP in the context of cardiogenic shock treatment, considering the current literature.

Hemodynamic effects of IABP

The IABP consists of a vascular catheter with a balloon mounted at its distal end. The balloon is inserted through a retrograde puncture of the femoral artery and its distal tip should be positioned in the descending thoracic aorta immediately after the emergence of the left subclavian artery (Figure 1). The tip of the catheter coincides with the pulmonary carina and should be confirmed by chest X-ray. In its adequate positioning, the helium-inflated balloon is synchronized with the cardiac cycle: inflated during diastole and deflated during systole, result-

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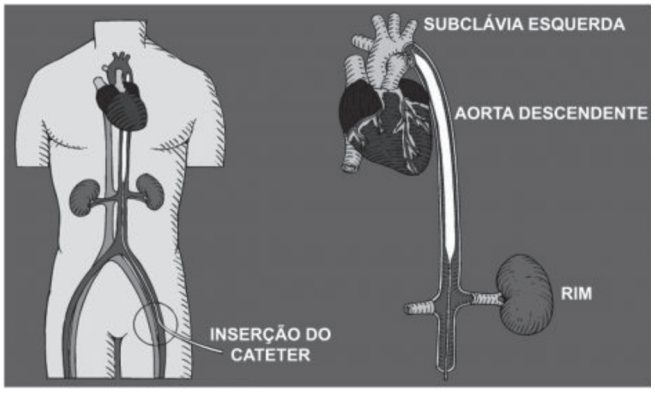

Figure 1. *Proper positioning of the intra-aortic balloon.*

ing in increased coronary and systemic flow during the diastolic peak (inflated IABP), reduction of the post-load and of the myocardial oxygen consumption (vacuum effect), coinciding with the rapid deinsufflation of the IABP at the beginning of systole[6]. Several studies evaluated the hemodynamic benefits of IABP. At baseline, most studies were unanimous in showing a reduction in systemic vascular resistance, a slight increase in cardiac index (0.5L/min), and increased coronary flow[7-9]. Recently, observational studies with small groups of patients have shown conflicting results in assessing the influence of IABP on tissue perfusion[10-12]. A randomized, single-center study by Prondzinsky *et al*.[13] compared two groups of patients with AMI complicated with cardiogenic shock. The authors did not observe significant differences in hemodynamic parameters (cardiac index, systolic work, systemic vascular resistance) in the group treated with IABP in relation to the group without IABP support.

Clinical impact of IABP use

The classic treatment strategy for ST-segment elevation AMI clearly evolved over the last decade from the fibrinolysis scenario to the primary angioplasty one. In the studies of patients with AMI without cardiogenic shock considered to be at high risk (incomplete coronary transluminal angioplasty – CTA, persistent ST elevation, Killip >1) treated with primary CTA, there was no obvious benefit with IABP circulatory assistance. Recent meta-analyzes on the subject have shown no benefit in reducing mortality, with evidence of increased incidence of stroke and bleeding[14,15]. There are few studies that suggest the benefit of IABP in patients with post-AMI cardiogenic shock treated with fibrinolytics. In the TACTICS study, 57 patients with AMI were randomized to receive thrombolytic therapy and IABP or exclusive thrombolytic therapy[16]. It demonstrated a positive impact of IABP associated with thrombolytic therapy in this population of patients with cardiogenic shock. It is worth highlighting the early interruption of the study due to the difficulty of patient allocation. However, these same benefits were not evidently demonstrated in patients submitted to the strategy of early percutaneous revascularization[17,18]. In 2009, a systematic review of the literature evaluated the use of IABP in patients with AMI and cardiogenic shock.

Table 1. *Clinical outcome of the IABP Shock Trial II study (Modified by Thiele H, et al., N Engl J Med. 2012; Lancet. 2013).*

		IABP	Control	Relative risk (95% CI)	p value
30-day mortality	Total	119/300 (39.7%)	123/298 (41.3%)	0.96 (0.79-1.17)	0.69
30-day events	Reinfarction	9/300 (3.0%)	4/298 (1.3%)	2.24 (070-7.18)	0.16
	Stroke	2/300 (0.7%)	5/298 (1.7%)	0.40 (0.08-2.03)	0.28
12-month mortality	Total	155/299 (52%)	152/296 (51%)	1.01 (0.86-1.18)	0.91
	Cardiac cause	150/299 (50%)	148/296 (51%)	1.00 (0.85-1.18	0.97
	Non-cardiac cause	5/299 (2%)	4/296 (1%)	1.23 (0.34-4.56)	1.00

This meta-analysis demonstrated the benefit of IABP in patients undergoing thrombolysis, but not in those submitted to primary angioplasty[19]. It is important to note that, in this review, observational studies were considered, mainly among the group of patients undergoing thrombolysis. More recently, Unverzagt *et al*.[20] performed a meta-analysis that considered only randomized studies. The study included five studies, with only two of them evaluating IABP circulatory assistance. The authors did not observe any benefit of using IABP in cardiogenic shock. This lack of evidence may justify the lower indication of IABP observed in reports of large international registries, which show a rate of use in patients with cardiogenic shock between 25% and 40%, despite the high levels of indications suggested in the US and European level before 2012[21]. Until 2012, the European and American consensus considered the use of IABP in the scenario of post-AMI cardiogenic shock as class I (level of evidence C). Based on the results of recent meta-analyzes, current consensus has changed its recommendations to Class II-A (American Heart Association – AHA) and Class II-B (European Society of Cardiology – ESC)[22,23]. Currently, the European consensus does not advocate the routine use of IABP, and it is recommended only as adjunctive therapy for patients with complications, such as a bridge for surgery (class II, level A evidence). In recent publications, Thiele *et al*.[24,25] reported an elegant, prospective, randomized, multicenter study. In this study of 600 patients with cardiogenic shock secondary to AMI, they selected 301 patients for circulatory support with intra-aortic balloon (IABP group) and 299 patients as control group (without intra-aortic balloon). All patients underwent early revascularization by percutaneous intervention or surgical treatment. The primary outcome evaluated was the 30-day all-cause mortality. Other secondary outcomes such as severe bleeding, peripheral ischemic complications, sepsis and stroke were also evaluated. In the final analysis at 30 days, 119 (39.7%) patients in the IABP group and 123 (41.3%) patients in the control group died (relative risk with IABP of 0.96, 95% CI 0.79-1.17, p=0.69). There were no significant differences between the IABP and the control groups regarding bleeding rates (3.3% and 4.4%, respectively; p=0.51), peripheral ischemic complications (4.3% and 3.4, p=0.53), sepsis (15.7% and 20.5%, p=0.15) and stroke (0.7% and 1.7%, p=0.28) (Table 1). The authors concluded that intra-aortic balloon use did not significantly reduce 30-day mortality in those patients with acute myocardial infarction complicated by cardiogenic shock who were submitted early to one of the revascularization strategies. At the end of 12 months, there was no reduction in all cause mortality with IABP. However, there may be benefit in patients with mechanical defects (mitral insufficiency or ventricular septal defect) or in patients with rapidly evolving shock. Some criticisms are made regarding the high crossover rate of patients in the control group for the IABP group, for reasons not associated with the development of a mechanical complication. However, once the adjusted analysis was made excluding this group of patients, there was no change in the study conclusion. There is also question about the possibility of them excluding serious patients with rapid shock deterioration, thus making the study cohort much more representative of those patients stabilized with vasopressor and/or inotropic support. Therefore, the study results may not apply to severe shock with rapid deterioration. More data and more follow-up time is needed to better understand which subgroups can benefit from using IABP. In a recent meta-analysis, seven studies totaling 790 patients with AMI and cardiogenic shock were contemplated[26]. The authors concluded that the available evidence demonstrates some benefit in hemodynamic parameters, but does not result in survival benefit. They then point out that there is no convincing data that supports the use of IABP in patients with cardiogenic shock after acute myocardial infarction.

CONCLUSION

The intra-aortic balloon remains the minimally invasive circulatory assistance device most commonly used by intensivists for cases of AMI complicated by cardiogenic shock. However, current evidence does not support its routine use in the majority of this population. This circulatory care device may have beneficial effects on some hemodynamic parameters, however, without impact on hospital and late survival.

R E S U M O

A definição clínica de choque cardiogênico é a de um quadro de baixo débito cardíaco e evidência de hipóxia tecidual, na presença de volemia adequada. O choque cardiogênico representa a principal causa de óbito relacionada ao infarto agudo do miocárdio (IAM), com índice de mortalidade em torno de 45% a 70%, na ausência de cuidados técnicos agressivos e altamente especializados. O balão intra-aórtico (BIA) é um dos dispositivos de assistência mecânica mais utilizados no mundo. Nas duas últimas décadas, cerca de 42% dos pacientes com IAM, que evoluíram com choque cardiogênico, receberam assistência circulatória mecânica com BIA. Sua indicação clínica tem sido baseada em estudos não randomizados e dados de registro. Estudos recentes têm demonstrado que o uso do BIA não reduziu a mortalidade hospitalar (30 dias) em pacientes com IAM e choque cardiogênico, tratados com a estratégia de revascularização precoce do miocárdio como objetivo primário planejado. As diretrizes da Associação Americana de Cardiologia e da Sociedade Europeia de Cardiologia reavaliaram suas recomendações, baseadas nos resultados de metanálises, incluindo o estudo *IABP-SCHOCK II Trial*, que não evidenciou aumento na sobrevida de pacientes que receberam suporte mecânico com BIA. Este artigo de revisão aborda o impacto clínico do uso do BIA no choque cardiogênico ocasionado pelo IAM.

Descritores: Balão Intra-Aórtico. Choque Cardiogênico. Infarto do Miocárdio.

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Percutaneous transbiliary biopsy

Biópsia percutânea transbiliar

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A B S T R A C T

Percutaneous drainage of the bile ducts is an established procedure for malignant obstructions, in which a histological diagnosis is often not obtained. We describe the biopsy technique of obstructive lesions through biliary drainage access, using a 7F endoscopic biopsy forceps, widely available; some are even reusable. This technique applies to lesions of the hepatic ducts, of the common hepatic duct and of all extension of the common bile duct.

Keywords: *Jaundice, Obstructive. Biliary Tract Neoplasms. Biopsy.*

INTRODUCTION

Malignant obstructions of the bile ducts are part of the routine abdominal surgery services, often with extreme difficulty in cytological or histological diagnosis, especially in the high lesions. In these, drainage of the bile duct by trans-hepatic percutaneous access (PTBD) is performed routinely. However, few services perform cytological investigation with a brush or even biopsy of the obstruction by this access, delaying or preventing specific oncological treatment[1,2].

In a large number of biliary lesions, size and location impede percutaneous access for biopsy and fragment removal for histopathological study[3,4]. Access through the biliary tract allows cytological examination of bile with a brush, but with low sensitivity and low availability. The forceps biopsy through the PTBD access is very little known in Brazil, and the technique described uses the more expensive and not widely available myocardial biopsy forceps[3]. In this paper, we describe the modified technique with a wired introducer sheath and an endoscopic gastric biopsy forceps, available at endoscopy services.

TECHNICAL NOTE

At the same time of the drainage or later, with the trans-hepatic access made, under prophylactic antibiotic therapy, we perform a cholangiography, identifying the site of the obstruction (Figure 1a). Under fluoroscopic guidance, we introduce a guidewire down to the point of obstruction and, over this, a 7F to 10F sheath, together with the dilator. Our preference is for a wired sheath that fits the curves better and does not kink. Wherever possible, we use the Flexor Ansel Sheath or Raabe Sheath short models. Once positioned within the obstruction, we keep the sheath firm and remove the guidewire and dilator (Figure 1b). We then introduce the 7F endoscopic biopsy forceps catheter, which has some reusable models. It is worth mentioning that there are models with needle or spike, with alligator type blades, among others. All can be used, however,

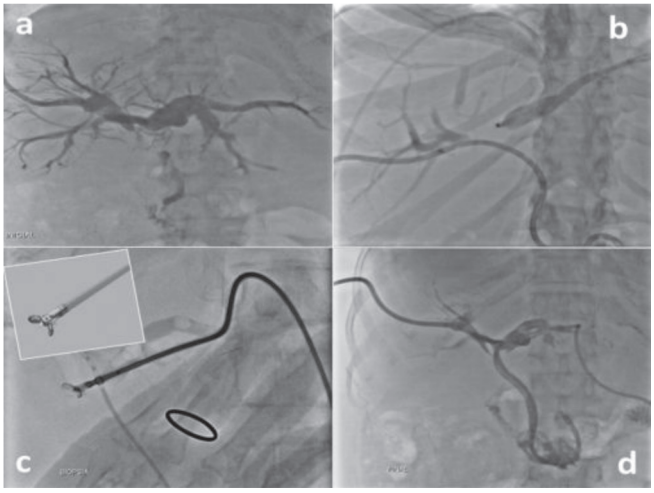

Figure 1. *A) Cholangiography with dilatation of the bile ducts and obstruction in the confluence of the hepatic ducts; B) Operator's hand keeping the sheath against the obstruction; C) Detail of the forceps used with a spike; D) The obstruction is crossed and two internal-external drains are placed.*

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because they are available in our service, we use the Capture Biopsy Forceps With Spike more often (Figure 1c). Under fluoroscopy, we introduce the forceps until it is out of the sheath and open it. With the forceps open, we push the set (sheath and catheter-forceps) towards the obstruction and, with an auxiliary maintaining positive pressure of the set against the injury, we close the forceps, thus necessitating four hands for execution. Still holding the sheath in the same place, we remove the forceps, macroscopically explore the material and place it in formalin, preferably buffered. We repeat the maneuver as many times as necessary until we obtain a satisfactory sample for the histological study, on average four to five times. Finally, we cross the obstruction with the guidewire, remove the sheath and introduce a biliary drain of thickness similar or superior to the sheath used (Figure 1d). If we can not overcome the obstruction, we place an external drain, also of similar or larger diameter than the sheath. We wash the biliary tree and, if the drain is internal, we leave the external drainage open for 24 hours. In the external drains, it has to be kept open.

DISCUSSION

As we have seen, it is a simple technique and quite similar to that already published with myocardial forceps[3,4], but with a cheaper device, much more available in surgery services, and with some models authorized for reuse. Another great advantage is the possibility of biopsying lesions in the hepatic ducts, in the common hepatic duct or in the common bile duct, even in patients with intestinal or bilio-digestive derivations.

The presence of the pathologist in the room is of great value, but it is not the rule in many services. As patients remain with biliary drains, access is ready for repeating the biopsy when and if necessary. After about one or two weeks, if the result is inconclusive, everything can be repeated on an outpatient basis. Without a pathologist in the room, we obtained a positive result in 60% in the first procedure, reaching more than 80% after the second.

A simple and easily available technique, it allows the approach of high or low biliary obstructive lesions, speeding up and optimizing the onset of treatment.

R E S U M O

A drenagem percutânea das vias biliares é um procedimento estabelecido para obstruções malignas, nos quais, muitas vezes, não se consegue um diagnóstico histológico. Descrevemos a técnica de biópsia da lesão obstrutiva através do acesso de drenagem biliar, utilizando um fórcipe de biópsia endoscópica 7F, amplamente disponível e alguns reutilizáveis. Esta técnica aplica-se a lesões dos ductos hepáticos, do hepático comum e de toda extensão do colédoco.

Descritores: Biópsia Guiada por Imagem. Neoplasias dos Ductos Biliares. Icterícia Obstrutiva.

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