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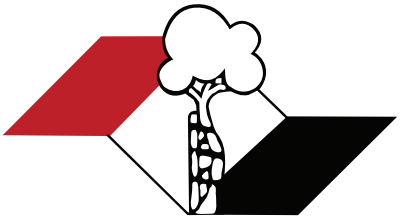

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ACTA ORTOPÉDICA BRASILEIRA

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(Reviewed January 2016)

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NUMBER OF WORDS RECOMMENDED ACCORDING TO THE PUBLICATION TYPE: The criteria specified below should be observed for each type of publication. The electronic counting of words should start at the Introduction and end at the Conclusion.

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Type of Article	Abstract	Number of words	References	Figures	Tables	Maximum number of authors allowed
Original	Structured, up to 200 words	2.500 Excluding abstract, references, tables and figures	20	10	6	6
Update / Review*	Non-structured, up to 200 words	4.000 Excluding abstract, references, tables and figures	60	3	2	2
Editorial*	No abstract	500	0	0	0	1

*These contributions shall be published at the Editors' criteria, with due replica, when applicable.

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The generic names should be used for all drugs. The drugs can be referred to by their trade name, however, the manufacturer's name, city and country or electronic address should be stated in brackets in the Materials and Methods section.

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Measurement units (3 ml or 3 mL, but not 3 milliliters) or standard scientific symbols (chemical elements, for example, Na and not sodium) are not considered abbreviations and, therefore, should not be defined. Authors should abbreviate long names of chemical substances and therapeutic combinations terms. Abbreviations in figures and tables can be used for space reasons, but should be defined in the legend, even if they were defined in the article.

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KEYWORDS: The article should include at least three and at most six descriptors in Portuguese and in English, based on the Descriptors of Health Sciences (DeCS) http://decs.bvs.br/ or Medical Subject Headings (MeSH) of the National Library of Medicine, available at http://www.nlm.nih.gov/mesh/meshhome.html

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CONCLUSION: The conclusion should be clear and concise, establishing a link between the conclusion and the study objectives. Avoiding conclusions not based on data from the study in question is recommended, as well as avoiding suggest that studies with larger samples are needed to confirm the results of the work in question.
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Levels of Evidence for Primary Research Question[a]

(This chart was adapted from material published by the Centre for Evidence-Based Medicine, Oxford, UK. For more information, please visit www.cebm.net.)

	Types of study			
Level	**Therapeutic Studies Investigating the Results of Treatment**	**Prognostic Studies – Investigating the Effect of a Patient Characteristic on the Outcome of Disease**	**Diagnostic Studies – Investigating a Diagnostic Test**	**Economic and Decision Analyses – Developing an Economic or Decision Model**
I	High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals	High quality prospective study[d] (all patients were enrolled at the same point in their disease with ≥80% of enrolled patients)	Testing of previously developed diagnostic criteria on consecutive patients (with universally applied reference ''gold'' standard)	Sensible costs and alternatives; values obtained from many studies; with multiway sensitivity analyses
	Systematic review[b] of Level RCTs (and study results were homogenous[c])	Systematic review[b] of Level I studies	Systematic review[b] of Level I studies	Systematic review[b] of Level I studies
II	Lesser quality RCT (eg, < 80% followup, no blinding, or improper randomization)	Retrospective[f] study	Development of diagnostic criteria on consecutive patients (with universally applied reference ''gold'' standard)	Sensible costs and alternatives; values obtained from limited studies; with multiway sensitivity analyses
	Prospective[d] comparative study[e]	Untreated controls from an RCT	Systematic review[b] of Level II studies	Systematic review[b] of Level II studies
	Systematic review[b] of Level II studies or Level I studies with inconsis tent results	Lesser quality prospective study (eg, patients enrolled at different points in their disease or <80% followup)		
		Systematic review[b] of Level II studies		
III	Case control study[g]	Case control study[g]	Study of non consecutive patients; without consistently applied reference ''gold'' standard	Analyses based on limited alternatives and costs; and poor estimates
	Retrospective[f] comparative study[e]		Systematic review[b] of Level III studies	Systematic review[b] of Level III studies
	Systematic review[b] of Level III studies		Case-control study	
			Poor reference standard	
IV	Case series[h]	Case series		Analyses with no sensitivity analyses
V	Expert opinion	Expert opinion	Expert opinion	Expert opinion

[a] A complete assessment of quality of individual studies requires critical appraisal of all aspects of the study design.

[b] A combination of results from two or more prior studies.

[c] Studies provided consistent results.

[d] Study was started before the first patient enrolled.

[e] Patients treated one way (eg, cemented hip arthroplasty) compared with a group of patients treated in another way (eg, uncemented hip arthroplasty) at the same institution.

[f] The study was started after the first patient enrolled.

[g] Patients identified for the study based on their outcome, called "cases" eg, failed total arthroplasty, are compared with patients who did not have outcome, called ''controls'' eg, successful total hip arthroplasty.

[h] Patients treated one way with no comparison group of patients treated in another way.

SUMMARY

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Original Articles

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ORIGINAL ARTICLE

EFFECTS OF HIGH-DOSE VITAMIN C AND HYALURONIC ACID ON TENDON HEALING

EFEITOS DE ALTAS DOSES DE VITAMINA C E ÁCIDO HIALURÔNICO SOBRE A CICATRIZAÇÃO DO TENDÃO

Yasar Mahsut Dincel[1], Oktay Adanir[2], Yavuz Arikan[1], Aysel Kara Caglar[3], Suzan Cansel Dogru[4], Yunus Ziya Arslan[4]

1. Department of Orthopedics and Traumatology, Metin Sabanci Baltalimani Bone Diseases Training and Research Hospital, Istanbul, Turkey.
2. Department of Orthopedics and Traumatology, Istanbul Bagcilar Training and Research Hospital, Istanbul, Turkey.
3. Department of Medical Pathology, Istanbul Bagcilar Training and Research Hospital, Istanbul, Turkey.
4. Department of Mechanical Engineering, Faculty of Engineering, Istanbul University, Avcilar, Istanbul, Turkey.

ABSTRACT

Objective: To assess the histopathologic and biomechanical effects of hyaluronic acid (HA) and high-dose vitamin C (VC) on rat Achilles tendon healing. Methods: Forty-eight Sprague-Dawley rats were randomized to HA and VC and control groups with equal numbers. Each group was further divided into two subgroups to be sacrificed on Day 15 (n=8) and Day 30 (n=8). The Achilles tendons were cut and repaired. While the control rats remained untreated, HA and VC were administered after repair. The repaired tendons were removed for biomechanical and histopathologic analyses. In the biomechanical tests, the tendons were stretched to failure and maximum forces were measured. For histopathologic examination, the specimens were interpreted semiquantitatively using Movin's grading scale and Bonar scores. Results: The highest mean forces were obtained in the HA group on Day 15 and in the VC group on Day 30, with a significant difference between HA and VC on Day 15 between control and VC on Day 30 ($p<0.05$). Histological examination showed both Movin and Bonar scores decreased in all groups on Day 30, with significant improvements in the HA and VC groups ($p<0.05$). Conclusion: Our results demonstrated that both VC and HA had therapeutic effects on tendon healing, especially in the late phase. ***Level of Evidence I; High quality randomized trial with statistically significant difference.***

Keywords: Hyaluronic acid. Vitamin C. Rats. Achilles tendon.

RESUMO

Objetivo: Avaliar os efeitos histopatológicos e biomecânicos do ácido hialurônico (AH) e altas doses de vitamina C (VC) na cicatrização do tendão do calcâneo em ratos. Métodos: Quarenta e oito ratos Sprague-Dawley foram randomizados em grupo AH, grupo VC e grupo controle, iguais em número. Cada grupo foi dividido em dois subgrupos a serem sacrificados no Dia 15 (n = 8) e no Dia 30 (n = 8). Os tendões do calcâneo foram cortados e reparados. Enquanto os ratos do grupo controle permaneceram não tratados, os do grupo AH/VC receberam AH e VC após o reparo. Os tendões reparados foram removidos para análises biomecânicas e histopatológicas. Nos testes biomecânicos, os tendões foram estirados até a falha e as forças máximas foram medidas. No exame histopatológico, as amostras foram interpretadas semiquantitativamente usando os escores de Movin e de Bonar. Resultados: As forças médias mais altas foram obtidas no grupo AH no Dia 15 e no grupo VC, no Dia 30, com diferença significativa entre os grupos HA e VC no Dia 15 e entre os grupos controle e VC ($p < 0,05$). No exame histológico, os escores de Movin e Bonar diminuíram em todos os grupos no dia 30, com melhora significativas nos grupos AH e VC ($p < 0,05$). Conclusões: Nossos resultados demonstraram que tanto a VC quanto o AH tiveram efeitos terapêuticos sobre cicatrização do tendão, especialmente na fase tardia. ***Nível de Evidência I; Estudo clínico randomizado de alta qualidade com ou sem diferença estatisticamente significante.***

Descritores: *Ácido hialurônico. Vitamina C. Ratos. Tendão do calcâneo.*

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INTRODUCTION

Achilles tendon rupture is typically seen in men during their thirties and forties who rarely engage in sports and spend most of their time in office work.[1] Researchers have examined many factors to better understand the mechanisms of tendon healing to speed this process. These factors include growth factors, mesenchymal stem cells, cytokines, gene therapy approaches, sodium hyaluronate, platelet concentrates, anticoagulants, and hyperbaric oxygen.[2,3] However, there is no gold-standard treatment that can improve tendon healing by applying exogenous agents.

Hyaluronic acid (HA) is known to have a preventive effect on adhesions, but its effects on tendon biomechanics are not fully known.

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Work conducted at the Department of Orthopedics and Traumatology, Istanbul Bagcilar Training and Research Hospital, Istanbul, Turkey and at the Department of Mechanical Engineering, Faculty of Engineering, Istanbul University, Avcilar, Istanbul, Turkey.
Correspondence: Yunus Ziya Arslan. Department of Mechanical Engineering, Faculty of Engineering, Istanbul University. Ýstanbul Universitesi Muhendislik Fakultesi Makine Muhendisligi Bolumu Avcilar, 34320 Istanbul, Turkey. yzarslan@istanbul.edu.tr

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Although HA has been used in humans after tendon repair, consensus on its benefits is lacking. Meanwhile, vitamin C (VC) has been shown to have beneficial effects on tendon healing, such as increased collagen fibril diameter, promotion of angiogenesis, and increased number of fibroblasts in the healing period.[4] However, the number of studies regarding the effects of VC on tendon healing is limited. Most of the previous studies focusing on the effects of HA and VC in tendon healing have included either histopathological or biomechanical results, but not both.[3-6] A few recent studies focusing on the therapeutic effects of HA have provided both histopathological and biomechanical results.[7] Furthermore, some studies (especially on HA) have examined the effects of these two drugs on adhesiveness of tendons rather than on tendon healing.[8] In this regard, the purpose of this experimental study was to investigate the histopathological, pathophysiological, and biomechanical results of applying HA and VC to Achilles tendon ruptures treated with primary repair.

MATERIALS AND METHODS

The study was approved by the local institutional ethics review board (approval number: 2014/22). A total of 48 adult male 7-month-old Sprague-Dawley rats weighing 300-350 g were used. After randomization, two study groups were formed to receive hyaluronic acid (HA group: n=16) and high-dose vitamin C (VC group: n=16), and the remaining 16 rats were assigned as the control group. In each group, the rats were further divided into two equal subgroups to be sacrificed on Day 15 and Day 30.

The rats were placed in the supine position on the operating table and received inhalation anesthesia. The site of the operation was disinfected using a povidone-iodine cleansing solution (Betadine, Kansuke, Istanbul, Turkey). A straight skin incision was made on the left side starting 1 cm proximal to the calcaneal insertion of the Achilles tendon and extending in a longitudinal proximal direction 2-3 cm toward the caudal surface. After excision of the subcutaneous connective tissue and tendon sheath, the Achilles tendon was exposed. In all the rats, the left Achilles tendons were cut transversely 4-5 mm proximal to the calcaneal insertion with a number 11 scalpel blade (Plusmed, Turkey) and repaired using the modified Kessler technique with a PDO II 4/0 suture (BOZ, Ankara, Turkey). In the HA group, 0.075 ml/kg HA (Hyaloglide) was administered via a micropipette on the site of the tendon repair. The wound site was closed with 3/0 prolene (Dogsan, Istanbul, Turkey) and covered with a sterile dressing after application of povidone-iodine (Betadine, Kansuke, Istanbul, Turkey). High-dose vitamin C (Vitabiol C) was administered intraperitoneally with an insulin syringe on alternate days, starting after skin closure until sacrifice. The control rats received no medication after primary tendon repair.

None of the rats were immobilized postoperatively. Eight rats in each group were sacrificed with high-dose anesthesia on Day 15 and Day 30. The repaired Achilles tendons were removed with excision of the calcaneal and femoral condyle insertions. Of the eight repaired Achilles tendons in each subgroup, five samples were used for biomechanical measurement and three for histopathologic examination. To eliminate any confounding effect on biomechanical measurements, care was taken to not remove the plantaris tendon during removal of the Achilles tendon. All the samples were taken to the biomechanical laboratory on the day of removal in sterile containers. For histopathologic examination, each sample was placed in a sterile 10% formaldehyde solution and sent to our pathology clinic on the same day.

Biomechanical tests

To mount the tendon specimens onto the tensile test machine, tendon-muscle and tendon-bone regions were securely fixed between sandpaper sheets, which were then attached to the grips of the testing machine. The tendon specimens were stretched to failure along their long axis at a constant speed of 6 mm/min. During the tensile test, data on the tensile force were recorded and maximum force that led to tendon rupture was determined.[9]

Histopathologic study

All tendon specimens were fixed in 20 ml of 10% formalin for 24 hours, placed in tissue cassettes and then in closed sample-tracking equipment for processing in alcohol, acetone, xylene, and paraffin for dehydration. Paraffin blocks were then obtained and sectioned at 4μm. Sections were stained with hematoxylin-eosin (H-E), Masson's trichrome (MT), and alcian blue at pH 2.5. Stained slides were covered with a drop of fixing solution and closed with a lamella. The slides were interpreted semiquantitatively using Movin's grading scale and Bonar's scores.[10]

For Movin's grading scale, eight variables were examined, which included (1) fiber structure, (2) fiber arrangement, (3) rounding of the nuclei, (4) regional variations in cellularity, (5) increased vascularity, (6) decreased collagen stainability, (7) hyalinization, and (8) glycosaminoglycan (GAG) content. The first seven variables were assessed on the H-E stained slides and the GAG content was assessed on the alcian blue-stained slides. Each variable was graded between 0 and 3: normal (0), slightly abnormal (1), abnormal (2), and markedly abnormal (3). Total semiquantitative histologic scores varied between 0(normal tendon) and 24 (the most severe abnormality).

Four variables were scored in the Bonar system: (1) tenocytes, (2) ground substance, (3) collagen, and(4) vascularity. A four-point scoring system was used, from 0, indicating a normal appearance, to 3, indicating a markedly abnormal appearance. For each assessment, the total score varied between 0(normal tendon) and 12(most severe abnormality).

Statistical analysis

For descriptive statistics, data were expressed as mean, standard deviation, median, and the minimum value. Distribution of the variables was measured by the Kolmogorov-Smirnov test. Histopathologic findings were analyzed using the Kruskal-Wallis and Mann-Whitney U tests. For biomechanical findings, group differences were analyzed using the one-way analysis of variance. The differences were evaluated at a level of significance of 0.05. All statistical analyses were performed using the SPSS 22.0 statistical software package.

RESULTS

Biomechanical findings

In the biomechanical tests, the highest mean force value was observed in the HA group on Day 15, followed by the control and VC groups. (Figure 1) On Day 15, no significant difference was seen between the VC, HA, and control groups, with the exception of between the HA and VC groups (p=0.002). On Day 30, the VC group yielded the highest mean force value, followed by the HA and control groups. A significant difference was found between the control and VC groups (p=0.0162). In group comparisons between Day 15 and Day 30, remarkable improvement was seen in the VC group after Day 30 (p=0.00005). In addition, the maximum force value between Day 15 and Day 30 in the HA group increased significantly (p=0.0074).

Histopathologic findings

Total semiquantitative histologic Movin and Bonar scores assessed on Day 15 and Day 30 for the HA, VC, and control groups are shown in Table 1 and Table 2, respectively. When compared to the HA

and VC groups, the control group exhibited significantly higher total scores on Day 15 and Day 30 ($p<0.05$). However, no significant difference were seen in total Movin or Bonar scores between the HA and VC groups, on Day 15 or Day 30 ($p>0.05$).
Compared with the baseline (Day 15), decreases in both Movin and Bonar scores were observed in all the groups on Day 30. While these decreases were not significant in the control group, the total scores were significantly improved on Day 30 in both the HA and VC groups ($p<0.05$).

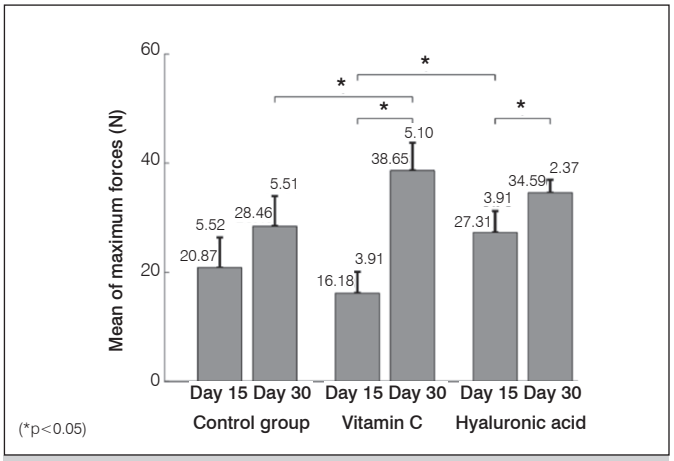

Figure 1. Mean of the maximum tensile force values of the tendons on Day 15 and Day 30.

Table 1. Semiquantitative Movin scores.

		Control group	Vitamin C	Hyaluronic acid	p
Day 15	Mean SD	18.3 0.6	12.0 0.0	13.3 1.2	0.032
	Median (Min-Max)	18.0 (18.0-19.0)	12.0 (12.0-12.0)	14.0 (12.0-14.0)	
Day 30	Mean SD	13.0 0.0	8.3 0.6	9.0 0.0	0.029
	Median (Min-Max)	13.0 (13.0-13.0)	8.0 (8.0-9.0)	9.0 (9.0-9.0)	
p for change between Day 15 and Day 30		0.051	0.034	0.034	

Kruskal-Wallis and Mann-Whitney U tests.

Table 2. Semiquantitative Bonar scores.

		Control group	Vitamin C	Hyaluronic acid	p
Day 15	Mean SD	10.0 0.0	8.0 0.0	8.7 0.6	0.029
	Median (Min-Max)	10.0 (10.0-10.0)	8.0 (8.0-8.0)	9.0 (8.0-9.0)	
Day 30	Mean SD	7.0 0.0	4.3 0.6	5.0 0.0	0.029
	Median (Min-Max)	7.0 (7.0-7.0)	4.0 (4.0-5.0)	5.0 (5.0-5.0)	
p for change between Day 15 and Day 30		0.100	0.025	0.025	

Kruskal-Wallis and Mann-Whitney U tests.

DISCUSSION

There is abundant literature on recovering maximum function after tendon repair, with particular focus on surgical techniques, application of exogenous agents to speed up healing, and the effect of comorbidities on tendon healing.[11] With respect to tendon repair and tendon healing, this present study is the first to examine the therapeutic effects of HA and vitamin C in both biomechanical and histopathologic aspects.
Derelioglu et al.[3] examined the effect of HA on tendon healing and found no beneficial effects on tendon resistance. In our study, HA showed a strengthening effect on tendon resistance.
Some experimental studies have reported notable reductions in postoperative adhesions after HA applications.[5,8,12] Dabak et al.[8] reported that rats treated with phospholipids and hyaluronic acid showed the lowest rates of adhesion, with no severe adhesions. In contrast, de Wit et al.[13] found no significant difference in adhesion formation between HA- and saline-treated rabbit tendons.
Derelioglu et al.[3] investigated the effects of HA, vitamin A, and vitamin E on tendon healing and adhesions and concluded that HA and vitamin A did not have a notable effect on the suppression of inflammatory response or the completion speed of the repair phase, while vitamin E was associated with a markedly reduced inflammatory response and more rapid achievement of mature collagen fibers and normal tendon structure. Greenwald et al.[14] reported that vitamins A and E played a beneficial role in tendon healing through their action on differentiation, migration, and proliferation of fibroblasts. Foland et al.[15] induced experimental tendinitis in horses and found that histopathologically, HA played a role in decreasing peritendinous fibrosis, fibroplasia, and anti-inflammatory response. Gaughan et al.[12] examined the effect of HA on tendon healing and adhesion formation in horses and found that HA reduced the number of inflammatory cells and the formation of new blood vessels, but did not have a notable effect on the development of normal tendon structure. In our histopathologic assessment, we also observed that high-dose vitamin C and HA had no effect on vascularity.
There are a large number of studies showing the benefits of HA associated with wound healing.[15] Yagishita et al.[16] found improved early tendon healing in rabbits treated with HA. De Wit et al.[13] compared HA- and saline-injected rabbit digital flexor tendons and reported significantly increased breaking strength on biomechanical testing, and significantly accelerated tissue repair upon histopathologic examination in HA-treated rabbits.
During the early inflammatory phase of wound healing, high concentration of HA leads to increased infiltration and cell proliferation in the wound area. CD45 immunohistochemical staining showed that the cells in the repair area were leukocytes, most likely fibroblasts. These fibroblasts produce collagen fibers which improve repair and bridging and thus increase the tensile strength of the damaged tendon.[13]
Collagen contains two amino acids, hydroxyproline and hydroxylysine, which are essential for molecular stability. When these amino acids are synthesized, enzymes serve as a catalyst and oxygen, iron ions, alpha-ketoglutarate, and ascorbic acid are also required. As a result of the production of hydroxyproline-free collagen polypeptides, unstable collagen molecules are created. Ascorbic acid is a cofactor needed for the function of the prolyl hydroxylase enzyme involved at this stage.[17]
Although collagen biosynthesis and baseline collagen levels are inversely correlated with age, the positive effect of ascorbic acid on collagen synthesis is independent of age. In ascorbate-induced collagen synthesis, regulation of collagen gene expression is directly and specifically activated, which is enabled by both increased collagen gene copy number and the stability of procollagen mRNA. Another mechanism which stimulates collagen gene expression is the increased malondialdehyde level, a product of elevated lipid peroxidation.[18]
The need for ascorbic acid in prolyl and lysyl hydroxylase activity during collagen biosynthesis is well known, and the importance of this vitamin is increasingly pointed out for matrix proteoglycan synthesis. An in vitro experimental study found that the optimal level of ascorbic acid to maintain flexor tendons from adult animals in organ culture with 48-h media would be more than 50 micrograms/ml.[19]
Another experimental study investigated the effect of local vitamin C injection on tendon adhesion and found that this vitamin reduced adhesions of healing tendons.[20] In our study, the role of vitamin C in reducing adhesions was not evaluated.
Omeroglu et al.[4] administered high-dose vitamin C for rat Achilles tendon healing and evaluated the histopathologic results. In

our study, we took their VC dose as a reference and found comparable results.

Unlike the studies in the literature, we not only conducted histopathologic analysis but also tested all the tendons biomechanically. The mean breaking forces were higher in the HA group on Day 15 ($p>0.05$) and in the VC group on Day 30 ($p<0.05$) than those of the control group. In-group comparisons indicated that the therapeutic effect of vitamin C on tendon healing was especially seen in the later period ($p=0.00005$). Moreover, the strength of the tendons in the HA group increased significantly from Day 15 to Day 30 ($p<0.05$). Our histopathologic findings showed a high correlation with the biomechanical results.

CONCLUSIONS

Our study demonstrated that both vitamin C and hyaluronic acid had therapeutic effects on tendon healing, especially in the late phase of tendon repair. Further experimental studies may provide more conclusive data for the use of these two substances in Achilles tendon injuries.

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ORIGINAL ARTICLE

PROSPECTIVE STUDY OF ASPIRIN FOR THROMBOEMBOLISM PROPHYLAXIS IN TOTAL HIP ARTHROPLASTY

ESTUDO PROSPECTIVO DA ASPIRINA COMO PROFILAXIA DO TROMBOEMBOLISMO EM ARTROPLASTIA TOTAL DO QUADRIL

Raul Carneiro Lins[1], Epitácio Leite Rolim Filho[1], Fernando de Santa Cruz Oliveira[1], Saulo Monteiro dos Santos[1], Tale Lucas Vieira Rolim[2], Flávio Kreimer[1]

1. Trauma and Orthopedics Service, Hospital das Clínicas, Department of Surgery, Universidade Federal de Pernambuco, Recife, PE, Brazil.
2. Orthopedics Service, Hospital Otávio de Freitas, Recife, PE, Brazil.

ABSTRACT

Objectives: To evaluate the effectiveness of aspirin as prophylaxis for deep venous thrombosis (DVT) in patients undergoing total hip arthroplasty (THA), and to analyze the incidence of bleeding during the post-operative period. Methods: This prospective study carried out in 2017 consisted of 37 patients indicated for THA with high risk for DVT. Immediately after the procedure, aspirin, elastic compression socks and early deambulation were initiated. Doppler ultrasound was performed in the legs 6 days and 6 weeks post-procedure to rule out venous thromboembolism. Hematometric variables and clinical criteria were used to detect bleeding. Results: The incidence of VTE (venous thromboembolism) 6 days post-procedure was 21.6%. By 6 weeks post-procedure, it dropped to 8.1%, ($p = 0.102$). Only 2.7% were diagnosed with VTE, 6 days and also 6 weeks post-procedure. Within the immediate postoperative period, hemoglobin was lower ($p < 0.001$), in contrast to 6 weeks after surgery, when it returned to baseline levels. Conclusion: Aspirin was an effective chemical prophylaxis for venous thromboembolism in high-risk patients who underwent THA. There was no clinical record of postoperative bleeding and hematometric levels suggested that there was no chronic bleeding. ***Level of Evidence II; Prospective study.***

Keywords: Arthroplasty, replacement, hip. Aspirin. Venous thrombosis/prevention & control.

RESUMO

Objetivo: Avaliar a eficácia da aspirina como profilaxia da trombose venosa profunda (TVP) em pacientes submetidos à artroplastia total de quadril (ATQ) e analisar a incidência de possíveis sangramentos no pós-operatório. Método: Este estudo prospectivo realizado em 2017 foi constituído por 37 pacientes, com indicação de ATQ, com alto risco de TVP. No pós-operatório imediato foram iniciadas administração de aspirina, uso de meias de compressão elástica e deambulação precoce. Realizou-se um ultrassom com dopplerfluxometria no 6º dia e na 6ª semana de pós-operatório para excluir tromboembolismo venoso. Para detectar sangramentos, foram usadas variáveis hematimétricas e critérios clínicos. Resultados: No 6º dia após o procedimento, a incidência de TEV (tromboembolismo venoso) foi 21,6% e na 6ª semana houve uma redução para 8,1% (p = 0,102). Apenas 2,7% foram diagnosticados com TVP tanto no 6º dia como na 6ª semana. No pós-operatório imediato houve uma redução da hemoglobina (p < 0,001), contrastando com a sexta semana de pós-operatório, quando esses níveis se elevaram para os níveis basais. Conclusões: A aspirina mostrou-se eficaz como profilaxia química da trombose venosa em pacientes de alto risco submetidos à ATQ. Não houve registro clínico de sangramento pós-operatório e os níveis hematimétricos sugeriram não ter havido sangramento crônico. ***Nível de Evidência II; Estudo prospectivo.***

Descritores: *Artroplastia de quadril. Aspirina. Trombose venosa/prevenção & controle.*

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INTRODUCTION

Total Hip Arthroplasty (THA) has become a standard treatment for patients with high level degenerative arthritis, providing improvements in these patients quality of life. It is estimated that, in the USA, 350.000 THA are performed every year.[1,2] In the UK, aproximately 70.000 surgeries of articular reconstruction using prosthesis are performed[3] and, in Brazil, a national data registry of the usage of prosthesis is being implemented in order to provide more concrete data regarding these surgeries.[4,5]

Among the most feared complications of the arthroplasty are the thromboembolic diseases (TED), such as deep venous thrombosis (DVT) and the pulmonar thromboembolism (PTE). Prior to the routine administration of prophylaxis to TED, the incidence varied from 40% to 60% of distal asymptomatic DVT (below the popliteal vein), 15% to 20% of proximal lower limbs thrombosis, and from 0,5% to 2% of PTE.[1,6-14] After the insertion of the utilization of prophylatic drugs, such as low molecular weight heparina, vitamin K inhibitors and

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Work conducted at the Department of Orthopedics and Traumatology, Hospital das Clínicas (UFPE). Av. Professor Moraes Rego s/n , Cidade Universitária , Recife, PE, Brazil. Correspondence: Rua Neto de Mendonça, 230, apto. 701, Tamarineira, Recife, PE, Brazil. 52050-100. raulclins@hotmail.com

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the brand new Xa factor inhibitors, a significant reduction in the distal asymptomatic DVT incidence was observed, decreasing to about 20%, and the symptomatics to 1-3%.[3,15,16]

On the other hand, the use of these medicines have led to an increased incidence of coagulation disturbs, with gastrointestinal or surgical site bleedings.[17-19] The routine administration of TED prophylaxis in patients undergoing THA is a consensus. However, until the present moment, neither the class of the drugs nor the time of use are well established for this matter.[1-6,16,20] The lack of multicentric studies, variety of protocols and different DTE risk factors among the patients make it difficult to standardize a ideal prophylaxis.[16,19]

The *American College of Chest Physicians* (ACCP), in their last update, in 2012, approved, for the first time, the isolated use of aspirin as TED prophylaxis in patients undergoing THA.[15,17-19,21] Among the advantages of aspirin there are the low cost, the easy access by the population in the public health system and the nonnecessity of keeping the patients hospitalized to monitor any coagulation disturbs that may occur, as in the use of warfarin.[9,20] Just like the ACCP, the *American Academy of Orthopaedic Surgeons* (AAOS) authorize the use of aspirin and recommends the mechanical prophylaxis associated with early deambulation for these patients.[8,9,11,20]

This study has the objetive to evaluate the efficiency of the isolated use of aspirin as prophylatic therapy in patients undergoing THA (high risk for TED), associated with early deambulation and elastic compression socks.

MATERIALS AND METHODS

Analytical prospective study carried out during the period bettween March and June of 2017, where 40 patients with cardiovascular risk among 1 and 2, based on Goleman criteria[22], were selected to realize THA. One patient were excluded because of an intraoperatory complication (acetabular fracture), and the other two were excluded because of non adhesion of the proposed prophylatic scheme. Provide that, we studied 37 patients with indication of THA, all of them with high TED risk, based on Caiafa and Bastos[23] criteria. The prophylatic scheme used consists of aspirin 650 mg per day, divided in two takes of 325 mg, with a 12 hours interval bettween them, during 30 days. The patients, after surgery, started the using of elastic compression socks, still in the post-anesthetic recovery room, and then they were oriented to deambulate, as soon as possible, already in the first post operative day. The selection of patients were determined by the Goldman criteria - reaching those characterized with cardiovascular risk bettween 1 and 2 - and by the Caiafa and Bastos criteria, including only those considered with high risk for TED[23]. We excluded patients with 3 or 4 goldman´s criteria, patients in previous use of anticoagulant drugs, recent gastrointestinal bleeding episodes, previous hematological diseases and revision surgeries. The risk factors for TED are presented in Chart 1.

The patients underwent to THA, under raquidian anesthesia, by the posterior lateral access, with the patients positioned in contralateral decubitus in relation to the operated side. After surgery, still in the post-anesthesia recovery room, the patients dressed the elastic compression socks, and after 12 hours aspirin was initiated, 650 mg divided in two takes of 325 mg, during 30 days. The deambulation were started and supervisioned by the physiotherapy team in the first post-op day, taking into consideration the pain as a potential limitant factor of the march. The criteria adopted to diagnose post operative bleedings were the ones recommended by the National Institute for Health and Care Excellence (NICE), which are patient death, more than 2 points decrease in hemoglobina, hemotransfusion of more than two units of red blood cells concentrates, necessity of surgical reassessment because of surgical site hematoma or retroperitoneal, cranial or thoracic bleeding.[24,25]

In the 6th post-operative day the patients underwent to a venous doppler ultrasound to check low deep venous thrombosis (below the popliteal vein), and they were examined to verify any signs of thromboembolic disease. The ultrasound exams were conducted by two radiologists with experience in ultrasonography with dopplerfluxometry, and every identified case of TED were confirmed by both of them. Considering the período of maximum incidence of TED in orthopaedic surgeries bettween the 6th and the 28th day after surgery,[15,25] the patients were submitted to another ultrasound exam, at the 6th week after surgery, by the same radiologists, using the same protocol, and they were interrogated regarding gastrointestinal or surgical site bleedings that may have occured. They have also collected blood samples to analyze hemoglobin and hematocrit levels.

Chart 1. Evaluation of DVT risk .

PROPOSED ASSESSMENT OF DVT RISK			
Protocol Screen			
1. Risk factors			
☐ General anesthesia	☐ COPD*	☐ Regional Ileitis	☐ Obesity
☐ Oral contraceptives	☐ Eclampsia	☐ Prolonged confinement to hospital bed (>3 days)	☐ IM paralysis
☐ Cancer*	☐ Large burns	☐ Limb immobilization	☐ Pre-eclampsia
☐ Long-term central venous catheter	☐ CHF	☐ Heart attack	☐ Puerperal
☐ Prolonged surgery	☐ Age >40 years	☐ Severe infection	☐ Chemotherapy
☐ Autoimmune disease	☐ Age >60 years*	☐ ICU hospitalization	☐ Ulcerative colitis
☐ Nephritic syndrome	☐ Trauma	☐ Severe trauma*	☐ HRT
☐ Large-diameter varicose veins	☐ None	☐ Other	
2. The following patients are considered as high risk of VTE			
☐ Major orthopedic surgeries of the hip/knee	☐ Stroke	☐ Transvesical prostatectomy	
☐ Major surgeries for cancer	☐ Thrombophilia		
☐ Spinal trauma	☐ Past history of DVT/PE		
3. Risk classification			
☐ Low (0 to 1 point)	☐ Medium (2 to 4 points)	☐ High (5 or more points)	

To diagnose TED, a qualitative variable were used: presence of venous clots below the popliteal vein, in only one or both lower limbs, symptomatics or not, confirmed by the two radiologists of the research team. On the other hand, to detect possible bleedings, caused by the aspirin, we took into consideration hematological quantitative variables: hematocrit and hemoglobin in the pre-operative, immediate post-operative and late post-operative period (6th week), besides the physical examination and the clinical history of gastrointestinal or surgical site bleeding referred by the patient.
This research Project was submitted for approval by the ethics committee in research with human beings of the *Centro de Ciências da Saúde (CCS)* of UFPE, and it was protocoled under the CAAE nº 66155517.2.0000.5208. The obtaining of the free and informed consent term was realized by the main researcher, including the steps contained in the document, following the orientations of the 466/12 resolution of the Health Ministry.
To analyze the data, we created a spreadsheet at Microsoft Excel, which was moved to a SPSS software, 18 version, where the analysis took place. To evaluate the demographic profile of the patients in this study, percentage frequencies of the studied variables were calculated and the frequency distributions were determined. For the quantitative variables, we calculated the following statistics: minimum, maximum, mean and standard deviation. The Chi-Square Test was applyed to compare the percentages that were found in the independente variables. The normality of the hemoglobin and hematocrit levels in the patients blood were evaluated by the Shapiro-Wilk Test, and, in those cases where the normality was indicated, we applied the Student Test for paired samples to compare the mean of hematocrit and hemoglobin levels relating to the pre-operative period, immediate post-operative period and late post-operative (6th week after surgery).
When comparing the prevalences of clots, we created a contingency table and applied the Exact Fisher Test. All of the conclusions were made taking into consideration the significance level of 5%.

RESULTS

The Table 1 presents the distribution regarding age and gender of the patients. The age varied form 18 to 71 with mean ± standard deviation (49,2 ±14,7). The majority is female19 (51,4%) with age up to 59 years old, mean of 26 (70,3%). The proportion comparation test was significant for the age factor (p-value= 0,014), indicating that the proportion of genders are similar. However, the percentage for each age group studied wasn't significant.
The Table 2 presents the prevalence of clots in the 6th post-operative day and at the 6th week after surgery. It was verified that in the 6th day there was a bigger prevalence of VTE (21,6%), despite there was a reduction at the 6th week to 8,1%. Although, the homogeneity test wasn't significant (p-value[1] = 0,102), indicating that the distribution of VTE in the 6th day and at the 6th week were similar. Furthermore, it was observed that, from the totality of patients, only 2,6% were diagnosed with DVT in both, the 6th day and at the 6th week after surgery.

Table 1. Patients distribution based on gender and age.

Factor	n	%	p-value
Gender			
Male	18	48,6	0,869
Female	19	51,4	
Age			
≤ 59	26	70,3	0,014
≥60	11	29,7	
Minimum-Maximum	18-71		-
Mean ± Standard deviation	49,2 ± 14,7		-

[1]p-valor for Chi-squared test to compare proportions (if p-value< 0.05, the level percentages for the evaluated characteristic differ significantly).

The Table 3 shows the descriptive analysis of hematocrit and hemoglobins levels based on the period of evaluation. It is observed that the hematocrit mean suffered a significant reduction bettween the pre and pos-op periods (mean of 39,81 in the pre-operative period decreases to 31,86 in the immediate post-operative period p-value < 0,001). On the other hand, at the 6th post-op week, there was a significant increment in the hematocrit mean (mean = 39,39, p-value < 0,001), getting statistically close to the pre-operative period numbers (p-value = 0,476). (Figure 1)
In relation to hemoglobin, there was a significant reduction in the immediate post-op (mean of 13,81 in the pre-op, and 11,10 in the immediate post-op, p-value <0,001), although, at the 6th post-op week, the hemoglobin levels raised (mean = 13,17, p-value = 0,001), but it remains statistically lower than the levels at the beginning of the treatment (p-value < 0,001). (Figure 2)
In the Table 4 we registered the distribution of the occurence of clots in the immediate post-op and at the 6th week. From the total, 8 patients (21,6%) presented clots in the immediate post-op, while only 3 cases (8,1%) were identified at the 6th post-op week. It was observed that the highest incidence of clots in the post-operative period occured in patients who were operated bilaterally (25%), when compared with the group that had only a one side surgery (21,7%).

Table 2. Prevalence of clots based on the studied period.

Factor	Period		p-value
	6th day	6th week	
VTE			
Yes	8(21,6%)	3(8,1%)	0,102
No	29(78,4%)	34(94,9%)	
DVT			
Yes	1(2,7%)	1(2,7%)	1,000
No	36(97,3%)	36(97,3%)	

[1]P-value from Chi-squared test for homogeneity.

Table 3. Descriptive analysis of hematocrit and hemoglobin leves between the pre-op, immediate post-op and late (6th week after surgery) post-operative periods.

Mean	Evaluation period		
	Pre-op	Immediate post-op	Late post-op
Hematocrit (HT)	39,81[a] ± 4,30	31,86 ± 3,93	39,39[a] ± 3,40
Hemoglobin (HB)	13,81 ± 1,38	11,10 ± 1,36	13,17 ± 1,29

[a] the means are statistically significant (p-value for Student's t-test = 0.476).

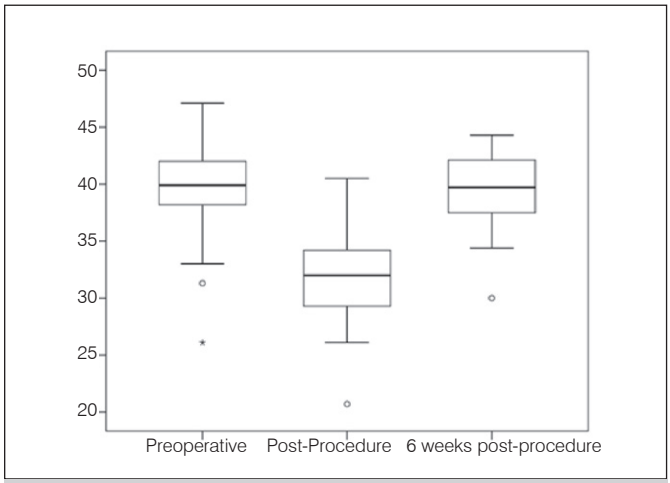

Figure 1. Box plot showing hematocrit level at the three assessment times.

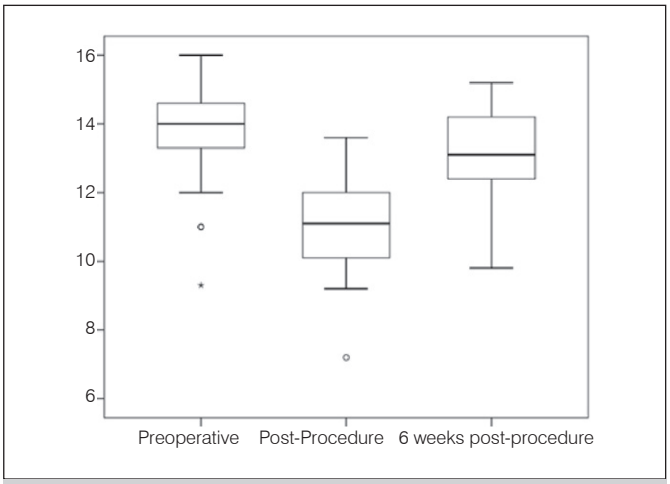

Figure 2. Box plot showing hemoglobin level at the three assessment times.

Table 4. Distribution of clots occurence in the 6th day and at the 6th week of the post-operative period.

Bilaterality	Clots 6th day		Clots 6th week	
	Yes	No	Yes	No
No	6(21,7%)	23(78,3%)	2(6,9%)	27(93,1%)
Yes	2(25,0%)	6(75,0%)	1(12,5%)	7(87,5%)
p-value	1,000		0,530	

[1]P-value for Fisher's exact test (if p-value < 0.05 the prevalence of clots differs bilaterally and unilaterally among groups).

However the independency test wasn't significant (p-value= 1,00), demonstrating that the prevalence of clots in both groups are similar. There wasn't any episodes of surgical site bleeding, nor even any bleeding signs according to the NICE criteria.

DISCUSSION

The non-standardization of multicentric studies, the heterogeneity of the studied groups and the variety of options for chemical and mechanical prophylaxis are some of the factors that collaborate to the absence of a consensus regarding the ideal and universal prophylaxis for patients undergoing total hip arthroplasty. [1-3]
Chari et al.,[26] in 2012, presented a meta-analysis study, comparing several protocols that exists in different countries, and concluded that there isn't a consensus about the ideal method for TED prophylaxis in patients undergoing THA, with different levels of recommendation regarding the chemical agentes, period of use and clinical criteria.
Aiming to turn the sample of our study more homogeneous, we selected patients with cardiovascular risks bettween 1 and 2, based on Goldman criteria,[22] and, according to the Caiafa and Bastos criteria[23], published in 2001, all of them were considered high risk for thromboembolic diseases. Besides, none of the selected patients presented previous history of neither gastrointestinal bleeding nor use of anticoagulants.
The use of aspirin as chemical prophylaxis for thromboembolic events in patients undergoing total hip arthroplasty is being reported as successful since the decade of 1990. McCardel et al[27] published, in 1990, a prospective work, using aspirin as prophylaxis and a Doppler ultrasound for screening of clots in lower limbs. They found an incidence of deep venous thrombosis of 5,7% in 159 patients submitted to THA. In our study, with a similar methodology, we found 2,7% of deep venous thrombosis in the 6th post-operative day and, also, at the 6th week.
Ibrahim et al.,[28] analyzed retropectively more than 28 thousand patients submitted to THA, comparing the use of aspirin and warfarin. They concluded that both drugs were equivalent in the VTE prophylaxis, but the aspirin presented a lower incidence of bleeding related complications than the warfarin. In our study, there wasn't any registry of bleeding related complications – such as gastrointestinal or surgical site bleeding – and, after 6 weeks of the surgery, hematocrit and hemoglobin levels have returned to the pre-operative levels.
An et al[20] published, in 2015, a meta-analysis about the prophylatic use of aspirin during the post-operative period of arthroplasty. They found a DVT incidence of 1,2%, and 0,3% of bleeding. In the present study, we found a DVT incidence of 2,6% in both the 6th day and at the 6th week (one case). Considering the incidence of VTE in the 6th post-op day, we identified, by a Doppler Ultrasound, 8 (21,6%) cases, and, at the 6th week, only 3 (8,1%) cases were diagnosed, showing the resolution of five of the previously identified clots.
We are aware that the small population of the study and the lack of a group control are limitant factors of our study. However, we worked to turn the group the most homogeneous possible in terms of variables related to the epidemiological profile of the patients. The lack of bleeding episodes confers safety to the use of aspirin as a prophylatic drug in the post-operative period of total hip artrhoplasty.

CONCLUSIONS

Our study recommends the use of aspirin as the chemical prophylatic agent for venous thromboembolism in patients undergoing total hip arthroplasty, associated with the use of mechanical prophylaxis and early deambulation – started in the first 24 hours after surgery (immediate pos-operative period).

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. RCL (0000-0001-5133-2118)* and FSCO (0000-0002-3178-1036)*: were the main contributors in drafting the manuscript. RCL, SMS (0000-0002-0436-2012)*, FSCO, and TLVR (0000-0001-8450-9805)*: performed the surgery, followed the patients, and gathered clinical data. ELRF (0000-0003-1305-6620)*, FK (0000-0001-6164-9987)*, and SMS evaluated the data from the statistical analysis. RCL, FSCO, TLVR, ELRF, FK, and SMS conducted the bibliographic research and revised the manuscript. All authors contributed to the intellectual concept of the study and approved the final version of the manuscript. *ORCID (Open Researcher and Contributor ID).

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ORIGINAL ARTICLE

CLINICAL MUSCULAR EVALUATION IN PATELLOFEMORAL PAIN SYNDROME

AVALIAÇÃO CLÍNICA MUSCULAR NA SÍNDROME DE DOR PATELOFEMORAL

Paulo Lobo Júnior[1], Itamar Alves Barbosa Neto[1], José Humberto de Souza Borges[1], Rodrigo Ferreira Tobias[1], Marcos Vinícius da Silva Boitrago[1], Márcio de Paula Oliveira[1]

1. IPE-HOME, Hospital Ortopédico e Medicina Especializada, Brazilia, DF, Brazil.

ABSTRACT

Objective: To define a profile of the muscle groups affected by patellofemoral pain syndrome (PFPS) to determine a pattern of functional weaknesses around the knee. Methods: Sixty-three female patients were randomly selected, and 17 included in this study, receiving a clinical evaluation with pre-established protocol which evaluated the quadriceps, abductors, range of motion in the internal rotators and ankle dorsiflexors, pelvic tilt, and dynamic valgus. Results: Losses were seen in abductor strength and ankle dorsiflexor range of motion in comparison with the contralateral limb (0.031 and 0.040, respectively). There was a loss of quadriceps strength and decreased amplitude of internal hip rotation when compared to the Kujala score (0.032 and 0.002, respectively). Dynamic valgus and pelvic fall were greater in comparison with the Kujala score (0.668 and 0.567, respectively). Conclusion: Clinical evaluation showed deficits in the quadriceps and abductor muscle groups, as well as decreased range of motion in the internal hip rotators and ankle dorsiflexors and increased dynamic valgus and pelvic drop. ***Level of Evidence IV; Case series.***

Keywords: Patellofemoral pain syndrome/physiopathology. Patellofemoral pain syndrome/therapy. Knee joint. Muscle, skeletal/physiology.

RESUMO

Objetivo: Definir o perfil de acometimento de grupos musculares envolvidos na síndrome de dor patelofemoral (SDPF) a fim de determinar um padrão de fraqueza funcional em torno do joelho. Métodos: Foram selecionados randomicamente 63 pacientes do sexo feminino, dos quais 17 foram incluídos no trabalho e submetidos a uma avaliação clínica com protocolo preestabelecido que avaliou quadríceps, abdutores, amplitude de movimento de rotadores internos e dorsiflexores de tornozelo, além de inclinação pélvica e valgo dinâmico. Resultados: Houve déficit de força de abdutores e diminuição de amplitude do movimento de dorsiflexores de tornozelo em comparação com o membro contralateral (0,031; 0,040, respectivamente). Houve déficit de força de quadríceps e diminuição de amplitude de rotação interna do quadril quando em comparação com o escore de Kujala (0,032; 0,002, respectivamente). Verificou-se aumento do valgo dinâmico e queda pélvica com relação ao escore de Kujala (0,668; 0,567, respectivamente). Conclusões: Após avaliação clínica dos pacientes incluídos, observaram-se déficits dos seguintes grupos musculares: quadríceps e abdutores, além da diminuição da amplitude de movimento de rotadores internos do quadril e dorsiflexores de tornozelo; por fim, foram identificados aumento do valgo dinâmico e queda pélvica. ***Nível de Evidência IV; Série de casos.***

Descritores: *Síndrome da dor patelofemoral/fisiopatologia. Síndrome da dor patelofemoral/terapia. Articulação do joelho. Músculo esquelético/fisiologia.*

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INTRODUCTION

The yearly incidence of anterior knee pain reaches 22 out of every 1000 randomly selected people,[1,2] approximately 17 of whom are young women.[1-3] Patellofemoral pain syndrome (PFPS) has a broadly discussed terminology due to the variety of symptoms it presents; this condition is also known as runner's knee, patellar pain, patellar chondropathy, patellar overload syndrome, and patellofemoral pain.[4,5] Furthermore, PFPS is a diagnosis of exclusion, after discarding other pathologies that may cause anterior knee pain, such as degenerative, structural, mechanical or neurological pathologies.[5,6]

The etiology of PFPS is multifactorial; notable components include impairment of neuromuscular control of the trunk, pelvis, and legs during functional activities, particularly with regard to the imbalance of forces involved in the musculature around the knee.[7] Moller et al.[8] found an unbalance between the quadriceps and the hamstrings in patients with PFPS compared with a control group when assessing muscle activities via electroneuromyography.

All authors declare no potential conflict of interest related to this article.

Work conducted at the Hospital Ortopédico e Medicina Especializada, Brasília, DF, Brasil and Centro de Ensino Unificado de Brasília, Brasília, DF, Brasil.
Correspondence: Itamar Alves Barbosa Neto. QRSW 6, BL A03, Apto. 305, sudoeste Brasília, DF, Brazil. 72445-060. neto_itamar@yahoo.com

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Currently, neuromuscular training has been gaining prominence as an excellent technique for use in clinical practice, but there is no consensus in the literature as to a specific method for neuromuscular training or even until what point neuromuscular imbalance can lead to anterior knee pain. Consequently, many authors have emphasized exercises to strengthen the vastus medialis obliquus (VMO).[9] But Cerny[10] reported that exercises strengthening the vastus lateralis were as important as those strengthening the VMO.

The objective of this study is to define a profile of muscular involvement and mechanical changes involved in PFPS in order to determine a pattern of involvement for functional weaknesses around the knee, optimizing future training protocols to treat PFPS.

MATERIALS AND METHODS

We randomly selected 63 female patients; of these, 17 with knee pain were effectively assessed after the exclusion criteria were carefully applied. All patients underwent magnetic resonance imaging (MRI) and were evaluated by the same team composed of three orthopedic physicians and two physiotherapists.

The inclusion criteria were: female patients between eighteen and forty-five years with anterior knee pain. The exclusion criteria were: any degenerative changes of the knee or hip, history of patellar dislocation, clinical evidence of knee instability, meniscal or other intra-articular injuries, evidence of edema, Osgood-Schlatter disease or Sinding-Larsen-Johanssen syndrome, patellar tendinopathy, chondral injury, osteoarthritis, neurological involvement affecting the gait, joint or muscle injuries in the hip, lumbar pain, sacroiliac pain, patients who previously received surgical treatment in the knee or hip joints, and bilateral complaint of anterior knee pain, since all patients were assessed in comparison with the healthy knee.

Within the sample group, muscular strength was assessed in the abductors (SA), in the external rotators of the hip (SEHR), and the quadriceps (QS). A calibrated Hand Held MicroFET 2 manual dynamometer (Hoggan Scientific, Salt Lake City, USA) was used to assess these parameters. Range of motion was assessed via ankle dorsiflexion (RAD) and internal rotation of the hip (RIHR). A calibrated AM-2 angle meter (Starrett, Athol, MA, USA) was also used.

The EVA and Kujala scores were calculated, in addition to the degree of dynamic valgus and pelvic drop.

Each calculation was repeated three times and the average of these values was used.

The results were statistically evaluated by the most appropriate method, using SPSS software (IBM, Armonk, NY, USA). All tests were performed at a 5% significance level.

This study was approved by the Brasil Platform for ethics in human research (CAAE: 60238116.9.0000.0023) and an informed consent form was signed by all patients.

RESULTS

Clinical evaluation of the groupings in which muscular strength was measured showed only a loss of strength in comparison with the contralateral knee, with a statistically significant result (0.031) for the abductors. (Table 1)

When range of movement was assessed, loss was seen in RAD (0.040), as demonstrated in Table 1.

Comparison of dynamic valgus and pelvic drop correlated to the Kujala score (0-100; the lower the score, the greater the weakness of the knee) showed statistically significant results (0.668 and 0.567, respectively). (Table 2) According to the B coefficient (linear regression coefficient) for each grade plus the difference between the mean averages for the legs in dynamic valgus or pelvic drop, there was a decrease of 1.502 and 2.544 times that of the Kujala score, respectively. (Table 2)

There was a loss in QS and decrease in RIHR when these variables were correlated to the Kujala score (0.032 and 0.002, respectively).

Table 1. Difference between mean values for lower limbs.

Difference between mean values for lower limbs.			
	Contralateral side	Affected side	Sig***
RAD*	41.17	39.83	0.040
SA**	23.26	21.03	0.031
The level of significance is 0.05, according to the Wilcoxon test for related samples			

*=amplitude of movement in ankle dorsiflexion; **= abductor strength; ***= Significance.

Table 2. Relation between difference in the means between lower limbs and Kujala score.

Relation between difference in the means between lower limbs and Kujala score.		
	B*	Sig ****
Pelvic Drop	-2.544	0.010
Dynamic Valgus	*-1502	0.003
QS**	0.714	0.032
RIHR***	1.133	0.002

*= relationship is inversely proportional between Kujala score and variable; **= quadriceps strength; ***= Amplitude of internal hip rotators; ****= significance.

(Table 2) According to the B coefficient, for each degree reduced between the mean difference for each leg in RIHR or for each Newton of force reduced in the difference between the mean QS values, there was a 1.133 and 0.714-fold reduction in the Kujala score, respectively.

DISCUSSION

PFPS is known to involve anterior knee pain without any chondral changes in the femoropatellar joint, according to Petersen et al.[11] Muscle imbalance is believed to be one of the main factors that increases the risk of PFPS.[4,12-15] This fact is confirmed by the results of this study, which found a significant reduction in SA and QS.

Recent studies have shown that PFPS does not appear in the knee joint, but rather in the decreased amplitude of internal rotation of the femur, due to weakness of the hip abductors (gluteus medius and minimus muscles).[16-20] Both of these results were statistically determined in this study.

Weakness of the gluteus medius and minimus muscles causes pelvic instability, and consequently the patient cannot support the pelvis for one minute while standing on the affected leg, thus determining pelvic drop, as reported by Petersen et al.[11] Moreover, weakness in these muscles lead to internal rotation of the femur, thus decreasing RIHR. These statements were confirmed by the assessment of pelvic angle in this study.

Besides pelvic instability, weakness of the hip muscles causes a leg alignment known as dynamic valgus.[21,22] This biomechanical and muscular mechanism may be strongly linked to the pathogenesis of PFPS.[11,23,24] This assessment pattern (dynamic valgus) was seen to have a strong influence on the pathogenesis of PFPS in our results (0.003).

To the best of our knowledge, no single assessment combining results related to the muscular forces around the knee and the biomechanical changes that corroborate with the etiology of PFPS can be found in the recent literature. Although we effectively evaluated 17 patients, a number that could represent bias in our results, this bias was minimized by the regularity and expressive statistical results of the evaluated parameters, and our study was strengthened by the selective exclusion method applied.

Understanding PFPS is absolutely essential in order to be able to treat this condition, and our results can guide future training efforts for treatment.

CONCLUSIONS

Patients with PFPS in this study demonstrated a reduction in SA, decrease in RIHR and reduction of RAD, and increase in pelvic tilt and dynamic valgus.

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. IABN (0000-0002-0738-3716)*, RFT (0000-000157390693)*, PLJ (0000-0001-7625-710x), and JHSB (0000-0002-9667-8128)*: were the main contributors in drafting the manuscript. MVSB (0000-0001-7455-3183)* and MPO (0000-0003-3147-5925)*: conducted the physical therapy evaluation, accompanied the patients, and gathered the clinical data. PLJ and JHSB evaluated the patients who met the inclusion criteria in the outpatient clinic. IABN and RFT evaluated the data from the statistical analysis. IABN, RFT, PLJ, and JHSB conducted the bibliographic research and revised the manuscript. All authors contributed to the intellectual concept of the study and approved the final version of the manuscript. *ORCID (Open Researcher and Contributor ID).

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ORIGINAL ARTICLE

TECHNICAL VARIATION IN AFFIXING HAMSTRING GRAFTS TO THE TIBIA IN ACL RECONSTRUCTION

VARIAÇÃO TÉCNICA PARA FIXAR O ENXERTO DE TENDÕES FLEXORES À TÍBIA NA RECONSTRUÇÃO DO LCA

Marcus Vinicius Danieli[1], João Paulo Fernandes Guerreiro[1], Alexandre Oliveira Queiroz[1], Carlos Roberto Padovani[2]

1. Hospital Uniorte and Hospital Santa Casa de Londrina, Londrina, PR, Brazil.
2. Instituto de Biociências da Unesp de Botucatu, Botucatu, SP, Brazil.

ABSTRACT

Purpose: To present a technical variation in tibial fixation of quadruple hamstring grafts during anatomic reconstruction of the anterior cruciate ligament (ACL). The secondary purpose was to decrease the costs associated with this procedure. Methods: Twenty patients who underwent ACL reconstruction were selected. A tibial tunnel was constructed using standard techniques, and a femoral tunnel was anatomically created using the outside-in technique. The hamstring autograft was passed (with its bend) into the tibial tunnel and affixed to the tibia using the suspensory technique and a simple staple. Femoral fixation was performed using a titanium interference screw. The patients underwent postoperative evaluations at 0, 3, 6 and 12 months using the subjective International Knee Documentation Committee (IKDC) form and Lysholm knee scores. Results: The IKDC and Lysholm score results improved over time ($p<0.001$) without major complications. The cost of the procedure could be reduced by using lower-cost hardware (staples). Conclusion: The proposed technique for anatomic ACL reconstruction using inverted hamstring grafts with their bend in the tibial tunnel, suspension-type fixation using a staple demonstrated good to excellent results after 1 year of follow up, with lower aggregate costs. ***Level of Evidence IV; Case series.***

Keywords: Anterior cruciate ligament reconstruction. Tendons. Orthopedic fixation devices.

RESUMO

Objetivo: Apresentar uma variação técnica na fixação do enxerto quádruplo de tendões flexores à tíbia na reconstrução anatômica do ligamento cruzado anterior (LCA). O objetivo secundário é diminuir o custo associado ao procedimento. Métodos: Foram selecionados 20 pacientes que seriam submetidos à reconstrução do LCA. O túnel tibial foi realizado usando técnica padrão, e o túnel femoral foi realizado pela técnica anatômica de fora para dentro. O enxerto (tendões flexores autólogos) foi passado com sua dobra dentro do túnel tibial e fixado com um agrafe simples pela técnica de suspensão. A fixação femoral foi realizada com parafuso de interferência de titânio. Os pacientes foram avaliados no pré-operatório e aos 3, 6 e 12 meses pós-operatórios usando o questionário International Knee Documentation Committee (IKDC) subjetivo e o questionário de Lysholm. Resultados: Os resultados dos escores dos questionários IKDC e Lysholm tiveram sempre melhora com o tempo ($p < 0,001$) sem maiores complicações. O custo total da cirurgia foi reduzido usando material de custo menor (agrafe). Conclusão: A técnica proposta para reconstrução anatômica do LCA com enxerto de tendões flexores invertido com sua dobra no túnel tibial, com fixação tipo suspensão com um agrafe, mostrou bons a excelentes resultados após 1 ano de acompanhamento, com menor custo agregado. ***Nível de Evidência IV; Série de casos.***

Descritores: *Reconstrução do ligamento cruzado anterior. Tendões. Dispositivos de fixação ortopédica.*

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INTRODUCTION

Anterior cruciate ligament (ACL) injuries are frequent in active young people and can potentially cause instability and reduce knee function.[1] Surgical treatment is recommended when patients complain of instability and to prevent associated injuries.[2] This treatment is so widely accepted that approximately 100,000 ACL reconstructions are performed each year in the United States,[3] and more than 90% of these surgeries yield good to excellent results.[4]

Cournapeau et al.[5] showed that much of the costs of ACL reconstruction are related to disposable arthroscopy materials and implants; the high incidence of this procedure consequently raises concerns about its costs. In Brazil, the Unified Health System (Sistema Único de Saúde, SUS) pays R$ 486.00 for a titanium interference screw (source: personal contact with SUS suppliers, checked against payment receipts on November 29, 2017). Using the data on incidence in the United States as an example (since

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Work conducted at the Santa Casa de Londrina Hospital, Londrina, PR, Brazil.
Correspondence: Av. Higienópolis 2600, Guanabara, Londrina, PR, Brazil. 86050-000. mvdanieli@hotmail.com

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these data are not available in Brazil), the total cost of using two interference screws in each ACL reconstruction is approximately R$ 97.2 million per year.

Until recently, the most common technique used in ACL reconstruction was based on tunnel isometry,[6] creating the femoral tunnel through the tibial tunnel. However, this technique does not place the graft in the original anatomical position of the ACL.[6-9] Placing the ACL graft in the original position can restore the original anatomy and biomechanics of the ligament, and this technique has been shown more effective in stabilizing rotational movements of the knee.[6,8]

This study proposes anatomic reconstruction of the ACL using flexor tendons, creating an outside-in femoral tunnel. In the tibia, a variation of the graft fixation technique uses the principle of suspension with a simple staple, reducing the cost of surgery. The objective of this study is to demonstrate that this technique is simple, reproducible, effective, and involves lower aggregate costs.

MATERIALS AND METHODS

The study was approved by the institutional review board (record No. 381/11), and all patients signed an informed consent form before inclusion in the study.

Between January 2011 and January 2012, 20 patients agreed to participate in the study. Inclusion criteria were patients between 18 and 45 years old with ACL injuries treated at the authors' outpatient clinic. Patients were excluded if they had arthritis, previous surgery, deformity, or associated injuries to other ligaments in the affected knee, or any injury to the other knee.

Surgical Technique: After spinal anesthesia, the semitendinosus and gracilis tendons were removed using the standard technique. Arthroscopy is then performed, and associated injuries are treated if necessary. Next, with the knee at 90º flexion, the standard tibial guide for ACL reconstruction was positioned in the center of the remaining tibial ligament through a medial portal at a 55º angle, and a guide wire inserted. A tunnel measuring 8 to 9 mm (according to the thickness of the graft) was then drilled. After this, with the knee remaining at 90º flexion, the camera was inserted through the medial portal and the same standard ACL tibial guide was inserted through the lateral portal to create the femoral tunnel in an outward-to-inward direction. (Figures 1 and 2) The guide was held at a 60º angle; the entry is approximately 2 cm proximal and 2 cm anterior to the lateral epicondyle of the femur, as described by Lubowitz et al.[10] Next, a guide wire was introduced and a tunnel created with the same diameter as the one in the tibia. The graft was passed from the femur to the tibia, with the fold facing downward, and subsequently attached to the tibia using the suspension technique at the tunnel exit and a simple, smooth staple. Note that the staple does not compress the graft against the bone, but only fixates the suspension. (Figure 3) Traction was then exerted on the graft with the knee at 30° flexion (to "pull" the tibia and reduce the anterior draw), (Figure 4) and the graft was then attached to the femur with an interference screw from the outside in.

Standard rehabilitation protocol was used in all patients, with immediate therapy recommended. Partial load with crutches was permitted for 10 to 15 days after surgery, and patients were evaluated at 10 days. Pain, knee-related symptoms, physiotherapy protocol, range of motion, stability (anterior drawer test, pivot shift, Lachman, valgus and varus), meniscal symptoms, limb alignment, and overall function were evaluated monthly.

Subjective IKDC (International Knee Documentation Committee) and Lysholm questionnaires were applied during the pre-operative period and at 3, 6, and 12 months post-surgery, and scores were calculated and recorded.

Multivariate analysis of variance was used for the repeated measurement model, along with Bonferroni's multiple comparison test,[11] considering 5% significance.

RESULTS

Mean patient age was 29.95 years, and the sample was composed of 17 men and 3 women. A total of 12 right knees and 8 left knees were included. Associated injuries were as follows: 14 cases of medial meniscal injury, 7 lateral meniscus injuries, 7 patients with chondral injury, and 3 with isolated ACL injury. (Table 1)

Three patients (15%) were lost to follow-up (two prior to 3 months post-procedure and 1 after 3 months). The data for these patients were excluded.

The results (scores) for the IKDC and Lysholm questionnaires at 0, 3, 6, and 12 months are shown in Tables 2 and 3. The results showed significant improvement over time ($p<0.001$).

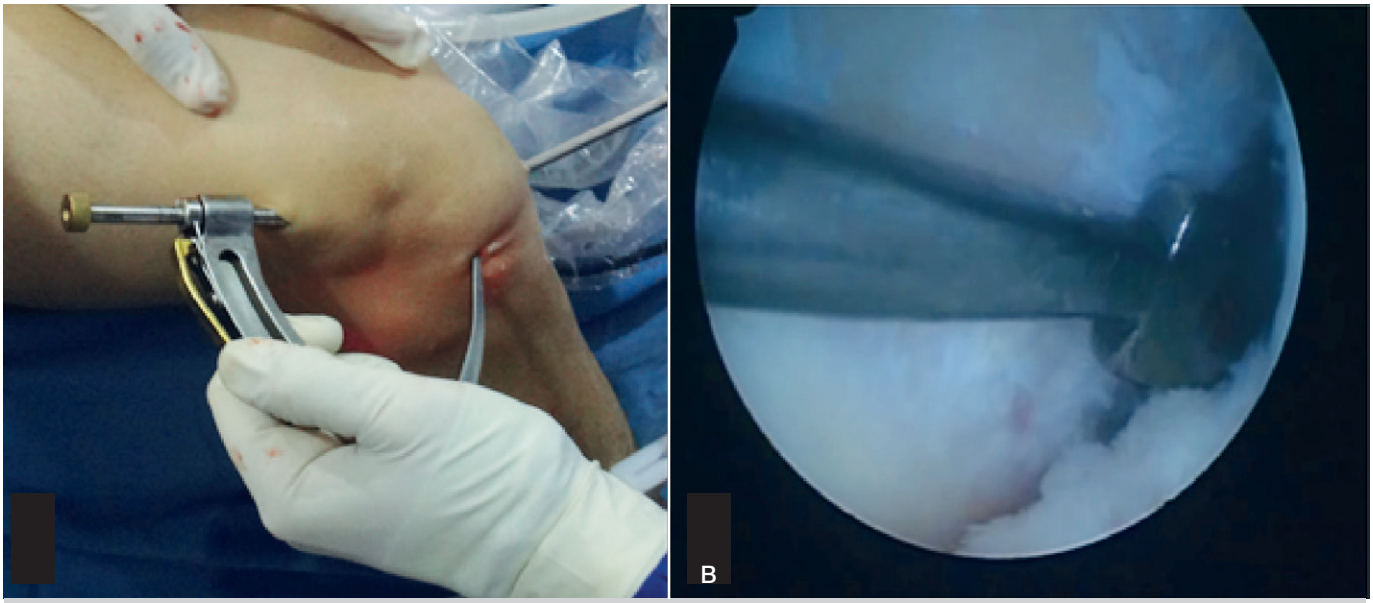

Figure 1. Tibial guide for the ACL, placed through the anterolateral portal to create the outside-in anatomic femoral tunnel (A). Intra-articular view (B). Right knee.

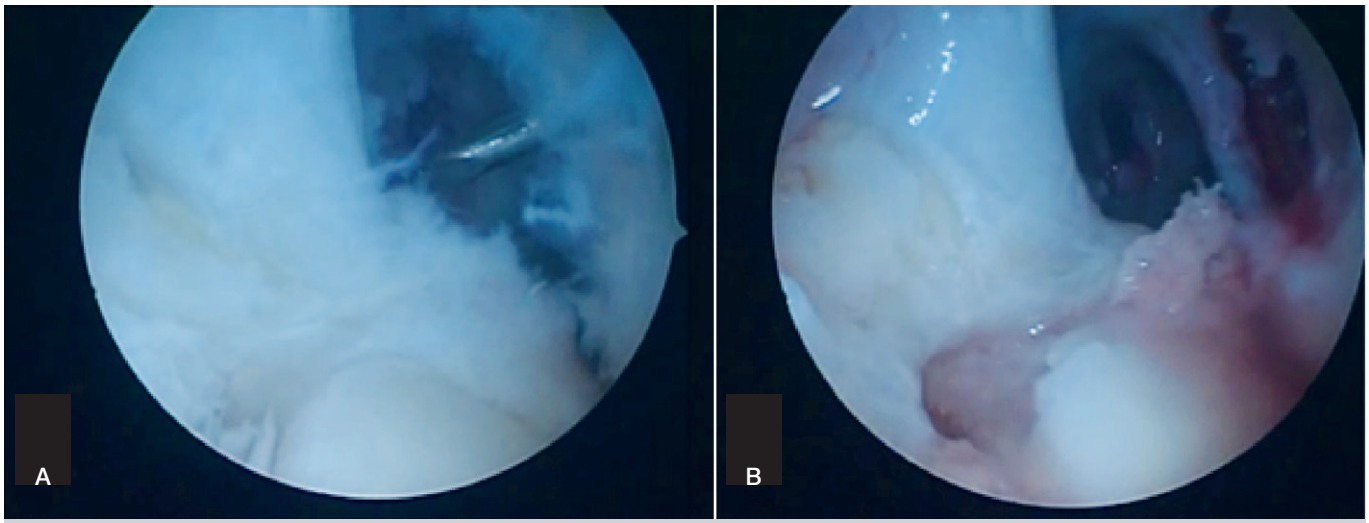

Figure 2. Femoral guide wire placed using the outside-in technique (A). Femoral and tibial tunnels - arthroscopic view (B). Left knee.

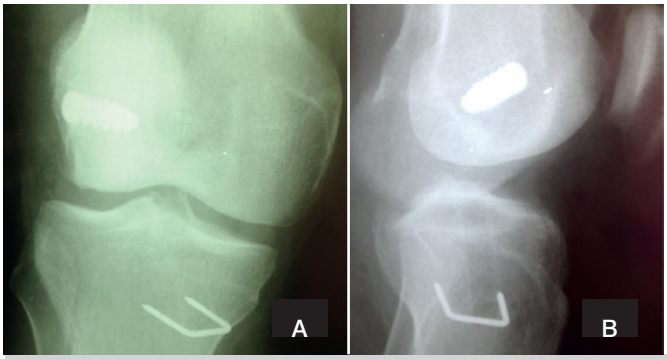

Figure 3. Postoperative X-rays: (A) AP and (B) lateral views showing tibial fixation with staple (right knee).

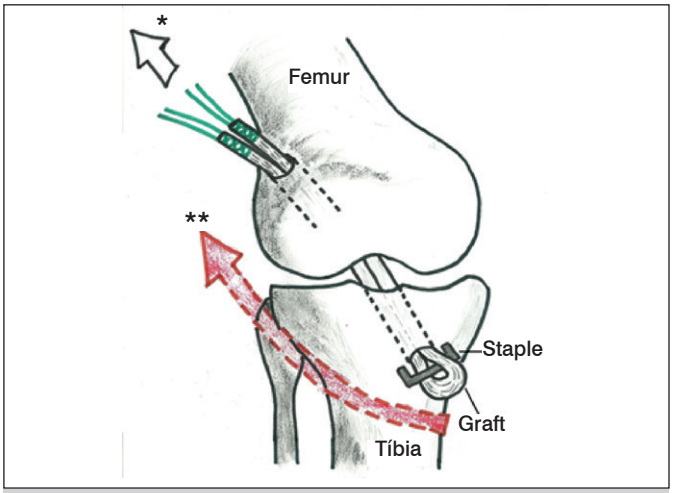

Figure 4. Illustration showing tibial fixation of the graft with a staple (inverted graft and suspension technique) in a right knee. Graft traction (*) and reduction of anterior draw (**).

Table 1. Age, sex, side, and associated injuries for each patient.

Patient	Age	Sex	Side	Associated injuries
1	18	M	R	MM
2	20	M	R	MM + LM + Chondral
3	19	M	R	MM + Chondral
4	35	M	L	MM + LM + Chondral
5	40	M	R	MM
6	21	M	L	Chondral
7	42	M	L	MM + Chondral
8	30	F	R	LM
9	31	M	R	
10	35	M	L	MM + LM + Chondral
11	45	M	L	MM
12	23	F	L	
13	34	M	R	MM + LM
14	17	M	L	MM + Chondral
15	34	M	R	LM
16	25	F	R	MM
17	36	M	R	
18	43	M	L	MM + LM
19	21	M	R	MM
20	30	M	R	MM

MM: Medial meniscus; LM: Lateral meniscus.

Table 2. IKDC questionnaire scores (mean and standard deviation) according to evaluation time.

		Evaluation Time			
	Pre-op	3 m post-op	6 m post-op	12 m post-op	P
IKDC	41.65 (4.74)	58.65 (3.11)	86.94 (2.08)	90.88 (2.30)	p<0.001

Table 3. Lysholm questionnaire scores (mean and standard deviation) according to evaluation time.

		Evaluation Time			
	Pre-op	3 m post-op	6 m post-op	12 m post-op	P
Lysholm	63.00 (5.75)	80.26 (7.87)	90.89 (5.14)	94.61 (2.79)	p<0.001

In terms of complications, two patients had limited extension (3º and 5º) compared with the normal side. However, this limitation did not compromise results during the evaluation period.
All patients returned to their pre-injury activity levels without major complaints such as pain, instability, insecurity, or muscle deficit. No patient had graft rupture as of the time of the last evaluation.

DISCUSSION

During the first 4 weeks after ACL reconstruction, graft fixation is the weak link, and bone density plays an important role in this factor.[12] Because its bone is spongy and denser than the tibia, fixation of the femur generally presents greater resistance.[13] Additionally, femoral fixation may be transverse or suspension-type, both of

which are more resistant than the techniques more commonly used in the tibia, which in turn mostly involve compression with interference screws.[14,15] This weakness can be compensated by fixation using suspension in the tibia, thus increasing resistance of the fixation in the immediate postoperative period, which is essential for safe rehabilitation and to allow the graft to integrate. This study demonstrated that this is possible using simple fixation material.

The technique described was possible because of the inverted folds in the graft, placing it within the tibial tunnel. This option was first described by Howell and Taylor,[16] but even though these authors also used simple fixation materials, they described a more laborious type of graft fixation.

During anatomic reconstruction of the ACL, the femoral tunnel can be created by either the medial or medial accessory portals (transportal technique) or from the outside in.[7,9,17-20] Cadaver studies have shown both techniques to be biomechanically similar.[7,8,18,19] For the transportal technique, the tunnel must be created with the knee at approximately 110º flexion, and the medial femoral condyle should be protected to prevent a short tunnel and chondral injury.[17] The outside-in technique has the advantage of better accuracy in positioning, with less risk of rupturing the posterior cortex of the femur (blow-out).[7,8,17,20] The disadvantage of this technique is cosmetic, the need for an additional yet small incision.[7,17] The outside-in technique was selected in this study, and none of the patients complained of the extra scar.

Another important technical detail is that the graft is first fixed to the tibia. It is then pulled, and finally secured to the femur. The advantage is reduction of anterior draw without the need for other maneuvers, because the graft transmits the traction and pulls the tibia. (Figure 4) This fixation sequence is theoretically more logical and biomechanically superior. However, this superiority must be confirmed through future biomechanical studies.

Cost of the procedure is an important factor due to the high incidence of this type of surgery. The most common fixation method in the Brazilian public health system (SUS) utilizes titanium interference screws (one for the tibia and another for the femur). SUS pays R$ 486.00 for each of these screws, and R$ 25.00 for a simple, smooth staple; as a result, replacing one of these screws with a staple saves R$ 461.00 per surgery. This practice reduces the final cost of the procedure and contributes to the country's economy.

Limitations

First, even though one year is a short follow-up period, the main objective of this study was to prove that the technique is easy and effective, with good to excellent results. Although the sample size was small, the results showed significant improvement over time. Another weak point is the absence of a control group. Sample size was also not calculated. Objective results were not presented, but all patients who completed the follow-up returned to their pre-injury activities without pain, instability, or graft rupture, and none required additional surgery.

CONCLUSIONS

The proposed technique for anatomic ACL reconstruction, using an inverted autologous quadruple flexor tendon graft with the fold within the tibial tunnel fixed with the suspension technique and a staple, and an anatomic femoral tunnel created with the outside-to-inside technique, showed good to excellent results in this series of 20 cases, with lower material costs. Additionally, this technique can be reproduced with common materials available for ACL surgery.

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. MVD (0000-0001-7547-7557)*: was the lead author, performed most of the surgeries, and drafted and revised the manuscript. JPFG (0000-0002-2026-9176)*: performed some of the surgeries and assisting in drafting the article. AOQ (0000-0003-2808-7892)*: performed some surgeries, and CRP (0000-0002-7719-9682)*: contributed to the statistics. All authors contributed to the intellectual concept of the study and approved the final version of the manuscript. *ORCID (Open Researcher and Contributor ID).

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ORIGINAL ARTICLE

PATIENT-DERIVED XENOGRAFTS AS A PRECLINICAL MODEL FOR BONE SARCOMAS

XENOENXERTOS DERIVADOS DE PACIENTES COMO MODELO PRÉ-CLÍNICO DE SARCOMAS ÓSSEOS

Walter Meohas[1], Regina Alcantara Granato[2], João Antonio Matheus Guimarães[3], Rhayra Braga Dias[3], Anneliese Fortuna-Costa[3], Maria Eugenia Leite Duarte[3]

1. Centro de Oncologia Ortopédica, Instituto Nacional de Traumatologia e Ortopedia, Rio de Janeiro, RJ, Brazil,
2. Department of Pathology, Universidade Federal Fluminense, Niterói, RJ, Brazil,
3. Research Division, Instituto Nacional de Traumatologia e Ortopedia, Rio de Janeiro, RJ, Brazil.

ABSTRACT

Objective: The purpose of this study was to reproduce a mouse model of bone sarcomas for use in cancer research. Methods: A fresh sample of the tumor tissue was implanted subcutaneously into nude mice. When the patient-derived xenograft (PDX) reached a volume of 1500 mm^3, it was harvested for re-implantation into additional mice. Histology was used to compare the morphological characteristics of different generations of sarcoma xenografts with the primary tumor. Results: Sixteen sarcoma tissue samples were engrafted into nude mice. Nine patients were diagnosed with osteosarcoma, two with chondrosarcoma, two with malignant peripheral nerve sheath tumor, one with synovial sarcoma, one with pleomorphic sarcoma, and one with Ewing's sarcoma. PDX tumors were generated in 11 of the 16 implanted specimens (69% success rate in P1). Six P1 tumors grew sufficiently for transfer into additional mice, producing the P2 generation, and three P2 tumors established the P3 generation. Conclusion: PDX tumors generated from bone sarcomas were successfully established in immunodeficient mice and reproduced the characteristics of the primary tumor with a high degree of fidelity. The preclinical PDX model described herein may represent an important tool for translational oncology research and for evaluating therapeutic strategies for bone sarcomas. ***Level of Evidence I; Experimental study.***

Keywords: Bone neoplasms. Sarcoma, experimental. Translational medical research.

RESUMO

Objetivo: O propósito deste estudo foi reproduzir em camundongos um modelo de sarcomas ósseos para uso em pesquisa oncológica. Método: Amostras frescas de tecido tumoral foram implantadas por via subcutânea em camundongos Nude. Quando o xenoenxerto derivado do paciente (PDX) alcançava 1500 mm^3, ele era retirado do animal e reimplantado em outros camundongos. Estudos histológicos foram realizados para comparar as características morfológicas de diferentes gerações de xenoenxertos com o tumor primário. Resultados: Dezesseis amostras de tecido sarcomatoso foram enxertadas em camundongos. Nove pacientes foram diagnosticados com osteossarcoma, dois com condrossarcoma, dois com tumor maligno de bainha de nervo periférico, um com sarcoma sinovial, um com sarcoma pleomórfico e um com sarcoma de Ewing. Foram gerados tumores PDX em 11 das 16 amostras enxertadas (taxa de sucesso de 69% em P1). Destes, seis tumores P1 cresceram o suficiente para serem transferidos para outros camundongos, dando origem à geração P2 e três dos tumores P2 estabeleceram a geração P3. Conclusões: Os tumores PDX de sarcomas ósseos foram estabelecidos com sucesso em camundongos imunodeficientes e reproduziram com alta precisão as características do tumor primário. O modelo pré-clínico de PDX descrito pode representar uma ferramenta importante para a pesquisa oncológica translacional e para avaliar estratégias terapêuticas para sarcomas ósseos. ***Nível de Evidência I; Estudo experimental.***

Descritores: *Neoplasias ósseas. Sarcoma experimental. Pesquisa médica translacional.*

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INTRODUCTION

Bone sarcomas are a heterogeneous group of rare highly malignant tumors of unknown origin that constitute 0.2% of all adult malignancies and 5% of malignant neoplasms of children and young people.[1] The clinical presentation of bone sarcomas is variable and nonspecific. In general, the symptoms of pain, swelling and functional loss are restricted to the lesion region. The pain can be intermittent, persistent, and progressive with irradiation. Another characteristic of bone sarcomas is the rapid local volume increase associated with altered skin coloration plus

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Work conducted at the Nacional de Traumatologia e Ortopedia, Rio de Janeiro, RJ, Brazil.
Correspondence: Maria Eugenia Leite Duarte. Instituto Nacional de Traumatologia e Ortopedia. Av. Brasil 500, São Cristóvão, Rio de Janeiro, RJ, Brazil. 20940-070. meugenia.into@gmail.com

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development of collateral circulation. Systemic symptoms such as fever, tiredness and weight loss are almost always associated with the metastatic spread of the disease.[2]

The classification of bone sarcomas is based on the cell type and the characteristics of the matrix produced by the tumor cells, which recapitulate the architecture of the original tissue. Most tumors differentiate into cell lines or tissues that make up the musculoskeletal system.[1] Osteosarcoma is the most frequent primary bone sarcoma (35%), followed by chondrosarcoma (25%) and Ewing's sarcoma (16%).[3] Preclinical studies are designed to increase the knowledge about the biology of malignancies, the development of new therapeutic strategies and their validation before the phase of clinical trials. Although several *in vitro* and *in vivo* preclinical models are being widely used for decades to study cancer biology, the high rates of phase III clinical trials failures indicate that these preclinical models may have poor clinical predictive power.[4-7]

Animal models are currently an important tool for preclinical studies aiming to increase the knowledge about the biology of malignancies, the development of new therapeutic strategies and their validation before the phase of clinical trials. In order to translate results obtained in animal models into the clinical scenario, it is necessary that the animal model accurately reproduce the natural history of the disease. As the etiology and pathogenesis of sarcomas are unknown, the development of tumor models in general is incomplete and poorly reproducible. [8]

Patient-derived tumor xenografts models, consisting on the implantation of fresh samples of patient's tumor into immunodeficient mice are increasingly being used in cancer research as a basis for the development of new therapeutic strategies. Although tumor generated from xenografts are being reproduced in a murine immunodeficient environment, they recapitulate the biology of the original tumor and are easy to handle and maintain.[9,10] Moreover, in these models it is possible to observe the development of metastases which allows to evaluate the behavior of the primary tumor mass and the secondary implant generated from the same tumor graft. Another important advantage of xenografts models is that human neoplastic cells proliferate in their native environment, maintaining the pattern of individual heterogeneity of each patient. Thus, from the tumor tissue implanted in the mice, it is possible to reproduce the pattern and biology of human tumor growth.[11-13]

Herein, we aimed to reproduce a mouse model of bone sarcomas for use in cancer research. This preclinical model will constitute an important platform for studies of sarcomas biology and may be used on therapeutic strategies as a prelude to subsequent translation to patients.

MATERIALS AND METHODS

This study was reviewed and approved by the Institutional Review Board (IRB) of the National Institute of Traumatology and Orthopedics (CAAE: 69859417.2.0000.5273), and all patients provided written informed consent as part of the above-mentioned IRB-approved protocol. Tumor tissue samples from patients with clinical diagnosis of a primary bone sarcoma were obtained at the time of biopsy or surgical resection from January 2017 to September 2017. Patients who were treated preoperatively with neoadjuvant chemoteraphy were also included in the study. The following clinical parameters were collect from all patients: age, gender, tumor location, histopathological diagnosis of the primary lesion and history of preoperative chemotherapy.

Tumor samples

A fresh sample of the patient tumor was obtained from a representative biopsy or from the surgical specimen resulting from resection or limb amputation. For tumor samples obtained from surgical resection, the fragments were collected from solid areas, avoiding areas of necrosis and hemorrhage and maintained in DMEM medium at 4°C until implantation. Tumor tissue samples were cut into 3 x 3 x 3 mm^3 pieces and a total of four pieces/animal was xenotransplanted. A single 2 x 5 mm cylindrical fragment of tissue obtained by incisional or fluoroscopy-guided needle biopsy represented samples from biopsies. Similar to the surgical specimens, tumor tissue was cut into 3 x 3 x 3 mm^3 pieces. Tumor samples were collected, handled and stored under sterile conditions.

- Establishment of patient-derived xenograft (PDX tumor model)

Six to eight-week-old athymic nude mice (B6.Cg-Foxn1^{nu}) were used in this study. All animal studies were approved by the Institutional Animal Care and Use Committee of the National Institute of Traumatology and Orthopedics (Protocol n° 005/2017). During the entire experimental period the animals were kept in a barrier facility on a high efficiency particulate arrestance (HEPA)-filtered rack and were fed ad libitum with autoclaved laboratory rodent diet. For all surgical experiments the mice were anesthetized with isoflurane inhalation (2,5-5,0 Vol% per liter oxygen). Under sterile conditions each tumor fragment was implanted into a subcutaneous area on the right and left flanks. Tumor dimensions were checked twice weekly using a digital caliper and tumor volume (TV) was calculated according to the formula: TV= (length x width^2)/2. When tumor size in the implanted area reached an approximate volume of 1500 mm^3 they were harvested (P1 generation) for transplantation to the next generation into additional mice (P2, P3) (Figure 1). Conventional radiography images were acquired at the end of the experiment when the animals were euthanized by an overdose of ketamine and xylazine. Growth failure was considered in the absence of tumor growth four months after implantation.

- Histopathological characterization of primary and patient-derived bone sarcoma xenograft (PDX)

Fresh xenograft samples were fixed in 10% buffered formalin and paraffin-embedded blocks were prepared for all tumors. Sections (4mm thick) were stained with hematoxylin-eosin (H&E) for histological comparisons between the patient tumor and xenografts.

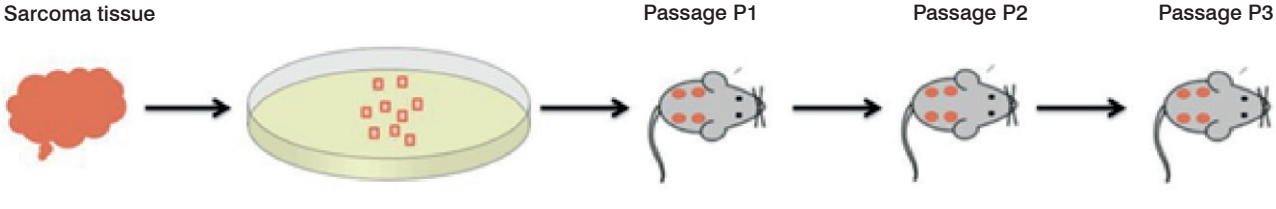

Figure 1. Methods for developing patient-derived xenograft model (PDX). Immunodeficient mice received human bone sarcoma tissue fragments (four pieces/animal) engrafted into the subcutaneous space of the flank.

RESULTS

In total, sixteen surgically removed sarcoma tissues from fifteen patients (eleven male and four female aged 10-51 years old) were engrafted into nude mice. All tumor samples were obtained from primary sites. Eight patients were diagnosed with osteosarcoma, two with chondrosarcoma, two with malignant peripheral nerve sheath tumor (MPNST), one with synovial sarcoma, one with pleomorphic sarcoma (malignant fibrous histiocytoma) and one with Ewing sarcoma. Patient demographics and clinicopathologic characteristics for the harvested tumors are summarized in Table 1.

Efficacy of establishment of primary patient-derived (PDX) bone sarcoma mouse xenograft

Only fresh tumor samples obtained on the day of the surgical removal were implanted into nude mice (Figure 2). PDX tumors were initially generated (P1) in 11 out of 16 implanted specimens. Six of P1 tumors grew sufficiently for transfer into further mice giving rise to P2 generation and three of P2 tumors established the P3 generation. Sarcoma tissue from five patients (two osteosarcomas, one grade I chondrosarcoma, one grade II chondrosarcoma and one with Ewing sarcoma) failed to engraft into the mice.

Elapsed time for engraftment in P1 animals was 59 days (19-125 days), 28 days in P2 (18-40 days) and 18 days in P3 (16-21 days). Table 2 summarizes successful engraftment cases and growth rates.

Histology of original patient tumor and PDX tumor

Microscopic examination of hematoxylin and eosin (H&E) stained histological sections demonstrated that the original tumor characteristics were preserved in the PDX. Mouse xenografts displayed strong histological similarity with the clinical specimens including tumor cellularity, tumor cell anaplasia, mitotic figures and formation of neoplastic extracellular bone matrix. Subgrafted xenograft tumors also retained the histopathological features of the original patient tumors indicating the same pattern of differentiation capacity (Figure 3 and 4).

DISCUSSION

In contrast to the frequency of adenocarcinomas, bone sarcomas are rare, and for this reason, preclinical models such as PDX are more restricted and difficult to develop.[14] On the other hand, it is well established that preclinical models is the key element in translational research with an obvious potential to promote significant advances in the area of cancer research, particularly for the development of new anti-neoplastic drugs.[8]

The process of generating xenograft models from primary or metastatic malignancies is already widely described in the literature.[15] This increasing interest in PDX derives in large part from the potential of the model to preserve tumor growth kinetics, potential for local invasion and the ability to metastasize, and to reproduce the response to polychemotherapy treatment. Another frequently addressed issue in the literature concerns the site of tumor implantation - heterotopic or orthotopic - for the PDX generation. The orthoxenografts have the advantage of developing in the same anatomical microenvironment of the patient original tumor. For bone tumors, orthotopic implants would provide also better quality of imaging documentation.[16] However, in the particular case of bone tissue, for an orthotopic tumor implantation it is necessary a complex surgical procedure that is greatly hampered by the delicate murine bone anatomy.

The method described in this paper, to generate PDX models in mice from fresh bone sarcomas has several advantages: it is simple to perform, does not require complicated operative procedures, has high engraftment rates and the mouse-to-mouse subgrafting retain the morphological characteristics of the original grafted tumor. Of

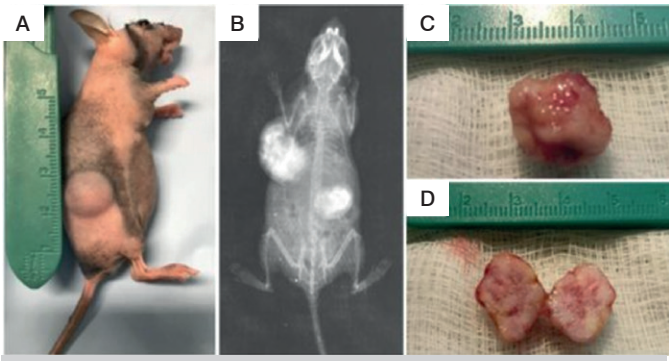

Figure 2. Bone sarcoma PDX. (A) First generation (passage 1) tumor growth six weeks after transplantation of patient-derived osteosarcoma into the subcutaneous of nude mice. (B) Representative X-ray image from PDX shown in (A). (C and D) Gross pathologic examination of first generation PDX displaying a bosselated 1,5 cm mass. (D) Cut surface has a fish flesh-like appearance characteristic of sarcomas, with focal areas of hemorrhage (pink).

Table 1. Clinical characteristics of donor patients used for generation of patient-derived xenografts (PDX).

Case No.	Age	Gender	Sarcoma histology	Location	Previous chemotherapy	Metastasis
1	23	Male	Osteosarcoma (telangiectatic)	Femur	No	Yes (lund and CNS)
2	11	Male	Osteosarcoma (central)	Femur	No	No
3	43	Male	Osteosarcoma (central)	Tibia	No	No
4	11	Male	Osteosarcoma (central)	Femur	Yes	No
5	17	Male	Osteosarcoma (central)	Femur	No	No
6	14	Female	Osteosarcoma (central)	Femur	Yes	Yes (lung)
7	13	Female	Osteosarcoma (central)	Fibula	Yes	No
8	14	Male	Osteosarcoma (central)	Femur	No	Yes (lung)
9	13	Female	Osteosarcoma (central)	Fibula	No	No
10	39	Male	Synovial sarcoma	Knee	Yes	No
11	23	Male	Grade I chondrosarcoma	Femur	No	No
12	40	Male	Grade II chondrosarcoma	Scapula	No	No
13	29	Male	Malignant peripheral nerve sheath tumor (MPNST)	Forearm	No	Yes (lung)
14	51	Female	Malignant peripheral nerve sheath tumor (MPNST)	Fibula	No	Yes (lung)
15	47	Male	Pleomorphic sarcoma (Malignant Fibrous Histiocytoma)	Knee	No	No
16	10	Male	Ewing sarcoma	Femur	Yes	No

CNS= Central nervous system.

Table 2. Characteristics of patient-derived xenografts (PDX) models for bone sarcomas.

Case No.	Histopathological diagnosis	Tumor sample source	Time for subcutaneous patient-derived xenograft (PDX) growth (days)		
			Passage 1	Passage 2	Passage 3
1	Osteosarcoma	Hip disarticulation	45	18	-
2	Osteosarcoma	Core needle biopsy	57	41	21
3	Osteosarcoma	Leg amputation	32	18	-
4	Osteosarcoma	Tumor ressection	48	29	-
5	Osteosarcoma	Core needle biopsy	125	-	-
6	Osteosarcoma	Tumor ressection	23	-	-
7	Osteosarcoma	Leg amputation	21	-	-
8	Osteosarcoma	Core needle biopsy	Failed	-	-
9	Osteosarcoma	Core needle biopsy	Failed	-	-
10	Synovial sarcoma	Hip disarticulation	19	-	-
11	Grade I chondrosarcoma	Tumor ressection	Failed	-	-
12	Grade II chondrosarcoma	Tumor ressection	Failed	-	-
13	Malignant peripheral nerve sheath tumor (MPNST)	Arm amputation	84	36	17
14	Malignant peripheral nerve sheath tumor (MPNST)	Core needle biopsy	64	30	17
15	Pleomorphic sarcoma (Malignant Fibrous Histiocytoma)	Tumor ressection	66	-	-
16	Ewing sarcoma	Tumor ressection	Failed	-	-

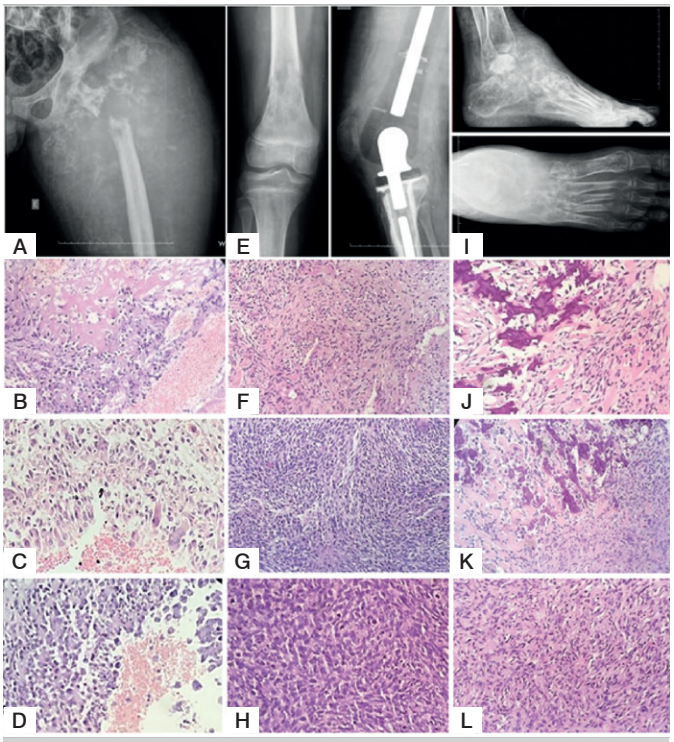

Figure 3. Radiographic and histologic features from primary and PDX tumors. (A) Telangiectatic osteosarcoma (OS) in a 23-year-old man (case 1). Radiograph of the proximal femur reveals a lytic lesion with extensive bone destruction and expansion into soft tissue. (B) Representative histology of the original patient tumor obtained by core needle biopsy and (C) during hip disarticulation. Microscopically telangiectatic OS is characterized by spaces containing blood (arrow head), with septa composed of malignant osteoblasts in a background of hypercellular and anaplastic stroma and tumor osteoid (*). (D) Blood-filled space lined by highly malignant osteoblasts in the xenograft tumor (P1) closely resembles the primary tumor. (E) Central OS in an 11-year-old boy (case 2). A diffuse lytic/blastic permeating lesion is seen in the lower femur with cortical destruction and tumor expansion into soft tissue. Limb-salvage surgery with endoprosthesis reconstruction after en-block tumor resection. (F) Malignant spindle or oval-spindle shape cell tumor with hyperchromatic nuclei surrounded by a small amount of cytoplasm. The production of neoplastic bone/osteoid is sparse. (G-H) The histology of primary OS characterized by the proliferation of spindly, oval or round neoplastic cells was retained in both P1 (G) and P2 (H) xenograft tumors. (I) Conventional OS in a 43-year-old man (case 3). Plain radiograph of ankle and foot showing a large ill-defined lytic lesion involving the talus and surrounding soft tissue. (J) Poorly formed neoplastic bone trabeculae are seen in the primary tumor in association with anaplastic cells displaying nuclear pleomorphism. (K-L) The xenograft tumor (P1) closely resembles the primary tumor including production of neoplastic bone, anaplasia and abundant mitotic figures (L). OS=Osteosarcoma. P1= PDX tumor in first passage; P2= PDX tumor in the second passage. H&E-stained sections. (B, F, G, J-L): Magnification x10; (C, D, H): Magnification x20.

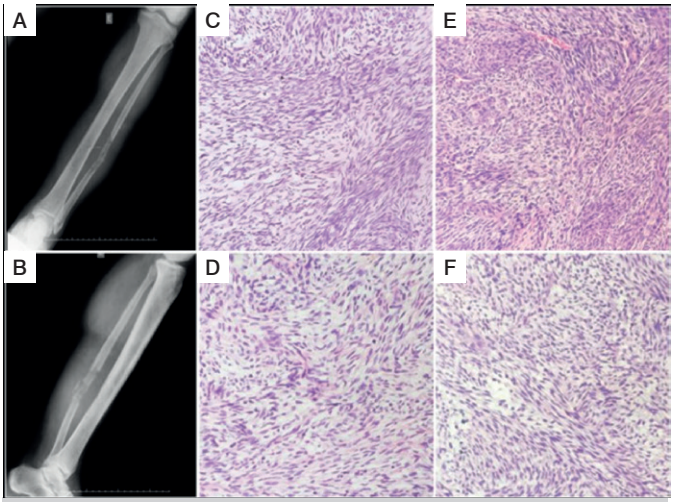

Figure 4. Radiographic and histologic features from MPNST primary tumor and PDX tumors. (A-B) MPNST in a 51-year-old woman (case 14). Large soft tissue mass overlying the fibula associated with extrinsic cortical erosion and bone destruction. (C) Primary MPNST characterized by neoplastic fusiform or spindle shaped cells arranged in dense cellular fascicles. (D-F) Histological features of corresponding patient tumor such as cell morphology, and the swirling cellular arrangement were largely reproduced in mouse passage P1 (D), P2 (E) and P3 (F) PDX tumors. MPNST= Malignant Peripheral Nerve Sheath Tumors. P1= PDX tumor in first passage; P2= PDX tumor in the second passage. P3= PDX tumor in the third passage. H&E-stained sections. (C-F): Magnification x10.

the 16 tumors that were implanted subcutaneously into the flanks of nude mice, 69% (11/16) successfully engrafted. Moreover, 54% (6/11) of P1 tumors were re-implanted into other animals and the remaining P1 tumors have not yet reached the established volume to be re-implanted. The morphology of the lesions developed in the PDX of different passages reproduced with high degree of fidelity the characteristics of the primary tumor. The retention of histological features, including cellular morphology and arrangement, histological subtype of corresponding sarcoma, and tissue architecture indicate that PDX tumors maintain the same pattern of differentiation of the original patient tumors. The phenotypic stability of PDX models was also confirmed in studies that demonstrated stable response rates to drug treatments up to 10 passages.[17]

In the present study we observed that a potential limiting factor to produce PDX tumors is a limited supply of tissue to develop the model, when the material is obtained from small tumor samples such as biopsy specimens. Also, in samples obtained from patients

with excessively large tumors with extensive areas of necrosis and in post-chemotherapy samples the possibility of obtaining lower engraftment efficiency should be taken into account. Another important challenge for bone tumors is the technical difficulty to reproduce orthotopic PDX models and to ensure high tumor take rates. However, considering the high degree of biological aggressiveness of sarcomas, it is possible that tumor take rates do not constitute a limitation for bone sarcomas in particular. Indeed, studies with human breast cancer demonstrated that more aggressive tumors had a higher take rate.[11] We believe that the cases that failed to engraft (5/16) were due to intrinsic tumor characteristics such as the relatively low biological aggressiveness of the sarcoma subtype (grade I and grade II chondrosarcoma), to the small sample size obtained by core needle biopsy, limiting the size of the implant (n=2) and the reduced potential for engraft due to necrosis, in one sample from a post-chemotherapy Ewing sarcoma.

As the PDX recapitulates the biology of the human tumor they are predictive of clinical outcome, and consist in an important tool for the development of a personalized treatment. These advances in the area of translational cancer research led the US National Cancer Institute (NCI) to consider the replacement of tumor conventional cell line repositories for PDX samples due to the high similarity of the PDX models with the natural history and clinical outcome of pediatric bone cancer.[18]

CONCLUSION

PDX tumors generated from bone sarcomas samples were successfully established in immunodeficient mice. The morphological similarities of PDX to the corresponding primary tumor confirm that the preclinical PDX model can be translated to clinical practice to stimulate the development of personalized approaches for the treatment of several types of bone sarcomas.

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. WM (0000-0003-1402-9667)*: performed the surgeries, the critical revision, and gave final approval for the manuscript. RAG (0000-0001-9060-9052)*: equally contributed to this work with WM in conceiving and designing the study, analyzed and interpreted the data, drafted and performed the critical revision of the article. JAMG (0000-0002-5647-2248)*: analyzed and interpreted the data and performed the critical revision of the manuscript. RBD (0000-0001-5465-1149)*: acquired, analyzed, and interpreted the data. AFC (0000-0002-3507-0493)*: contributed the research project, acquired, analyzed, and interpreted the data, and drafted/review. MELD (0000-0003-2248-2410)*: contributed the research project, interpreted the data, drafted and performed the critical revision. All authors contributed to the intellectual concept of the study and approved the final version of the manuscript. *ORCID (Open Researcher and Contributor ID).

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PRIMARY BONE LYMPHOMAS: RETROSPECTIVE ANALYSIS OF 42 CONSECUTIVE CASES

LINFOMA ÓSSEO PRIMÁRIO: ANÁLISE RETROSPECTIVA DE 42 CASOS CONSECUTIVOS

Telma Murias dos Santos[1], Juan Pablo Zumárraga[1], Fábio Mazetti Reaes[1], Carlos Henrique Maçaneiro Junior[1], André Mathias Baptista[1], Olavo Pires de Camargo[1,2]

1. Orthopedic Oncology Group, Instituto de Ortopedia e Traumatologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.
2. Department of Orthopedics and Traumatology, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

ABSTRACT

Objective: It is difficult to define parameters for management and factors associated with primary bone lymphoma (PBL). This article presents the experience in a single institution with 42 patients with PBL over a 16-year period (2000–2016). Methods: Fifty-five patients were retrospectively evaluated, and forty-two were included (76.3%). Results: Median age at diagnosis was 51.5 years, and median follow-up was 102.7 months. One patient had HIV. Pain in the affected site was the most prevalent symptom. The average time between symptom onset and diagnosis was 5.4 months. The vertebrae were most affected (n=16, 33.3%). According to the International Prognostic Index Score (IPI), 64.3% of the patients were classified as having low-grade lymphoma and 25.7% as low-intermediate. The most common histology was diffuse large B cell lymphoma (DLBCL) (85.7%). Immunophenotyping was CD20 positive in 93.5% of patients, and 11 patients had pathological fracture. All patients received chemotherapy and 30% of the regimens included rituximab. Thirty-eight percent of patients received radiation therapy. Overall survival was 50%, and survival median time was 80 months. Age and chemotherapy regimen influenced patient survival. Younger patients and patients who received RCHOP had better prognoses. Conclusions: The choice of chemotherapy regimen associated with age influenced survival for patients with PBL. ***Level of Evidence IV; Case series.***

Keywords: Lymphoma/physiopathology. Lymphoma/therapy. Lymphoma, large B-cell, diffuse. Bone neoplasms. Drug therapy.

RESUMO

Objetivo: É difícil definir parâmetros para o tratamento e os fatores associados ao prognóstico de linfoma ósseo primário (LOP). Apresentamos a experiência de uma única instituição, com 42 casos de LOP durante 16 anos (2000-2016). Métodos: Cinquenta e cinco pacientes avaliados retrospectivamente e quarenta e dois incluídos (76,3%). Resultados: A mediana da idade foi 51,5 anos e a mediana do seguimento foi 102,7 meses. Um paciente era portador do vírus da imunodeficiência humana. Dor no membro foi o sintoma mais prevalente. O tempo médio entre os sintomas e o diagnóstico foi de 5,4 meses. O sítio anatômico mais afetado foram as vértebras (n = 16, 33,3%). Em relação à International Prognostic Index Score (IPI), 64,3% dos pacientes tinham baixo grau e 25,7% tinham baixo-intermediário. O diagnóstico histológico mais comum foi linfoma difuso de grandes células B (LDGCB), com 85,7% dos casos. A imunofenotipagem foi positiva para CD20 em 95,3%. Onze pacientes tinham fratura patológica. Todos receberam quimioterapia, sendo que 30% dos regimes incluíam rituximabe. A radioterapia foi utilizada em 38% dos pacientes. A porcentagem total de sobrevida foi de 50% e o tempo médio de sobrevida foi de 80 meses. A idade e o regime de quimioterapia juntos influenciaram diretamente a sobrevida dos pacientes. Os pacientes jovens, assim como os que receberam RCHOP, tiveram prognóstico de sobrevida melhor. Conclusão: A escolha do regime de quimioterapia associada à idade do paciente influenciou a sobrevida dos pacientes com LOP. ***Nível de Evidência IV; Série de casos.***

Descritores: *Linfoma/fisiopatologia. Linfoma/terapia. Linfoma difuso de grandes células B. Neoplasias ósseas. Tratamento farmacológico.*

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INTRODUCTION

Primary bone lymphoma (PBL) is rare cancer that accounts for 5% of non-Hodgkin's lymphomas (NHL) and 3% of all malignant bone diseases.[1] Most studies feature the same epidemiological characteristics, such as predominance in males, initial symptoms of the disease, diagnosis in the 5th and 6th decades of life, and relatively favorable survival prognosis.[1-4] Even so, there is no consensus on best management because of the limited number of patients reported in the case series. There is also little agreement about treatment options and their results. The method of diagnosis often varies; more precise diagnosis allows better treatment choices. Streamlined staging has helped reduce the number of patients with

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Work conducted at the Instituto de Ortopedia e Traumatologia, Hospital das Clinicas (HCFMUSP), Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.
Correspondence: Juan Pablo Zumárraga. Rua Ovídio Pires de Campos, 333, Cerqueira Cesar, São Paulo, SP, Brazil. 05403-010. juanpzumarraga@hotmail.com

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PBL, excluding cases with evidence of systemic disease during the first six months of diagnosis.[5] Treatment has been evolving since 1960, when radiation therapy was the method of choice, yielding high rates of local control of the disease but also high levels of systemic failure.[6-8] Evidence of considerable increases in survival rates after adding chemotherapy to PBL treatment are frequent in the literature. Currently, treatment includes a combination of chemotherapy and radiation versus the traditional radiation alone.[4,9] In the late 1990s, rituximab, a monoclonal anti-CD20 antibody, was added to chemotherapy and became the standard treatment for B-cell lymphomas. After rituximab was used for treatment, survival improved significantly for diffuse large B-cell lymphoma (DLBCL). Even so, the role of this drug in treating PBL is not yet clear because of the limited number of patients with this diagnosis. It is difficult to evaluate the benefits of rituximab in treating this disease because of its favorable prognosis for survival. An initial experience treating PBL in our service was published in 2002.[10] At that time, our patients did not receive rituximab.[10] We therefore resolved to review the cases of PBL diagnosed at our institution after 2002, to analyze how changes in diagnosis and treatment currently impact patients.

MATERIALS AND METHODS

The study was approved by the HCFMUSP institutional review board (process 11313). This cross-sectional retrospective study utilized records from 55 patients diagnosed with PBL by the Orthopedic Oncology Group at IOT-HC-FMUSP from 2000 to 2016. Thirteen of the medical records were excluded due to lack of information, and 42 were included in the study. All the patients were diagnosed with PBL and received primary treatment. Age, sex, clinical stage (in accordance with the Ann Arbor system), serum lactic dehydrogenase level (LDH), presence of B symptoms, and IPI[11] were acquired from the medical records. The histological diagnosis was performed or reviewed by pathologists from our institute, and the patients were classified according to the World Health Organization (WHO) classification for hematopoietic and lymphatic tissue tumors.[12] Immunophenotype was identified with a immunohistochemical panel on paraffin-embedded tissue, using the following antibodies: BCL-2, BCL-6, CD3, CD5, CD10, CD15, CD20, CD30, CD45, CD79, and Ki-67. All patients received at least two cycles of rituximab to be considered for the medication use group. The clinical and demographic characteristics were described according to the following measures: average, standard deviation, median, minimum and maximum for quantitative variables, and absolutes and relatives for the qualitative variables.[13] The average survival time estimated was according to characteristic using the Kaplan-Meier method.[14] It was not possible to estimate the average survival for the entire cohort because the number of deaths was lower than 50%. Survival was compared between the categories using the log-rank test.[14] The risk rate was estimated retrospectively (CI=95%) with bivariate Cox regression. The multiple Cox model was estimated using the variables that showed a descriptive level less than 0.2 ($p<0.2$), and only the variables with statistical significance remained in the final analysis. All tests were performed at a 5% significance level. The data were analyzed using Statistical Package for the Social Sciences software. This review follows our 2002 publication,[10] and describes clinical and histological presentation, treatment, and results.

RESULTS

Most patients were men (61.9%), median age at diagnosis was 51.5 years, and median follow up was 102.7 months (from 4 to 114 months). One patient was HIV positive (2.4%). One patient had B symptoms (2.4%). Pain in the affected limb was the most prevalent symptom (100%). The average time between the appearance of symptoms and diagnosis was 5.4 months. The most affected areas were the vertebrae (n=16, 33.3%), the femur (n=12, 23.8%), and the tibia (n=4, 9.5%). LDH was elevated in 13 patients (30.9%). Eleven patients (26.2%) had pathological fracture at diagnosis. Twenty-three percent of patients were surgically treated, and arthrodesis was most commonly performed. Using the International Prognosis Index Score (IPI), 64.3% of patients were low grade and 25.7% were low-intermediate. The most common histological diagnosis was DLBCL, affecting 85.7% of patients. Immunophenotyping was performed in all cases, and 95.3% were CD20 positive. (Tables 1 and 2) All patients received chemotherapy, isolated, or in association with rituximab, and 38.1% of cases also received radiation therapy. Cases of pathologic fracture, imminent fracture, or medullary compression were treated surgically. Only two cases with pathological fracture did not receive surgical treatment. (Figures 1 and 2) The total percentage of survival was 50% and average survival was 80 months. The risk of death increased by 4% for each year of the patient's age. Age and chemotherapy regimen together had a direct influence on patient survival. Young patients as well as those who received R-CHOP had a better prognosis for survival. It was not possible to estimate the average time for the entire cohort because the number of deaths was lower than 50%. (Figures 3 and 4)

Table 1. Population distribution according to characteristic.

Variable	Description (N=42)	
Sex, n (%)		
Female	16	(38.1)
Male	26	(61.9)
Age (years)		
Mean (SD)	49.4	(18.4)
Median (min-max)	51.5	(11-77)
Location, n (%)		
Vertebra	14	(33.3)
Femur	10	(23.8)
Tibia	4	(9.5)
Ilium	3	(7.1)
Humerus	3	(7.1)
Other	8	(19.0)
Clinical presentation n (%)		
Pain in affected site	42	(100.0)
Fever	1	(2.4)
Duration of symptoms (months)		
Mean (SD)	5.2	7
Median (min-max)	2	1 to 36
LHD		
Mean (SD)	834.9	954.3
Median (min-max)	549.5	168-593.4
Pathological Fracture		
No	31	73.8
Yes	11	26.2
Histology		
DLBCL	37	88
Diffuse small-cell lymphoma	2	4.8
Diffuse small-cell and large B-cell lymphoma	2	4.8
T-cell lymphoma	1	2.4
IPI		
Low	27	64.3
Low-intermediate	15	45.7

Table 2. Average survival according to data from comparative tests.

		CI	95%		CI	95%			
Variable	**Mean Value**	**Below**	**Above**	**RR**	**Below**	**Above**	**Deaths**	**Total**	**%**
	time (months)								
Age									
(<) / (=) Median	732.0	480.9	983.1	1.00			6	19	31.6
(>) Median	205.9	00.0	446.7	2.26	0.87	5.88	15	23	65.2
Sex									
Female	552.2	282.6	821.8	1.00			8	16	50.0
Male	408.5	144.2	672.9	1.00	0.41	2.40	13	26	50.0
Symptom duration									
(<) / (=) Median	229.8	00.0	491.7	1.00			15	23	65.2
(>) Median	748.3	507.4	989.3	0.44	0.17	1.14	6	19	31.6
HIV									
No	425.9	208.6	643.1	1.00			21	41	51.2
Yes	155.0	155.0	155.0	0.05	0.00	538.75	0	1	00.0
LHD									
Normal	453.0	133.8	772.2	1.00			8	17	47.1
Abnormal	461.6	214.0	709.3	0.85	0.35	2.07	13	25	52.0
Location									
Trunk	545.0	284.0	805.9	1.00			9	19	47.4
Limbs	444.2	190.3	698.1	0.91	0.38	2.18	12	23	52.2
Pathological Fracture									
No	490.0	238.0	741.9	1.00			14	31	45.2
Yes	83.7	35.3	132.0	1.46	0.59	3.63	7	11	63.6
Immunophenotyping									
CD3	71.5	55.6	87.4	1.00			1	2	50.0
CD20	68.2	41.3	95.0	1.84	0.24	14.24	13	22	59.1
Both	680.7	429.3	932.1	1.03	0.13	8.44	7	18	38.9
IPI									
Low	452.0	204.1	700.0	1.00			13	27	48.1
Low-Intermediate	505.4	216.5	794.2	1.29	0.53	3.13	8	15	53.3
Radiation therapy									
No	375.2	134.0	616.5	1.00			15	26	57.5
Yes	681.4	415.6	947.2	0.74	0.28	1.91	6	16	37.5
Chemotherapy									
CHOP	80.6	50.5	110.7	1.00			18	28	64.3
R-CHOP	824.0	541.0	1107.1	0.31	0.09	1.06	3	14	21.4
Total	455.8	249.2	662.5				21	42	50.0

DISCUSSION

The medical literature does not feature an extensive volume of publications on PBL, mainly because of the rarity of this disease. Most of the lymphoma cases actually presented extra-osseous disease. Therefore, most of the published studies are retrospective series. The present study was no exception; we analyzed 55 consecutive cases over 15 years, 13 of which were excluded due to lack of complete information in the medical records. In our previous study from 2002,[10] 57 of the 81 cases were excluded due to lack of data in the patient chart. Comparatively, in the larger published series, we found one study involving 119 cases over 38 years, and in another 82 cases over 40 years.[15,16] This makes the present study the largest series reported in Latin America. We also observed that our service had twice the number of cases of the other studies in half the time, which reflects improvement in the ability to diagnose patients with PBL. The average amount of time from appearance of symptoms to date of diagnosis was 5.4 months, similar to the data reported in other studies.[16] This also

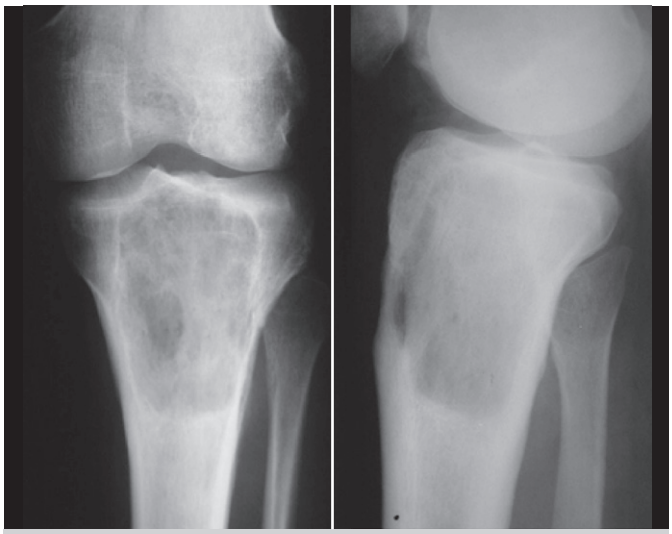

Figure 1. X-ray image of a primary bone lymphoma in the proximal tibia (prior to chemotherapy).

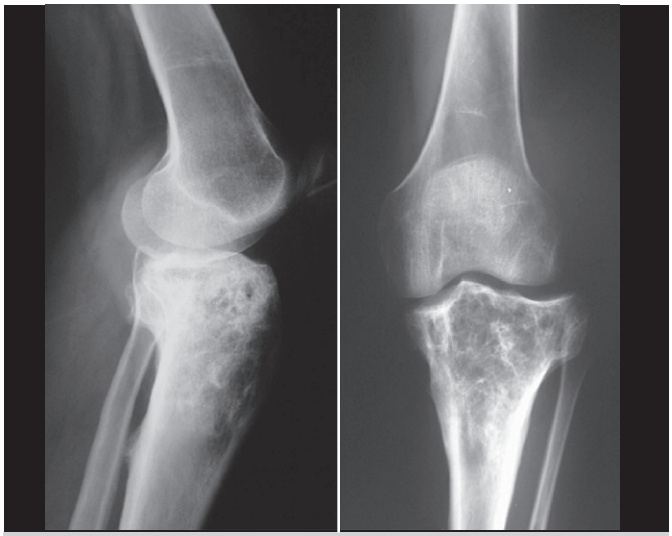

Figure 2. X-ray image of a primary bone lymphoma in the proximal tibia (after chemotherapy).

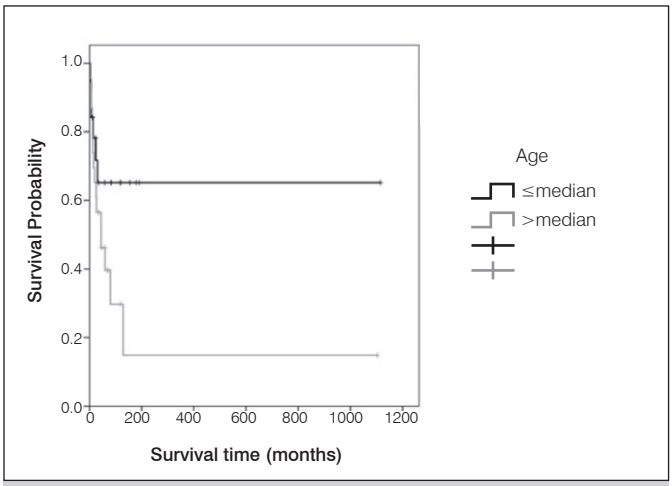

Figure 3. Average survival, according to age at diagnosis.

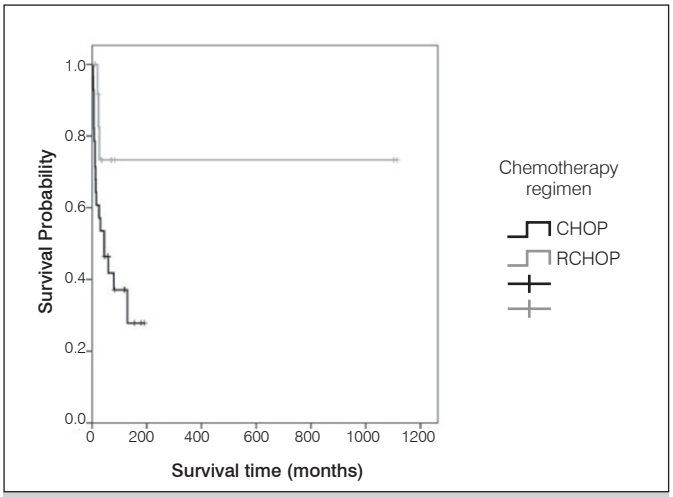

Figure 4. Average survival, according to chemotherapy regimen.

shows the improved access to public health that residents in some areas of Brazil currently enjoy. However, and particularly in our study, time of diagnosis did not affect the prognosis of patients with PBL. As expected, the epidemiological characteristics of PBL were found in our series: the median age was in the fifties and sixties, men were more prevalent, and pain was the main symptom. An important difference from the literature is that the most frequently affected site was the vertebrae, as we also found in our previous publication.[10] Other studies generally show that the femur is most frequently affected.[15,16] Few prognostic factors were found in the statistical analysis. In our study, age appears to be a prognostic factor, which is compatible with the literature;[4,16] younger patients had a more favorable prognosis for survival. There is no consensus on the significance of the prognosis and location of disease involvement (axial or appendicular). We also did not find a statistically significant difference in site affected in relation to survival prognosis in our series.[3,10,17] The IPI scale is not used universally for reporting PBL, but in our study we found that most patients were classified as low grade, which is similar to the findings of publications that use this same scale.[15] The fact that the majority of publications do not use the IPI shows that this scale does not play a definitive role in the prognosis for PBL. In terms of treatment, chemotherapy is always used to treat PBL, even when the disease is localized.[5,16] We also found that rituximab, a monoclonal antibody directed against B-cell marker CD20, which is expressed in NHL, has been used to treat bone lymphoma since 1997.[17,18] However, this medication has only been approved for use in the Brazilian public health system since 2012. Consequently, only 13 patients (30%) in our series received this medication, which may have had a negative impact on survival prognosis in our cases. In the present study, lower age as well as the use of rituximab were significantly associated with better survival prognosis in patients with PBL. Because it is a rare disease, compilation of a large number of PBL cases is a lengthy process, which leads to a bias in relation to the diagnosis and treatment of this disease, in turn compromising analysis of the prognosis in the patients studied. In comparison with our previous study,[10] we observed significant differences in relation to current diagnosis and treatment of PBL. For example, in the previous study fewer than 80% of the patients received chemotherapy as part of their treatment; in our current study, 100% of patients were treated with chemotherapy. We can conclude that chemotherapy should continue to be used in all cases of PBL, with the addition

of radiotherapy and surgery in specific situations. We should also mention that immunotherapy with rituximab should be part of chemotherapy treatment for a better survival prognosis in patients affected by this disease.

CONCLUSION

The use of rituximab in the treatment regimen and lower patient age were associated with better survival prognosis in patients with PBL.

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ORIGINAL ARTICLE

SQUAMOUS CELL CARCINOMA IN THE FOOT: CASE SERIES AND LITERATURE REVIEW

CARCINOMA EPIDERMOIDE NO PÉ: SÉRIE DE CASOS E REVISÃO DA LITERATURA

Irocy Guedes Knackfuss[1†], Vincenzo Giordano[2], Alexandre Leme Godoy-Santos[3], Nurimar Conceição Fernandes[1] Olavo Pires de Camargo[3]

1. Department of Orthopedics and Traumatology, Faculdade de Medicina da Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil (In memoriam).
2. Prof. Nova Monteiro Orthopedics and Traumatology Service, Hospital Municipal Miguel Couto, Rio de Janeiro, RJ, Brazil.
3. Department of Orthopedics and Traumatology, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, SP, Brazil.

ABSTRACT

Objectives: To report a case series of squamous cell carcinoma (SCC) in the foot, describing previous risk factors, surgical treatment, histopathological findings, and functional and oncological results. Methods: Nine consecutive patients diagnosed with SCC of the foot were treated at a single institution and prospectively analyzed for risk factors related to the disease, surgical outcome, and histopathological, functional and oncological results. All patients had identifiable risk factors for SCC. Results: Definitive treatment consisted of partial (6 patients) or total (3 patients) amputation of the foot. The functional score was good or excellent in the surviving patients. Early identifiable risk factors are present in most patients. Biopsy when this diagnosis is suspected, in association with oncological principles, avoids diagnostic and treatment errors. Conclusion: Despite delayed diagnosis and surgical treatment with partial and total amputations of the foot in our series, we observed good oncological outcomes that avoided systemic spread of the disease and achieved expected functional results. ***Level of Evidence V; Case series.***

Keywords: Carcinoma, squamous cell. Foot. Amputation. Metastasis.

RESUMO

Objetivo. Relatar uma série de casos de carcinoma epidermoide no pé, descrever os fatores de risco prévios, os achados histopatológicos, o tratamento cirúrgico e os resultados funcionais e oncológicos. Métodos: Nove pacientes consecutivos com diagnóstico de CE na região do pé foram tratados em uma única instituição e analisados, prospectivamente com relação aos fatores de risco da doença, ao desfecho do tratamento cirúrgico e aos resultados histopatológicos, funcionais e oncológicos. Todos os pacientes apresentavam fatores de risco identificáveis. Resultados: O tratamento definitivo consistiu em amputação parcial (seis), amputação total (três). O escore funcional foi bom ou excelente nos pacientes sobreviventes. Fatores de risco identificáveis precocemente estão presentes na maioria dos pacientes. A biópsia na suspeita diagnóstica e o uso de princípios oncológicos evitam erros de diagnóstico e de tratamento. Conclusão: Em nossa série, apesar do diagnóstico tardio e do tratamento cirúrgico com amputações parciais e totais do pé, observamos bons resultados oncológicos que evitaram a disseminação sistêmica da doença e resultados funcionais esperados. ***Nível de Evidência V; Série de casos.***

Descritores: *Carcinoma de células escamosas. Pé. Amputação. Metástase.*

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INTRODUCTION

Squamous cell carcinoma (SCC) is a rare condition in the foot.[1,2] The disease was first described in 1828 by Marjolin, and its malignancy was recognized by Dupuytren.[3,4] SCC originates in keratinocytes and may develop a precursor lesion or de novo lesions.[4] Verrucous carcinoma, which is not strongly malignant but still locally invasive and destructive, rarely leads to metastases.[2,4] When untreated, the lesions may grow to large diameters. In the plantar region, they are irregularly shaped, well-demarcated, verrucous, and are also known as epithelioma cuniculatum.[5] Reports in the literature state that 13% occur in the legs, and this is the most common primary cancer of soft tissue in the foot, with an incidence slightly greater than melanoma and synovial sarcoma.[6]

Despite numerous publications on the subject in the literature, many orthopedic physicians demonstrate a lack of familiarity with this condition in their case reports, which invariably delays diagnosis and optimal treatment.[2,5-13] Treatment is usually palliative and includes aggressive and broad resection of the tumor.[8-10] Metastatic disease and recurrence of the lesion are uncommon, and are largely associated with incomplete initial excision of the tumor.[11]

All authors declare no potential conflict of interest related to this article.

Work conducted in the Department of Orthopedics, Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil, and in the Department of Orthopedics and Traumatology, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, SP, Brazil.
Correspondence: Alexandre Leme Godoy-Santos. Departamento de Ortopedia e Traumatologia da Universidade de São Paulo. Rua Dr. Ovídio Pires de Campos, 333, Cerqueira Cesar, São Paulo, SP, Brazil. 05403-010. alexandrelemegodoy@gmail.com

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The objectives of this study are to report a series of cases of SCC in the foot and to describe previous risk factors, histopathological findings, surgical treatment, and functional and oncological outcomes.

MATERIALS AND METHODS

The study included patients who were surgically treated for primary SCC of the foot over a 2-year period. The study excluded all patients with metastases related to the SCC at the time of admission, patients with SCC of the skin in other areas of the body, and patients with any other type of benign or malignant skin disease in the ankle/foot region.

The patients sought orthopedic treatment via referral from the Department of Dermatology (n=8) or spontaneous request (n=1). The main complaint was the presence of chronic lesions on the foot, which did not heal, occasionally bleeding and not permitting the patients to use closed shoes. Two patients had secondary infections, with purulent drainage at the time of the first medical visit. Data were collected on patient age, sex, predisposing factors from external conditions, duration of symptoms, location and size of the lesion, tumor staging, and definitive surgical treatment.[14,15] Postoperative complications were analyzed, along with functional results according to the Musculoskeletal Tumor Society Score (MSTS)[16] and oncological outcomes (remission, local recurrence, metastasis, and death from the disease). The MSTS score is described in Table 1. The location of the lesion was described according to the areas defined by Kirby et al.[17] (Figure 1)

All patients were subjected to routine laboratory examinations and X-rays. A computed tomography scan of the abdomen was performed in two patients with metastasis to the regional lymph nodes. Incisional biopsy was performed routinely, and after the diagnosis was confirmed, the patients were surgically treated as follows: resection of the metatarsal ray was performed in 4 patients, the hallux was amputated in 2 patients, transmetatarsal amputation was performed in 1 patients, and transtibial amputation in 2 patients. We informed the patients that data relating to these cases would be published, and they provided consent (study was approved by institutional review board under number 6070/3004).

Statistical analysis

The results were analyzed using descriptive statistics for all variables. The potential link between the duration of symptoms and lesion size was assessed using Pearson correlation analysis, with $p<0.05$. Potential differences between recurrence rates (recurrence or metastasis) and functional score based on primary definitive treatment were evaluated by Fisher's exact test, with $p<0.05$. Statistical analysis was performed using SPSS v.15.0 software (SPSS Inc., Chicago, IL).

RESULTS

Nine patients were included in the study, eight men and one woman. Mean patient age at treatment was 60 years (range: 45–86 years). Seven individuals were Caucasians and two were Black. In seven cases the tumor was located in the forefoot (Kirby zone 5), one case on the dorsum of the midfoot (Kirby zone 3), and one case on the midfoot plantar region (Kirby zone 4). The fourth toe was affected most often. The time interval between the first symptoms and the first visit ranged from six to 120 months, with an average of 30.7 months. The clear imbalance in this variable resulted from an extremely late diagnosis in case 9, with 120 months of evolution. The average lesion size in its largest linear dimension was 5.2 cm (range: 3.0–8.0 cm). There was no statistical correlation between the time until diagnosis and lesion size ($p>5\%$). Among the predisposing factors, all patients had some social or professional activity related to sun exposure and six (66.7%) smoked more than one pack of cigarettes per day. The demographic data for the patients included in the study are shown in Table 2.

One (11.0%) patient presented osseous invasion, which was seen in simple X-rays of the affected foot. (Figure 2) In the other eight patients, the X-rays were normal. None of the two patients with metastasis to the regional lymph nodes presented tomographic alterations in the abdomen. Microscopically, the most frequent

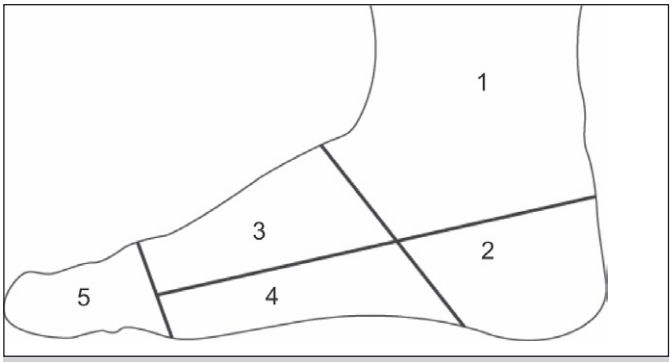

Figure 1. Zones, according to Kirby et al.

Table 2. Demographic data for the study population.

Case	Age	Sex	Race	Evolution time (months)	Location	Predisposing factor(s)
1	72	M	C	12	Right hallux	SE, tobacco use
2	44	F	B	24	Left 2nd toe	SE
3	78	M	C	07	Left 4th toe	SE
4	57	M	C	24	Right hallux	SE, tobacco use
5	40	M	C	06	Left foot, dorsum.	SE, tobacco use
6	86	M	C	24	Left 4th and 5th toes	SE, tobacco use
7	56	M	B	24	Right hallux	SE, tobacco use
8	49	M	C	36	Left 4th toe	SE
9	55	M	C	120	Bottom of right foot	SE, tobacco use

Source: DOT-UFRJ, 2017. Abbreviations: M - male, F - female, C – Caucasian, B - Black, SE - sun exposure.

Table 1. Description of MSTS score.

Score	Pain	Function	Emotional	External support	Functional Independence	Gait	Percentage (%)
5	None	No restrictions	Motivated	None	Independent	Normal	100
4	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	80
3	Not disabling	Recreational limitation	Satisfied	Orthesis	Limited	Minimal alteration	60
2	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	40
1	Incapacitating	Partial limitation	Accepts	Cane/crutch	Home	Very altered	20
0	Extremely incapacitating	Total restriction	No support	Two crutches	Dependent	Difficult	0

Source: DOT-UFRJ, 2017.

Figure 2. Case 9. Squamous cell carcinoma, ulcerative type; (A) plantar surface of the right foot, (B) anteroposterior X-ray view, (C) lateral surface of the right foot, and (D) profile X-ray view. Note the severe bone destruction caused by tumoral invasion.

histological type was well-differentiated SCC, in eight cases (88.9%). (Figure 3) According to the TNM System for Malignant Tumor Classification from the Union for International Cancer Control (UICC), in six patients (66.6%) the primary tumor was type T1, in two patients (22.0%) was type T2, and one patient (11.0%) was type T3. The complete classification is shown in Table 3.

Postoperative radiation therapy was not indicated for any patient. During the entire treatment period, the patients were monitored on an outpatient basis. The mean postoperative follow-up period was 51 months (range: 6–120 months). Two cases progressed to metastatic disease, leading to patient death (cases 1 and 9). Two cases recurred, and were treated with surgical revision and more proximal amputation (cases 3 and 6). There was no statistically significant relationship between initial definitive treatment and recurrence (p>5%). No patient developed postoperative complications requiring additional surgical intervention, such as infection or dehiscence of the surgical scar.

The mean MSTS score was 90% (varying from 80% to 100%), and all patients who were disease-free showed good or excellent functional results. There was no statistically significant relationship between initial definitive treatment and functional score (p>5%).

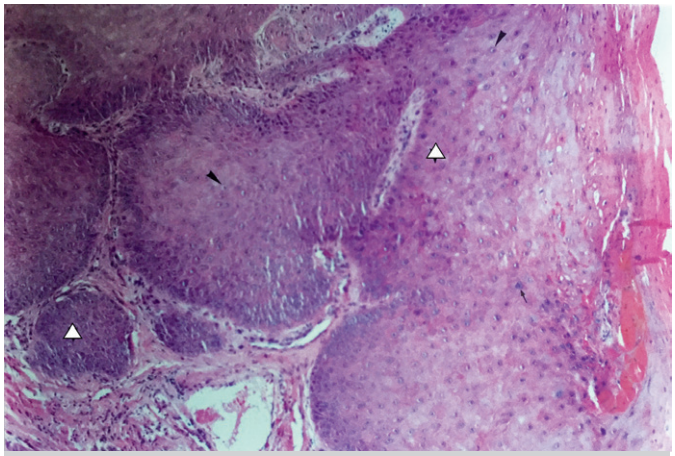

Figure 3. Case 1. Squamous cell carcinoma, ulcerative type. Photomicrograph of histological sample of the neoplasia, characterized by marked proliferation of cells in the epidermis, which appear as masses going deeper into the dermis (Δ). Note depolarization and mild cellular anomalies, characterized by occasional nuclear irregularity (λ) and prominent nucleoli (▶). Hematoxylin and eosin, 100x.

DISCUSSION

SCC of the foot is a rare malignant tumor of the epidermis. Although this is the most frequent malignant tumor found in the soft parts of the foot, its incidence has been described as roughly 0.6 to 3.0%.[1,7,12,13] It is commonly associated with chronic sun exposure, due to elastic degeneration of the dermis, irregular pigmentation, and telangiectasia.[14,18,19] However, SCC can also develop on ulcers, chronic granulomas, and fistular sinuses after ingestion of arsenic and exposure to tobacco smoke or radiation.[9,12,14,20] In broad terms, affected patients are in their 50s and 60s, and the disease affects men more frequently than women, at a ratio of 3:1.[2,12] Caucasians are more likely to develop SCC.[7,10] In this study, eight of the nine patients were men, the mean age at diagnosis was 60 years, and all participants reported daily exposure to ultraviolet radiation, which is common in tropical countries; three patients also smoked more than one pack of cigarettes per day.

The diagnosis is based on a high index of suspicion. Any changes in color, shape, or size, or sudden onset of pain in benign lesions of

Table 3. Morphological and histological characteristics of tumors, and TNM classification for the study population.

Case	Morphological type	Histological type	Primary Tumor	Regional lymph nodes	Metastasis
1	U	PD	T2	N1	M0
2	V	WD	T1	N0	M0
3	V	WD	T1	N0	M0
4	U	WD	T1	N0	M0
5	V	WD	T2	N0	M0
6	U	WD	T1	N0	M0
7	V	WD	T1	N0	M0
8	V	WD	T1	N0	M0
9	U	WD	T3	N1	M0

Source: DOT-UFRJ, 2017. Abbreviations: U - ulcerative, V - verrucous, WD - well differentiated, PD - poorly differentiated.

the foot should raise concerns about possible malignancy.[11] Furthermore, particular attention is recommended for any chronic lesion that has difficulty healing. Incisional biopsy should be performed first for definitive confirmation of the diagnosis;[10] scrape biopsy is not considered appropriate.[2] Microscopically, there is disruption of the basal membrane and dermis invasion by well-differentiated keratinocyte-like cells. Corneal pearls may be present. An increase in the number of atypical cells, greater degree of anaplasia, and increased number of mitotic figures indicate little differentiation of the tumor.[2,12] In some cases, the basal membrane remains intact and the carcinoma develops *in situ*.[2,6]

Treatment is based on surgical resection of the tumor. In general, lesions with regular margins should be treated with local excision.[2,6,8-10,18] Safety margins of at least 3.0–5.0 mm should be maintained, in accordance with the dermatological literature.[6] In more aggressive lesions, it is difficult to establish safety margins, and consequently more proximal amputation of the foot is indicated.[9,10] Complete excision of the tumor rarely leads to recurrence. In our study, two patients experienced recurrence, probably due to inadequate resection of the primary lesion, and required a higher level of amputation (cases 3 and 6). In untreated cases, SCC of the foot spreads to the regional lymph nodes.

The prognosis is determined by the presence of metastasis, lymph node involvement, treatment, and local recurrences. There is generally greater potential for metastatic disease when SCC develops on chronic ulcers, known as Marjolin ulcers. SCC is spread hematogenically as well as through the lymphatic vessels, depending on its location and its degree of aggressiveness.[7,12] In general, metastasis to the lymph vessels without bone or tendon involvement is extremely rare. But when ganglionic metastasis does occur, approximately 31% of patients die within five years.[9,19,20] In the present study, two patients developed metastatic disease, and died from related causes.

Prophylactic radiation of the inguinal lymph nodes and intraarterial infusion of the affected limb with methotrexate and floxuridine have been suggested after excision of the primary tumor.[9] However, prophylactic lymph node resection is controversial. Glass et al. recommend palpating the inguinal lymph node chain for 36 months after tumor excision.[20] Lymph node biopsy should always be performed after this period if enlarged or painful lymph nodes persist.[9]

CONCLUSIONS

Epidermoid carcinoma in the foot region is generally diagnosed late and subject to non-optimal initial treatment, requiring radical procedures with compromised functional results. Risk factors that can be identified early are present in the majority of patients. Biopsy in suspected cases and the use of oncologic principles can avoid errors in diagnosis and treatment. In our series, despite late diagnosis and surgical treatment with partial and total amputation of the foot, good oncological results were seen, which avoided systemic spread of the disease and provided the desired functional outcomes.

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. IGK (in memoriam)*: selected patients and acquired data. VG (0000-0002-4429-312X)*: acquired data, designed the study, interpreted the results, and drafted the article. ALGS (0000-0002-6672-1869)*: acquired data, designed the study, interpreted the results, and drafted the article. NCF (0000-0001-6037-0685)*: conducted the histological analysis, and interpreted and reviewed the data. OPC (0000-0002-1128-7292)*: evaluated the oncological basis critically reviewed the article. All authors contributed to the intellectual concept of the study and approved the final version of the manuscript. *ORCID (Open Researcher and Contributor ID).

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ORIGINAL ARTICLE

INCIDENCE OF PEDESTRIAN TRAFFIC INJURY IN SÃO PAULO, BRAZIL, IN 2016

INCIDÊNCIA DE ATROPELAMENTOS EM SÃO PAULO, BRASIL, EM 2016

Rodrigo Tadashi Martines[1], Washington Gomes de Araujo[1], Cintia Leci Rodrigues[1], Jane de Eston Armond[1]

1. Department of Collective Health, School of Medicine, Universidade de Santo Amaro, Sao Paulo, SP, Brazil.

ABSTRACT

Objective: Globally, more than 1.2 million people die from traffic accidents each year. In order to reduce the rate of traffic accidents and their subsequent social consequences in Sao Paulo, Brazil, the aim of this study was to characterize pedestrian victims of traffic accidents and occurrences. Methods: This is a cross-sectional, quantitative, descriptive and retrospective epidemiological study of 2723 pedestrians injured in traffic accidents during 2016 in Sao Paulo. Results: Of the total sample, 37.3% participants were female and 62.7% male; incidence was highest in the 10-19 year old age group (19.9%) and lower limb injuries were most frequent (28.6%). Of the cases attended in urgent health care units, 75.6% progressed to hospital discharge. Accidents were more frequent in the afternoon (44.6%), and most commonly involved cars (47.2%). Conclusions: This study showed the importance of making detailed records of traffic accidents to guide the government in intensive education efforts to develop a healthy society and respect for traffic regulations, to promote urban improvements involving signage and pavement, and to maintain pre-hospital and hospital care teams in strategic locations to minimize the time elapsed between the accident and care provided to the victim. ***Level of Evidence II; Retrospective study.***

Keywords: Pedestrians. Accidents, traffic. Wounds and injuries. Multiple trauma. Automobile driving. Cross-sectional studies.

RESUMO

Objetivo: Mundialmente, mais de 1,2 milhão de pessoas morrem por ano vítimas de acidentes de trânsito. Visando a redução das taxas de acidentes de trânsito e suas consequências sociais em São Paulo, Brasil, o objetivo deste estudo foi caracterizar as vítimas de acidentes e ocorrências de trânsito. Métodos: Este é um estudo epidemiológico transversal, quantitativo, descritivo e retrospectivo de 2.723 pedestres vítimas de acidentes de trânsito durante 2016 em São Paulo. Resultados: Do total da amostra, 37,3% participantes eram mulheres e 62,7% homens; a incidência foi maior no grupo de 10 a 19 anos (19,9%) sendo as lesões de membros inferiores as mais frequentes (28,6%). Dos casos encaminhados às unidades de pronto atendimento, 75,6% evoluíram para alta hospitalar. Os acidentes foram mais frequentes no período da tarde (44,6%) e a maioria associada a automóveis (47,2%). Conclusões: O estudo mostrou a importância de realizar o registro detalhado de acidentes de trânsito para orientar os governantes para a educação intensiva da população visando o desenvolvimento de uma sociedade sadia e o respeito às leis de trânsito, promover melhorias urbanas quanto à sinalização e ao pavimento das vias e para manter equipes de atendimento pré-hospitalar e hospitalar em locais estratégicos para minimizar o intervalo de tempo entre o acidente e o atendimento das vítimas. ***Nível de Evidência II; Estudo retrospectivo.***

Descritores: *Pedestres. Acidentes de trânsito. Ferimentos e lesões. Traumatismo múltiplo. Condução de veículo. Estudos transversais.*

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INTRODUCTION

The world economic growth has facilitated the increase of vehicle circulation, which makes traffic more complex and dangerous.[1] According to the Brazilian Traffic Code (1997), traffic is defined as the use of lanes by people, vehicles and animals isolated or in groups, driven or not, for the purposes of circulating, parking and loading or unloading vehicles.[2]

Globally, more than 1.2 million people die from traffic accidents each year and it represents the fifth leading cause of death.[1] In Brazil, external causes are ranked in the third position. In this country, 8200 traffic accidents with pedestrians were recorded in 2013, which is equivalent to a rate of 4.1 per 100 000 inhabitants. Among the reasons for traffic injuries and deaths are structural factors such as roads and urban lanes maintenance, increased fleet of vehicles, use of alcohol associated with driving and non-use of safety equipment.[3] Due to the vulnerability of pedestrians, the traffic accidents represent an important cause of morbidity and mortality in Brazil.[4]

Traffic accidents produce high emotional and social costs for victims and their families. They are able to generate mental damage, days

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Work conducted at the Department of Collective Health, School of Medicine, Universidade de Santo Amaro, São Paulo, SP, Brazil.
Correspondence: Rua das Uvaias 101, apto 103, São Paulo, SP, Brazil. 04055-110. tdmartines@yahoo.com

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of absence and decrease of productivity from work.[5] Psychological consequences and posttraumatic stress disorders resulting from ground transportation accidents are potentially disabling in the long-term.[6]

In epidemiology, traffic accidents have different distributions for gender, age, social groups and areas of risk, indicating situations of vulnerability of people and places.[7-9] The characterization of the traffic accidents and the victims contribute to urban planning and to the implementation of effective strategies in the prevention of accidents by the government.[10]

In 2010, the United Nations (UN) proclaimed the period from 2011 to 2020 as the Decade of Action for Traffic Safety. In this period countries should stabilize and reduce traffic fatalities by implementation of an action plan focused on the five pillars of interventions: road safety management, safer roads and mobility, safer vehicles, safer road users, and post-crash response. Therefore, the Brazilian Ministry of Health implemented the Transit Life Project in 2010 with focus on the strengthening of policies for injury prevention and death in traffic, through qualification of information, planning, monitoring and interventions evaluation.[11]

Faced with the challenges of reducing the number of traffic accidents and their social consequences, and for adequacy of pre-hospital and hospital care of trauma in the city of Sao Paulo, the aim of this study was to characterize the pedestrians injured in traffic accident in regard to gender, age, period of occurrence, association with alcohol and drug use, location of accidents, trauma diagnosis, medical evolution of the victims and vehicles involved, in order to guide the government in urban and hospital development strategies.

METHODS

This study is a cross-sectional, quantitative, descriptive and retrospective epidemiological study of pedestrians injured in traffic accident records, during 2016 in the city of Sao Paulo, state of Sao Paulo, Brazil.

Secondary data was collected on July 31, 2017 through the Violence and Accident Surveillance Information System (SIVVA) in the city of Sao Paulo, managed by the Health Surveillance Coordination of the Municipal Health Secretary of Sao Paulo (COVISA - SMS) in conjunction with Health Surveillance Supervisors (SUVIS). It analyzed notifications of traffic accidents involving pedestrians during the period from January 1, 2016 to December 31, 2016.

The group study consisted of 2723 pedestrian victims of traffic accidents. The variables were distributed as follows: characteristics of victims regarding gender (male and female), age group (in years), alcohol and drug use, main trauma diagnosis and medical evolution of the victims, characteristics of occurrences regarding time of the day (morning, afternoon, night and early hours), urban area (north, south, east, west, southeast and central) and types of vehicles (car, motorcycle, bicycle, heavy vehicle and others) involved in accidents.

After data collection, they were tabulated and processed in EXCEL software. Afterwards, descriptive statistical analyzes were performed, calculating the absolute and relative frequencies of variables.

According to the recommendation of the Resolution 466/12 of the Brazilian National Health Council (CNS) this work didn't need approval by the University Ethics Committee, since secondary data was used and was available in a public domain database.

RESULTS

According to the records from the SIVVA, in Sao Paulo during 2016, there were 2723 pedestrians injured in traffic accidents, 1017 (37.3%) female and 1706 (62.7%) male. It was observed that there was a higher incidence of accidents in 1the age group of 15-19 years (12.3%), followed by 20-24 years (11.0%) and 5-9 years (9.4%). Regarding alcohol consumption, 59 (2.2%) victims were under the effect of alcohol. As for illicit drugs use, only 17 (0.6%) pedestrians were under the influence of narcotics. (Table 1)

Table 1. Distribution of pedestrian victims of traffic accident. according to age, gender, alcohol and drug use in São Paulo, 2016.

Age (years)	Female N (%)	Male N (%)	Alcohol (+) N (%)	Alcohol (-) N (%)	Alcohol ignored N (%)	Drugs (+) N (%)	Drugs (-) N (%)	Drugs ignored N (%)	Total N (%)
0 a 4	71 (2.6)	136 (5.0)	0 (0)	60 (2.2)	147 (5.4)	0 (0.0)	58 (2.1)	149 (5.5)	207 (7.6)
5 a 9	77 (2.8)	178 (6.5)	0 (0)	88 (3.2)	167 (6.1)	0 (0.0)	88 (3.2)	167 (6.1)	255 (9.4)
10 a 14	71 (2.6)	135 (5.0)	1 (0.0)	64 (2.4)	141 (5.2)	1 (0.0)	64 (2.4)	141 (5.2)	206 (7.6)
15 a 19	137 (5.0)	199 (7.3)	4 (0.1)	100 (3.7)	232 (8.5)	2 (0.1)	102 (3.7)	232 (8.5)	336 (12.3)
20 a 24	98 (3.6)	202 (7.4)	10 (0.4)	103 (3.8)	187 (6.9)	7 (0.3)	103 (3.8)	190 (7.0)	300 (11.0)
25 a 29	60 (2.2)	126 (4.6)	5 (0.2)	59 (2.2)	122 (4.5)	1 (0.0)	60 (2.2)	125 (4.6)	186 (6.8)
30 a 34	57 (2.1)	113 (4.1)	6 (0.2)	65 (2.4)	99 (3.6)	3 (0.0)	65 (2.4)	102 (3.7)	170 (6.2)
35 a 39	56 (2.1)	113 (4.1)	7 (0.3)	63 (2.3)	99 (3.6)	0 (0.0)	69 (2.5)	100 (3.7)	169 (6.2)
40 a 44	46 (1.7)	93 (3.4)	7 (0.3)	49 (1.8)	83 (3.0)	2 (0.1)	49 (1.8)	88 (3.2)	139 (5.1)
45 a 49	54 (2.0)	86 (3.2)	3 (0.1)	43 (1.6)	94 (3.5)	0 (0.0)	44 (1.6)	96 (3.5)	140 (5.1)
50 a 54	60 (2.2)	79 (2.9)	5 (0.2)	39 (1.4)	95 (3.5)	0 (0.0)	42 (1.5)	97 (3.6)	139 (5.1)
55 a 59	57 (2.1)	68 (2.5)	6 (0.2)	54 (2.0)	65 (2.4)	1 (0.0)	57 (2.1)	67 (2.5)	125 (4.6)
60 a 64	54 (2.0)	66 (2.4)	1 (0.0)	47 (1.7)	72 (2.6)	0 (0.0)	48 (1.8)	72 (2.6)	120 (4.4)
65 a 69	35 (1.3)	30 (1.1)	2 (0.1)	31 (1.1)	32 (1.2)	0 (0.0)	34 (1.2)	31 (1.1)	65 (2.4)
70 a 74	38 (1.4)	28 (1.0)	2 (0.1)	23 (0.8)	41 (1.5)	0 (0.0)	23 (0.8)	43 (1.6)	66 (2.4)
75 a 79	22 (0.8)	18 (0.7)	0 (0)	18 (0.7)	22 (0.8)	0 (0.0)	18 (0.7)	22 (0.8)	40 (1.5)
80 a 84	15 (0.6)	24 (0.9)	0 (0)	11 (0.4)	28 (1.0)	0 (0.0)	11 (0.4)	28 (1.0)	39 (1.4)
85 a 89	8 (0.3)	6 (0.2)	0 (0)	6 (0.2)	8 (0.3)	0 (0.0)	6 (0.2)	8 (0.3)	14 (0.5)
90 e +	1 (0.0)	5 (0.2)	0 (0)	1 (0.0)	5 (0.2)	0 (0.0)	1 (0.0)	5 (0.2)	6 (0.2)
Blank/ Ignored	0 (0.0)	1 (0.0)	0 (0)	0 (0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Total	1017 (37.3)	1706 (62.7)	59 (2.2)	924 (33.9)	1740 (63.9)	17 (0.6)	942 (34.6)	1764 (64.8)	2723 (100.0)

Source: Violence and Accident Surveillance Information System (SIVVA) - Health Surveillance Coordination of the Municipal Health Secretary of Sao Paulo (COVISA - SMS) - Health Surveillance Supervisors (SUVIS).

Table 2 shows the distribution of pedestrian victims of traffic accidents records by time of the day and urban area of the accidents. The time of the accidents was recorded in 985 (36.2%) cases with a higher incidence in the afternoon with 439 (44.6%), followed by 201 (20.4%) in the evening, 183 (18.6%) in the morning and 162 (16.4%) in early mornings. In urban area data, 393 (14.4%) occurrences registered the address of the accidents. Based on those records without the ignored location of the accidents, 116 (29.5%) occurred in the South, 103 (26.2%) in the Southeast, 102 (25.9%) in the East, 46 (11.7%) in the West, 21 (5.3%) in the North and 5 (1.2%) in the Central area. The other 2327 (85.6%) accidents had the address of occurrences ignored.
The type of vehicle involved in the pedestrian traffic accidents is shown in Table 3. There were 1286 (47.2%) occurrences with cars, 630 (23.1%) with motorcycles, 157 (5.8%) with bicycles, 151 (5.5%) with heavy vehicles (buses, trucks and others). In 463 accidents (17.0%) the type of vehicle involved was not registered, considered blank or ignored.
Based on the International Classification of Diseases 10 (ICD-10) and considering the different anatomical regions of the human body, lesions diagnosed in lower limbs (28.6%) were the most frequent. Head and neck injuries (20.7%), upper limbs (10.9%), chest (2.4%) and abdomen, back and pelvis (2.4%) followed, respectively, traumas in lower limbs. Regarding lesion types, contusions were predominant in 262 (9.6%) cases. The diagnosis was not recorded in 70 (2.57%) cases. The main diagnosis of injuries resulting from pedestrian traffic accidents can be observed in Table 4.
Regarding care provided to pedestrian victims of traffic accidents, 2058 (75.6%) evolved to hospital discharge, 201 (7.4%) transferred to other health services, 95 (3.5%) needed hospitalization, and 20 (0.7%) resulted in death or died while in care. (Table 5)

DISCUSSION

Traffic accidents involving pedestrians represent a public health problem due to morbidity and mortality in Sao Paulo. With an expected population of 12.04 million of people in 2016, the coefficient of injury to pedestrians was 22.6 per 100 000 inhabitants. From 2723 records of traffic accidents with pedestrians, 62.7% involved males and 19.9% youth aged from 10 to 19 years. This observed data was similar to that found in other studies in which most victims were also male and young.[12-15]
In the age group from 0 to 19 years the rate of traffic accidents with pedestrians reached 36.9%, which indicates the vulnerability of children and adolescents as pedestrians due to their short stature and unawareness of traffic danger. This population does not have sufficient vision capacity above vehicles and also is not properly visualized by drivers at the rear of cars. In addition, children are still developing their psychomotor state, moving towards the achievement of a complete balance and dexterity, including factors of anatomy, physiology, environment and social relation.[13]

Table 3. Distribution of types of vehicles involved in traffic accidents with pedestrians in Sao Paulo, 2016.

Type of vehicle	Notifications N (%)
Car	1286 (47.2)
Motorcycle	630 (23.1)
Bicycle	157 (5.8)
Bus/Truck/Other	151 (5.5)
Subway or Train	7 (0.3)
Air Transport	1 (0.0)
Other	28 (1.0)
Blank or Ignored	463 (17.0)
Total	2723 (100.0)

Source: Violence and Accident Surveillance Information System (SIVVA) - Health Surveillance Coordination of the Municipal Health Secretary of Sao Paulo (COVISA - SMS) - Health Surveillance Supervisors (SUVIS).

Table 4. Main diagnosis of trauma in pedestrian victims of traffic accidents in São Paulo, 2016.

ICD 10 and diagnosis	N (%)	% Anatomical region
Head and Neck		
S09.9 Unspecified injury of face and head	148 (5.4)	20.7
S00.9 Superficial injury of unspecified part of head	88 (3.2)	
S01.8 Open wound of other parts of head	58 (2.1)	
S09.8 Other specified injuries of head	57 (2.1)	
S01.9 Open wound of unspecified part of head	53 (1.9)	
Other ICDs of head and neck	161 (5.9)	
Thorax		
S20.2 Contusion of thorax	31 (1.1)	2.4
Other ICDs of thorax region	35 (1.3)	
Abdomen, back and pelvis		
S30.0 Contusion of lower back and pelvis	18 (0.7)	2.4
Other ICDs of abdomen, lower back and pelvis	47 (1.7)	
Upper limbs		
S40.0 Contusion of shoulder and upper arm	50 (1.8)	10.9
Other ICDs of upper limbs	248 (9.1)	
Lower limbs		
S80.0 Contusion of knee	104 (3.8)	28.6
S90.0 Contusion of ankle	59 (2.2)	
Other ICDs of lower limbs	615 (22.6)	
Other diagnosis		
T00.9 Multiple superficial injuries, unspecified	174 (6.4)	32.4
T07 Unspecified multiple injuries	168 (6.2)	
T14.9 Unspecified injuries	154 (5.7)	
Other ICDs of unspecified region	385 (14.1)	
Blank	70 (2.6)	2.6
Total	2723	100.0

Source: Violence and Accident Surveillance Information System (SIVVA) - Health Surveillance Coordination of the Municipal Health Secretary of Sao Paulo (COVISA - SMS) - Health Surveillance Supervisors (SUVIS)

Table 2. Distribution of traffic accidents with pedestrians by periods and urban areas of occurrences in Sao Paulo, 2016.

Period / Urban area	Central N (%)	East N (%)	North N (%)	Southeast N (%)	South N (%)	West N (%)	Ignored N (%)	Total N (%)
Morning 7am – 12:59pm	3 (0.1)	16 (0.6)	4 (0.1)	13 (0.5)	19 (0.7)	12 (0.4)	116 (4.3)	183 (6.7)
Afternoon 1pm – 6:59pm	1 (0.0)	38 (1.4)	6 (0.2)	32 (1.2)	39 (1.4)	20 (0.7)	303 (11.1)	439 (16.1)
Evening 7pm - 12:59am	0 (0.0)	12 (0.4)	6 (0.2)	18 (0.7)	17 (0.6)	6 (0.2)	142 (5.2)	201 (7.4)
Early hours 1am – 6:59am	0 (0.0)	9 (0.3)	3 (0.1)	15 (0.6)	12 (0.4)	4 (0.1)	119 (4.4)	162 (5.9)
Blank/ Ignored	1 (0.0)	27 (1.0)	2 (0.1)	25 (0.9)	29 (1.1)	4 (0.1)	1650 (60.6)	1738 (63.8)
Total	5 (0.2)	102 (3.7)	21 (0.8)	103 (3.8)	116 (4.3)	46 (1.7)	2330 (85.6)	2723 (100.0)

Source: Violence and Accident Surveillance Information System (SIVVA) - Health Surveillance Coordination of the Municipal Health Secretary of Sao Paulo (COVISA - SMS) - Health Surveillance Supervisors (SUVIS).

Table 5. Medical evolution of the victims of traffic accidents in São Paulo in 2016.

Medical evolution	N (%)
Follow up	22 (0.8)
Discharge	2058 (75.6)
Observation	90 (3.3)
Hospitalization	95 (3.5)
Received in death	4 (0.1)
Transferred	201 (7.4)
Death in care	16 (0.6)
Blank or ignored	237 (8.7)
Total	2723 (100.0)

Source: Violence and Accident Surveillance Information System (SIVVA) - Health Surveillance Coordination of the Municipal Health Secretary of Sao Paulo (COVISA - SMS) - Health Surveillance Supervisors (SUVIS).

Given this data, traffic education, especially for children and youth is one of the instruments that can contribute to the reduction in medium and long-term accident rates. Effectively safe traffic can be achieved when citizens become more aware of their civil responsibilities and more respectful to the rights of others. Society will have citizens who develop these values if, from an early age, children and adolescents are educated to become conscious pedestrians and drivers.[16]

Considering the elderly population (over 60 years), the data analyzed indicated a rate of 12.8% cases of traffic accidents with pedestrians, suggesting the need for a closer look at this population. Elderly are backwards to children and adolescents since they lose their sensory, balance, muscular and intellectual capacity, characterized by physiological and functional decline, thus becoming increasingly vulnerable.[13] In the elderly between 60 and 74 years old involved in the accidents, approximately 25% evolved to death. For the population over 75 years, this rate may reach 50%.[4]

Traffic accidents with pedestrians are very violent. The greater physical vulnerability of the elderly population contributes to increased lethality. They represent an absolutely unequal shock, which can lead to serious injuries, even when vehicles are travelling at low speeds.[17] In this way, it is necessary to stimulate the formation of attitudes of respect to elderly pedestrians with education and traffic awareness, as well as to invest in the construction of accessible and inclusive urban lanes that allow the right of universal mobility with safety.

Analyzing the time of the day of recorded traffic accidents with pedestrians, there is a higher incidence (44.6%) of accidents in the afternoon, which suggests the relation between occurrences and a greater circulation of people. In this period, there is an increased flow of school children through the streets, due to the end of classes and of workers who have left their labour activities. According to Almeida et al.,[18] accidents occurring at night present high gravity and can be related to less traffic on the streets, which allow the speeding of cars. In addition, the combination of alcoholic beverages and driving contribute to greater lethality of trampling.

The data analyzed suggest that there is no relationship between alcohol and drug use by pedestrians with the risk of trampling. Only 6% of registered cases were related to victims who consumed alcohol and 1.8% used some type of illicit drug.

According to Table 2, it is observed that data indicates the deficiency to record the location of the traffic accidents. With 85.6% of ignored locations, it is not possible to inquire whether there is a direct relationship between traffic accidents in regions that are more susceptible to being hit. In this way, public authorities will not have a baseline to focus on prevention of pedestrian accidents location of a higher risk.

The rate of traffic accidents with pedestrians caused by cars and motorcycles in Sao Paulo, in 2016, reached 70.3% of the occurrences. According to the Brazilian Institute of Geography and Statistics – IBGE, the fleet of vehicles in Sao Paulo is approximately 5.4 million cars and 895 thousand motorcycles.[19] Certainly, a large share of this fleet is concentrated in urban areas, thus leading to increased risk of traffic accidents with pedestrians. In this way, the need for adequate traffic education is reassured, such as respecting traffic signals and crosswalks by drivers and pedestrians, improving road signs, streets pavement and lighting, controlling speed and vehicles that run red lights.

Regarding types of injuries, it is observed that there is a predominance of contusion and multiple traumatisms. It is evident once again that trampling is always characterized by an unequal shock that causes greater damage to the victims because they do not use safety equipment at the moment of occurrence. Despite the fragility factors of pedestrians, 75.6% evolved to hospital discharge and only 0.7% to death. In any case, the activation of rescue teams, pre-hospital and hospital care, rehabilitation treatments, time away from labour activities, and consequences of trampling represent social and psychological impacts, in addition to high costs for public administration and victims.

In traffic accidents with pedestrian prevention actions, besides the signs and adjustments of roadways, the occurrences of these accidents are also associated with a lack of attention or distraction of both drivers and pedestrians.

According to Lennon et al.[20] the act of crossing or walking on the streets represent the smallest part of the time, but they are associated with a high risk of being hit. Crossing the street is a complex exercise that requires high demand for perception and cognitive ability of the pedestrian. External factors, such as the use of Smartphone when walking, generate distractions and may interfere with instant decision processes. These factors may compromise the assessment of imminent danger, interfere with the perception of distance and approach speed of vehicles causing the pedestrian to make mistaken decisions that exacerbate the risk of being hit.

The analysis of the factors that interfere in the occurrence of traffic accidents is a complex procedure because they are numerous and interrelated. There must be an enlargement of the attention on the traffic accident phenomenon from analysis of its characteristics of street lanes, pedestrians and vehicles involved. This aspect highlights the importance of intersectoral practices to confront the problem.[18]

CONCLUSION

This study revealed the importance of keeping correct records of the occurrences data, so they can guide the government for intensive education of schoolchildren, adolescents, adults, elderly people and, mainly, drivers of vehicles for the development of a healthy society and respect for traffic regulations. In addition, they will be able to promote urban improvements in signalling and street's pavement, and maintain pre-hospital and hospital care teams in strategic locations to minimize the time between the accident and the victim's care.

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PROFILE OF PATIENTS WITH OSTEOPOROTIC FRACTURES AT A TERTIARY ORTHOPEDIC TRAUMA CENTER

PERFIL DE PACIENTES COM FRATURAS OSTEOPORÓTICAS NUM CENTRO TERCIÁRIO DE TRAUMA ORTOPÉDICO

Michael Minsu Shu[1], Andre Langes Canhos[1], Guilherme Pereira Ocampos[1], Perola Grimberg Plapler[1], Olavo Pires Camargo[2], Marcia Uchoa de Rezende[1]

1. Osteometabolic Diseases Group, Instituto de Ortopedia e Traumatologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, SP, Brazil.
2. Department of Orthopedics and Traumatology, Faculdade de Medicina, Universidade de São Paulo, SP, Brazil.

ABSTRACT

Objective: To evaluate the profile of patients with osteoporotic fractures treated at a tertiary orthopedic hospital. Methods: Using questionnaires, 70 patients with osteoporotic fractures (OF) were compared with 50 outpatients with multiple osteoarthritis (OA) followed through an outpatient clinic. Results: The OF group was older ($p < 0.001$), less heavy ($p=0.003$), had lower BMI ($p=0.006$), was more likely to be white ($p=0.011$), was less likely to be married ($p=0.008$), and had previous falls, previous fractures, old fractures (>1 year), falls in the last 12 months, fractures due to falls, and needed more assistance ($p<0.05$). They also had lower Lawton & Brody Instrumental Activities of Daily Living scores ($p <0.05$) and reported less lower limb disability, foot pathology, muscle weakness, hypothyroidism, and vitamin D intake than patients in the OA group. White race, previous falls, and previous fractures increase the risk of osteoporotic fractures by 10.5, 11.4, and 4.1 times, respectively. The chance of fracture dropped 29% for each one-unit increase in Lawton & Brody IADL score. Married participants had fewer fractures than participants with other marital status. Conclusion: Together, race, marital status, previous falls, foot pathologies, previous fractures, and IADL scores define the profile of patients with osteoporotic fractures. ***Level of Evidence III; Case control study.***

Keywords: Osteoporotic fractures. Osteoporosis. Epidemiology. Diagnosis. Bone density. Prevalence.

RESUMO

Objetivo: Avaliar o perfil dos pacientes com fraturas osteoporóticas atendidos em hospital de atendimento terciário ortopédico. Métodos: Setenta pacientes com fraturas osteoporóticas (FO) foram comparados a 50 pacientes com acompanhamento ambulatorial de osteoartrite (OA) por meio de questionários. Resultados: O grupo FO apresentou média de idade maior ($p < 0,001$), menor peso ($p = 0,003$), menor IMC ($p = 0,006$), maior frequência de pacientes brancos ($p = 0,011$), menor frequência de casados ($p = 0,008$), mais quedas prévias, fraturas prévias, fratura antiga (> 1 ano), queda nos últimos 12 meses, fratura por causa da queda e necessitam de mais auxílio ($p < 0,05$); menor Lawton e Brody AIVD (Atividades instrumentais da vida diária, $p < 0,05$), reportando menos deficiência de membros inferiores, patologia nos pés, fraqueza muscular, hipotireoidismo e consumo de vitamina D do que pacientes do grupo OA. Raça branca, quedas e fraturas prévias aumentam o risco de fraturas osteoporóticas em 10,5, 11,4 e 4,1 vezes respectivamente. A chance de fratura foi reduzida em 29% a cada aumento de uma unidade no Lawton e Brody AIVD. Casados fraturam menos que outros estados civis. Conclusão: Conjuntamente, a raça, estado civil, quedas prévias, patologias nos pés, fraturas prévias e AIVD definem o perfil dos pacientes com fraturas osteoporóticas deste centro. ***Nível de Evidência III; Estudo de caso-controle.***

Descritores: *Fraturas por osteoporose. Osteoporose. Epidemiologia. Diagnóstico. Densidade óssea. Prevalência.*

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INTRODUCTION

Osteoporosis is a chronic disease characterized by progressive reduction of bone mass, leading to decreased bone strength and greater risk of fractures;[1] it is considered a public health problem worldwide. It has been estimated that 9 million osteoporotic fractures occur each year, the equivalent of one fracture every 3.5 seconds.[2] Although this is the most common bone disease,[3] many patients are not treated until the first fracture occurs. The Brazilian population is in the process of aging, as can be seen in the epidemiologic pyramids for the years 2017 and 2050.[4] This aging is accompanied by an increase in the prevalence of osteoporosis and the incidence of falls and fractures.[5] These fractures are associated with increased

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Work conducted at the Osteometabolic Diseases Group, Instituto de Ortopedia e Traumatologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, SP, Brazil.
Correspondence: Marcia Uchoa de Rezende. Rua Dr. Ovídio Pires de Campos, 333, Cerqueira Cesar, São Paulo, Brazil. 05403-010. murezende@icloud.com

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mortality, decreased functional capacity and quality of life,[6-9] and increased spending in the health system. It is estimated that approximately 50% of women and 20% of men 50 years of age or over will suffer an osteoporotic fracture during their lives.

Even though osteoporosis and osteopenia are a growing problem in older people, attempts to analyze the characteristics of osteoporotic patients in Brazil are rare.

The objective of this study was to evaluate the epidemiological profile of the population affected by osteoporotic fractures (fractures of the proximal femur, the proximal humerus, the distal radius, and the thoraco-lumbar spine) treated in a tertiary orthopedic hospital over a three-month period, with or without a previous diagnosis of osteopenia or osteoporosis, in an attempt to correlate the clinical characteristics present in patients treated for osteoarthritis during the same period.

Primary objective: To explore the epidemiological profile of patients with osteoporotic fractures treated in a tertiary orthopedic hospital, identifying factors potentially related to this fracture in relation to patients treated for osteoarthritis during the same period.

Secondary objective: To describe the types of osteoporotic fractures treated in a tertiary center, along with function and bone mineral density in these patients.

MATERIALS AND METHODS

This study was conducted at the Osteo-Metabolic Diseases Group at the Instituto de Ortopedia e Traumatologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (IOT-HC-FMUSP) with the approval of the institutional review board (number 76629217.3/0000.0068).

All participants were patients with osteoporotic fractures treated over a three-month period in 2017 and patients with osteoarthritis of the knee (of this group, only those treated in the osteometabolic disease group at a tertiary orthopedic hospital).

Inclusion criteria: Study group (osteoporotic fractures, OF): Patients above 45 years of age presenting any one or a combination of the following fractures: proximal femur, proximal humerus, distal radius, and thoraco-lumbar spine, with a mechanism of low-energy trauma. Patients with high-energy fractures were not included.

Control group (patients with osteoarthritis, OA): Patients above 45 years with clinical/radiographic diagnosis of osteoarthritis of the knee,[10] isolated or not, with and without comorbidities.

Exclusion criteria: Age below 45 years; suspicion or confirmation of pathological fractures; patient unwilling to participate.

Interventions

The participants filled out a questionnaire (Table 1) collecting data on demographic profile, fracture type, race, patient level of education, habits, personal history, previous fractures, level of physical activity, aids for locomotion, place and time of the accident which caused the fracture, use of medications and behavioral measures to treat osteoporosis, and functional assessment [Katz and Lawton and Brody].[11,12] Patients with proximal femur fracture completed the Harris Hip Score (HSS)[13] and fragility score (SHARE) questionnaires.

Statistical analysis

Patient characteristics were described using absolute and relative frequencies according to groups for the qualitative variables, and association was verified using the chi-square or Fisher's exact tests. Summary measures (mean and standard deviation or median, minimum, and maximum) were calculated according to groups for quantitative variables and the groups were compared using Student's t-test or the Mann-Whitney test.

The unadjusted odds ratio was estimated for each variable to approximate the chance of osteoporosis with the respective intervals, with 95% confidence.

The multiple logistic regression model was used to explain the osteoporosis group, selecting the variables that showed statistical significance in the bivariate tests and using backward stepwise selection with a 5% criterion for entry and exit of the variables ($p<0.05$). IBM SPSS for Windows software version 20.0 was used for these analyses, and Microsoft Excel 2003 was used to tabulate the data. The tests were performed at a 5% significance level.

RESULTS

The results of the questionnaires applied to 70 patients with osteoporotic fractures (OF) and 50 patients with osteoarthritis (OA) of the knee (or osteoarthritis of multiple joints including the knee) are summarized in Tables 2–4.

Table 2 shows that in isolation, patients with osteoporosis were statistically older on average ($p<0.001$), were less heavy and had lower BMI ($p=0.003$ and $p=0.006$, respectively), the frequency of white race was statistically higher in patients with osteoporosis ($p=0.011$), patients with osteoporotic fractures were statistically less likely to be married ($p=0.008$), and this group had more previous falls, previous fractures, old fractures (> 1 year), falls over the past 12 months, fractures from falls, and needed more assistance ($p<0.05$) than patients with OA. Patients with osteoporotic fractures reported less disability in the lower limbs, pathology in the feet, muscle weakness, hypothyroidism, and vitamin D consumption than patients with OA. Using the functional scale by Lawton and Brody,[12] their scores for instrumental activities of daily living (IADL) were lower ($p<0.05$).

Table 3 shows that together, race, marital status, previous falls, pathologies in the feet, muscle weakness, hypothyroidism, previous fractures, and Lawton and Brody IADL score[12] explained the patients with osteoporosis independent of the other characteristics we assessed ($p<0.05$). White patients were 10.48 times more likely to present osteoporosis than nonwhite patients, single patients and those with other marital status had a statistically greater chance of osteoporosis than married patients, patients who had previous falls were 11.39 times more likely to have osteoporosis than patients without previous falls, and patients with previous fractures were 4.13 times more likely to have osteoporosis than patients without previous fractures. Pathologies of the feet, muscle weakness, and hypothyroidism presented similar protections for osteoporosis, with the chance of osteoporosis approximately 86% less for each of these characteristics, and each one-unit increase in the Katz and Lawton IADL score[12] decreased the chance of osteoporosis by 29%.

Table 4 shows the profile of patients with osteoporotic fractures treated in a tertiary trauma center, with an 81% incidence of patients with hip fractures, confirming that osteoporosis accompanies this fracture in mean bone densitometry values.

DISCUSSION

Osteoporosis is a chronic disease characterized by progressive decrease in bone mass, leading to decreased bone strength and greater risk of fractures.[1] This disease can be characterized as primary or secondary. Primary osteoporosis can occur in both sexes at any age, but often occurs after menopause in women and later in men.[1]

In this study we observed that the patients with osteoporotic fractures were older, a greater number were women (similar to the group with OA), weighed less, had lower BMI, and whites were more prevalent (Table 2), consistent with findings in other studies.[1,14,15] Perhaps because of the size and characteristics of the sample (older adults, Caucasians, and hip fractures were more prevalent) (Tables 2, 3 and 4),

Table 1. Evaluation of post-osteoporotic fracture patients and controls.

Identification	
Age	
Sex	Male: 0 / Fem: 1
Weight	
Height	
Race	White: 0 / Nonwhite: 1
Marital status:	Married: 0 / Widowed: 1 / Single: 3 / Other = 4
Lives with	Number of people
Kinship	Alone: 0 / Companion: 1 / Child: 2 / Grandchild: 3 / Other: 4
Education	Illiterate: 0 / Literate: 1
Number of years of school	
Father or mother with hip fracture?	No: 0 / Yes: 1
Current smoker?	No: 0 / Yes: 1
Glucocorticoids	No: 0 / Yes: 1
Rheumatoid arthritis?	No: 0 / Yes: 1
Secondary osteoporosis?	No: 0 / Yes: 1
Alcohol: >3 drinks per day?	No: 0 / Yes: 1
Sedatives?	No: 0 / Yes: 1
Previous falls?	No: 0 / Yes: 1
Cognitive deficit?	No: 0 / Yes: 1
Visual impairment?	No: 0 / Yes: 1
Disability of lower limbs?	No: 0 / Yes: 1
Foot pathology?	No: 0 / Yes: 1
Change in balance?	No: 0 / Yes: 1
Muscle weakness?	No: 0 / Yes: 1
Changes in gait?	No: 0 / Yes: 1
Postural hypotension?	No: 0 / Yes: 1
Dizziness?	No: 0 / Yes: 1
Depression/Apathy/Confusion?	No: 0 / Yes: 1
Diabetes?	No: 0 / Yes: 1
HBP?	No: 0 / Yes: 1
Hypothyroidism?	No: 0 / Yes: 1
Previous fractures?	No: 0 / Yes: 1
Old fracture (> 1 year)?	No: 0 / Yes: 1
Current fracture?	No: 0 / Yes: 1
Date of current fracture?	
Fractured limb	Spine: 0 / Lumbar Spine: 1 / R Hip: 2 / L Hip: 3 / R Wrist: 4 / L Wrist: 5 / R Shoulder: 6 / L Shoulder: 7
Physical activity before fracture?	No: 0 / Yes: 1
Type of activity	Weight training: 0 / Stretching 1 / Water or pool exercise: 2 / Walking: 3 / Cycling: 4
Physical activity after fracture?	No: 0 / Yes: 1
Type of activity	Weight training: 0 / Stretching 1 / Water or pool exercise: 2 / Walking: 3 / Cycling: 4
Frequency	1x month: 0 / 2X month: 1 / 3X month: 2 / 1X week: 3 / 2X week: 4 / 3X week: 5 / >4X week: 6 / Never: 7
Fear of falling?	No: 0 / Yes: 1
Fall in last 12 months?	No: 0 / Yes: 1
Number of falls?	
Where?	At home: 0 / Outside the home: 1
Factors	Dizziness: 0 / Tripped: 1 / Slipped: 2 / Weakness or lower limb instability: 3 / Other: 4
Fracture from fall?	No: 0 / Yes: 1
Assistance	Cane: 0 / Crutches: 1 / Walker: 2 / Wheelchair: 3 / None: 4
Mechanism of trauma?	Fall from height: 0 / Same-level fall: 1 / Direct trauma: 2 / Twisting: 3 / Carrying weight: 4
Time of Accident	7:00 -11:00: 0 / 11:01 - 15:00 1 / 15:01 - 19:00 2 / 19:01 - 22:00 3 / 22:01 - 7:00 4
Previous conduct related to current fracture?	Analgesic medication: 0 / Cast or vest: 1 / Surgery: 2 / Physical therapy: 3
Prior diagnosis of osteoporosis?	No: 0 / Yes: 1
Calcium supplementation?	No: 0 / Yes: 1
Sun exposure 3x week?	No: 0 / Yes: 1
Vitamin D supplementation?	No: 0 / Yes: 1
If yes, how many IU?	
Taking medication for osteoporosis?	No: 0 / Yes: 1
Katz ADL	No: 0 / Yes: 1 - (Maximum: 6)
Lawton & Brody IADL	No: 0 / Yes: 1 - (Maximum: 8)

Table 2. Description of characteristics present in both groups and the results of unadjusted analyses.

	Group						
Variable	**Control**	**Osteoporosis**	**Total**	**OR**	**IC (95%)**		**p**
	(N = 50)	(N = 70)	(N = 120)		Below	Above	
Sex (female), n (%)	39 (78)	49 (70)	88 (73.3)	0.66	0.28	1.53	0.329
Age (years), mean SD	66.7 9.6	75.1 11.7	71.6 11.6	1.07	1.03	1.12	<0.001*
Weight (Kg), mean SD	72.9 11.2	66 13.1	68.8 12.8	0.96	0.92	0.99	0.003**
Height (cm), mean SD	162.3 7.3	161.4 8.8	161.8 8.2	0.99	0.94	1.04	0.601**
BMI (Kg/m), mean SD	27.9 4.3	25.3 5.1	26.3 5	0.89	0.82	0.97	0.006**
Education (years of school), median (min.; max.)	8 (0; 30)	8 (0; 18)	8 (0; 30)	0.98	0.91	1.05	0.648£
Race (White), n (%)	35 (70)	62 (88.6)	97 (80.8)	3.32	1.28	8.61	0.011
Marital status, n (%)							0.008
Married	33 (66)	25 (35.7)	58 (48.3)	1.00			
Widowed	7 (14)	22 (31.4)	29 (24.2)	4.15	1.53	11.24	
Single	3 (6)	11 (15.7)	14 (11.7)	4.84	1.22	19.21	
Other	7 (14)	12 (17.1)	19 (15.8)	2.26	0.78	6.58	
Lives with, median (min.; max.)	1 (0; 3)	1 (0; 6)	1 (0; 6)	1.301	0.95	1.78	0.370£
Father or mother with hip fracture, n (%)	3 (6)	4 (5.7)	7 (5.8)	0.95	0.20	4.44	>0.999*
Current smoker, n (%)	6 (12)	8 (11.4)	14 (11.7)	0.95	0.31	2.92	0.923
Glucocorticoids, n (%)	3 (6)	5 (7.1)	8 (6.7)	1.21	0.27	5.29	>0.999*
Rheumatoid arthritis, n (%)	0 (0)	2 (2.9)	9 (7.5)	2.71	0.04	0.91	0.751
Secondary osteoporosis, n (%)	7 (14)	4 (5.7)	11 (9.2)	0.37	0.10	1.35	0.198*
Alcohol: >3 drinks per day, n (%)	3 (6)	2 (2.9)	5 (4.2)	0.46	0.07	2.87	0.648*
Sedatives, n (%)	7 (14)	9 (12.9)	16 (13.3)	0.91	0.31	2.62	0.856
Previous falls, n (%)	13 (26)	38 (54.3)	51 (42.5)	3.38	1.54	7.43	0.002
Cognitive deficit, n (%)	3 (6)	9 (12.9)	12 (10)	2.31	0.59	9.01	0.217
Visual impairment, n (%)	25 (50)	30 (42.9)	55 (45.8)	0.75	0.36	1.56	0.439
Disability in lower limbs, n (%)	13 (26)	7 (10)	20 (16.7)	0.32	0.12	0.86	0.020
Foot pathology, n (%)	18 (36)	6 (8.6)	24 (20)	0.17	0.06	0.46	<0.001
Changes in balance, n (%)	19 (38)	25 (35.7)	44 (36.7)	0.91	0.43	1.92	0.798
Muscle weakness, n (%)	24 (48)	21 (30)	45 (37.5)	0.46	0.22	0.99	0.045
Changes in gait, n (%)	24 (48)	24 (34.3)	48 (40)	0.57	0.27	1.19	0.131
Postural hypotension, n (%)	10 (20)	13 (18.6)	23 (19.2)	0.91	0.36	2.29	0.845
Dizziness, n (%)	13 (26)	18 (25.7)	31 (25.8)	0.99	0.43	2.26	0.972
Depression/Apathy/Confusion, n (%)	11 (22)	17 (24.3)	28 (23.3)	1.14	0.48	2.70	0.770
Diabetes, n (%)	19 (38)	22 (31.4)	41 (34.2)	0.75	0.35	1.60	0.454
HBP, n (%)	30 (60)	35 (50)	65 (54.2)	0.67	0.32	1.39	0.278
Hyperthyroidism, n (%)	14 (28)	8 (11.4)	22 (18.3)	0.33	0.13	0.87	0.021
Previous fractures, n (%)	8 (16)	35 (50)	43 (35.8)	5.25	2.16	12.78	<0.001
Old fracture (> 1 year), n (%)	8 (16)	35 (50)	43 (35.8)	5.25	2.16	12.78	<0.001
Physical activity before fracture, n (%)	19 (38)	21 (30)	40 (33.3)	0.70	0.33	1.51	0.359
Fear of falling, n (%)	34 (68)	44 (62.9)	78 (65)	0.80	0.37	1.72	0.560
Fall in last 12 months, n (%)	17 (34)	41 (58.6)	58 (48.3)	2.74	1.29	5.83	0.008
Fracture from fall, n (%)	2 (4)	67 (95.7)	69 (57.5)	536.00	86.23	3331.95	<0.001
Assistance, n (%)	5 (10)	35 (50)	40 (33.3)	9.00	3.19	25.36	<0.001
Prior diagnosis of osteoporosis, n (%)	14 (28)	26 (37.1)	40 (33.3)	1.52	0.69	3.33	0.295
Calcium supplementation, n (%)	14 (28)	20 (28.6)	34 (28.3)	1.03	0.46	2.30	0.945
Sun exposure 3x week, n (%)	24 (48)	36 (51.4)	60 (50)	1.15	0.56	2.37	0.711
Vitamin D supplementation, n (%)	28 (56)	22 (31.4)	50 (41.7)	0.36	0.17	0.76	0.007
Taking medication for osteoporosis, n (%)	4 (8)	8 (11.4)	12 (10)	1.48	0.42	5.23	0.537
Katz ADL, median (min.; max.)	6 (2; 6)	6 (1; 6)	6 (1; 6)	0.73	0.46	1.16	0.090£
Lawton & Brody IADL, median (min.; max.)	8 (1; 8)	7.5 (0; 8)	8 (0; 8)	0.83	0.70	0.99	0.015£

Chi-square test; * Fisher's exact test; ** Student's t-test; £ Mann-Whitney test.

Table 3. Result of the joint model describing the osteoporosis group according to evaluated variables.

Variable	OR	IC (95%)		p
		Below	Above	
Race (White)	10.48	1.61	68.20	0.014
Marital status				
Married	1.00			
Widowed	4.93	0.94	25.99	0.060
Single	57.15	2.81	1162.39	0.008
Other	10.85	1.80	65.56	0.009
Previous falls	11.39	2.18	59.45	0.004
Foot pathologies	0.13	0.02	0.74	0.022
Muscle weakness	0.15	0.03	0.77	0.024
Hypothyroidism	0.14	0.03	0.75	0.022
Previous fractures	4.13	1.12	15.23	0.033
Katz & Lawton IADL	0.71	0.53	0.95	0.020

Multiple logistic regression.

Table 4. Description of characteristics that were evaluated only in patients with osteoporosis.

Variable	Description
Fractured limb, n (%)	
Lumbar Spine	2 (2.9)
Hip	57 (81.4)
Wrist	4 (5.7)
Shoulder	7 (10)
Physical activity after fracture, n (%)	
No	47 (67.1)
Yes	23 (32.9)
Ca Supplementation, n (%)	
No	35 (71.4)
Yes	14 (28.6)
SHARE FI exhaustion, n (%)	
No	29 (58)
Yes	21 (42)
SHARE FI Appetite, n (%)	
Reduced	8 (16)
Maintained	37 (74)
Increased	5 (10)
HSS Pain	
mean SD	32.2 12.6
median (min.; max.)	40 (8; 44)
HSS Function	
mean SD	26.3 12
median (min.; max.)	27.5 (0; 47)
HSS ADM	
mean SD	2.4 0.8
median (min.; max.)	2.2 (0.9; 4)
HSS ADM Deformity	
mean SD	3.3 1.3
median (min.; max.)	4 (1; 4)
HSS Total	
mean SD	65.1 19.6
median (min.; max.)	72 (20.9; 97)
DMO COL T-Score	
mean SD	-2 1.8
median (min.; max.)	-2.1 (-4.8; 2.6)
DMO FN T-Score	
mean SD	-2.7 0.6
median (min.; max.)	-2.6 (-3.7; -1.7)
DMO TH T-Score	
mean SD	-2.5 0.8
median (min.; max.)	-2.8 (-3.8; -1.3)
DMO Troc T-Score	
mean SD	-2.4 0.7
median (min.; max.)	-2.4 (-2.9; -1.9)

Although there were 70 patients with osteoporosis, some information was missing for all variables.

consumption of glucocorticoids, and consumption alcohol and tobacco were not seen to have a large influence, as described in the literature,[1,14-16] but we found a protective relationship against osteoporotic fractures in married patients in relation to those with other marital status. (Tables 2 and 3) Pluskiewicz et al.[16] reported a tendency for more fractures in widows.

Patients with osteoporosis presented more previous falls and more falls in the past 12 months, which together with the bone fragility caused by osteoporosis explains the higher incidence of fractures resulting from falls, old fractures (>1 year), and previous fractures. The higher number of falls can be partially explained by greater age and occasional sarcopenia in the OF group,[1,15,17] although these patients reported less disability of the lower limbs, feet pathologies, and muscle weakness than younger patients with OA. (Tables 2 and 3) This could be partially explained by patients with OA who receive outpatient care for arthritis of the knee (isolated or involving multiple joints) which includes an educational program and periodic evaluations of functionality, raising awareness among these patients of the functional loss and deformities they exhibit.[18,19] This differs from the group receiving care for fracture, who still need to be assessed functionally and complete an educational program to develop awareness of what led to the osteoporotic fracture, the types of osteoporosis, the risks of their condition, and necessary treatment, along with consolidation of the fracture in question. Because a significant number of patients in the OF group did not report muscle weakness, muscle weakness was statistically indicated as a "protective factor" against osteoporotic fractures. (Tables 2 and 3) Muscle weakness was not assessed objectively. We believe that patients with fractures from fragility are not aware of muscle weakness, since these patients fall more often, have more previous fractures, and present lower scores for instrumental activities of daily living. (Tables 2 and 3) To explore this fact, a future prospective study in this group of patients will objectively explore muscle strength.

Lower vitamin D intake among the OF group in relation to the OA group associated with more previous fractures may indicate a failure in primary and secondary prevention of osteoporotic fractures. As mentioned, the OA group was monitored by a multidisciplinary team for OA and comorbidities.[9,18]

Secondary osteoporosis occurs when an underlying illness, disability, or drug causes osteoporosis. We failed to ask specifically about hyperthyroidism, and found that the OF group showed less hypothyroidism than the AO group, indirectly corroborating the fact that hyperthyroidism tends to be more frequently associated with osteoporosis, among the endocrine diseases.[20]

Considering the surgical treatment that the hip fracture requires, in this tertiary center we found a much greater number of hip fractures than other fractures caused by osteoporosis (spine, wrist, and shoulder). (Table 4) However, the patients had densitometric osteoporosis and most did not take calcium replacement, vitamin D, or medication for osteoporosis, (Tables 2 and 4) showing the need for an educational program and multidisciplinary treatment for these patients which takes into account the financial, physical, and psychosocial problems that affect the individual, family, and community.[1]

CONCLUSIONS

Together, race, marital status, previous falls, foot pathologies, previous fractures, and IADL scores define the profile of patients with osteoporotic fractures in this center.

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AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. MMS (0000-0001-7462-1617)* and ALC (0000-0002-9115-2418)* designed the study, acquired the data, and drafted the text. GPO (0000-0003-0052-6769)*, PGP (0000-0003-2395-7545)*, OPC (0000-0002-1128-7292)*, and MUR (0000-0002-2020-9501)* developed the study, analyzed the data, drafted and revised the text. All authors contributed to the intellectual concept of the study and approved the final version of the manuscript. *ORCID (Open Researcher and Contributor ID).

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ORIGINAL ARTICLE

TRAUMATIC INJURIES OF THE CERVICAL SPINE: CURRENT EPIDEMIOLOGICAL PANORAMA

LESÕES TRAUMÁTICAS DA COLUNA CERVICAL: PANORAMA EPIDEMIOLÓGICO ATUAL

Marco Aurélio Cotegipe Negrelli[1], Rafael Garcia de Oliveira[1], Ivan Dias da Rocha[2], Alexandre Fogaça Cristante[2], Raphael Martus Marcon[1], Tarcísio Eloy Pessoa de Barros Filho[2]

1. Spine Group, Instituto de Ortopedia e Traumatologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.
2. Department of Orthopedics and Traumatology, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

ABSTRACT

Objective: To collect data from patients with cervical fracture who were treated surgically in a tertiary health service, in order to better understand the current scenario of this kind of injury in our population. Methods: This retrospective survey examined consecutive cases of patients with cervical spine trauma who received surgical treatment during 2013 and 2014. The data were subjected to descriptive statistical analysis. Results: Fifty-two patients were treated with surgery during 2013 and 2014. All patients classified as Frankel A and B developed respiratory failure. Patients classified as Frankel A, B, and C had significantly higher rates for postoperative complications ($p < 0.01$) than patients classified as Frankel D and E, except for the rate of postoperative infections ($p = 0.717$). Hospitalization time was also longer in the first group ($p < 0.01$). Conclusion: Patients with cervical trauma who present with neurological deficit at hospital admission should receive special attention, since the rate of postoperative complications is higher and hospital stays are lengthier in this group. In addition, patients with Frankel A and B classification should be monitored in an intensive care unit. ***Level of Evidence III; Retrospective comparative study.***

Keywords: Epidemiology. Spinal injuries. Cervical vertebrae/injuries.

RESUMO

Objetivo: Levantar dados de prontuário dos pacientes com fratura cervical submetidos a tratamento cirúrgico em um serviço de saúde terciário, para melhor compreensão do cenário atual desse tipo de lesão em nosso meio. Métodos: O estudo realizou o levantamento retrospectivo de casos consecutivos de pacientes com trauma da coluna cervical submetidos ao tratamento cirúrgico durante os anos de 2013 e 2014. Os dados foram submetidos à análise estatística descritiva. Resultados: Cinquenta e dois pacientes foram operados neste serviço entre os anos de 2013 e 2014. Todos os pacientes classificados como Frankel A e B evoluíram com insuficiência respiratória. Quando comparados, os pacientes Frankel A, B e C e Frankel D e E, a taxa de todos os tipos de complicações pós-operatórias foi maior no primeiro grupo, com significância estatística ($p < 0,01$), exceto a taxa de infecções pós-operatórias ($p = 0,717$). Além disso, o tempo de internação foi maior no primeiro grupo ($p < 0,01$). Conclusão: Pacientes com trauma cervical que se apresentem com déficit neurológico na admissão hospitalar devem receber especial atenção, uma vez que a taxa de complicações pós-operatórias e os dias de internação são maiores. Além disso, pacientes Frankel A e B devem ser monitorados em ambiente de terapia intensiva. ***Nível de Evidência III; Estudo retrospectivo comparativo.***

Descritores: *Epidemiologia. Traumatismos da coluna vertebral. Vértebras cervicais/lesões.*

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INTRODUCTION

Traumatic spine injuries are a severe public health problem, especially with respect to the context in which they occur and their severity potential. These injuries are associated with high-energy trauma such as auto accidents, and have a major impact in our field, sometimes leading to tragic outcomes such as irreversible spinal cord injury and death.[1,2]

The total frequency of spinal cord injury (SCI) is estimated from 27 to 47 per million in the entire population and approximately 6% in polytraumatized patients; 40% of this total may present some degree of neurological deficit, whether in the spinal cord lesion or injury to the nerve root.[1] These data, however, are difficult to obtain due to the high association of SCI with fatal outcomes, which complicates the diagnosis.[3] Injuries to neurological structures are more closely related to spinal trauma due to the spine's anatomical characteristics, such as greater mobility and lower bone mass. The upper vertebrae, C1 and C2, have low correlation with SCI due to the greater diameter of the vertebral canal in this region.[4]

All authors declare no potential conflict of interest related to this article.

Work conducted at the Spine Group, Instituto de Ortopedia e Traumatologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil. Correspondence: Alexandre Fogaça Cristante. Rua Dr. Ovídio Pires de Campos, 333, São Paulo, SP, Brazil. 04018-001. aacristante@uol.com.br

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The most frequent trauma mechanisms are accidents (39–55%), causes related to urban violence (14–29%), falls (18–23%), and sports injuries (7–11%).[5] A bimodal peak can be seen in the age distribution of traumatic spinal fractures and dislocations, which are more common in young adults (15–24 years) and middle-aged individuals (>55 years).[6]

The initial diagnosis is extremely important for proper patient management. A high rate of suspicion and care protocols for polytraumatized patients (Prehospital Trauma Life Support and Advanced Trauma Life Support) recommend maintaining a cervical collar until the presence of cervical injuries can be ruled out. Some authors advocate routine computerized tomographic (CT) scans in initial care provided to trauma patients to reduce the rates of diagnostic neglect.[7]

Several classifications have been created to categorize the various types of fracture in order to indicate precise treatment and allow comparison in different studies.[8] The most common classifications used currently are the Subaxial Cervical Spine Injury Classification (SLIC) and the AO classification for cervical fractures.[9,10]

Intervention can be divided into two stages: fracture reduction and internal fixation. The literature is still controversial regarding the time and the ideal method for achieving reduction, which can be closed (with skull traction) or open (via anterior or posterior approaches). The closed procedure is not without risks, since cervical facet dislocations may be associated with traumatic disc hernias at the injury site in up to 54% of the cases, with the risk that these disc fragments could worsen the neurological injury by invading the vertebral canal during reduction.[11,12] Some authors recommend nuclear magnetic resonance imaging (NMR) prior to installing skull traction to rule out the presence of hernia.[7,11,12] However, NMR is not always easily available, and if the patient is awake and alert many physicians install the cranial halo in the urgent care ward without NMR, with the backing of more recent studies such as Vaccaro et al.,[7] and obtain good results and low complication rates.[11,13,14]

Due to the scarcity of data in the Brazilian literature, especially with regard to epidemiological information on patients with cervical trauma (since much of the data is lost in pre-hospital care and many services do not record this information in a comprehensive manner), we decided to survey cases of cervical fracture and/or dislocation which were treated with surgery in our service in 2013 and 2014.

Therefore, the objective of this study is to collect data from the medical records of these patients to better understand the current scenario of traumatic cervical spine injuries in our area. This information can help improve actions in the areas of prevention, care, and management of patients with this type of injury.

MATERIALS AND METHODS

This study was approved by the institutional review board (IOT-HCFMUSP process number 1186), as well as by the Plataforma Brasil ethics committee (70950417.4.0000.0068).

We performed a retrospective survey of the data contained in the records of consecutive patients with a diagnosis of cervical spine trauma who were treated and operated on in a tertiary-care hospital during 2013 and 2014, a total of 52 cases.

Epidemiological and preoperative data including clinical history, trauma mechanism, associated injuries, radiological classification, and severity of neurological injury were collected, along with surgical data such as access routes, surgical time, single or staged treatment, and need for intraoperative blood transfusion. Other data were related to patient hospitalization such as length of stay, neurological progress, death rate, and postoperative complications.

The exclusion criteria were patients with cervical spine injuries of tumoral or infectious origin, patients treated without surgery, and pediatric patients (under 18 years of age).

The statistical analysis was performed using STATA, Statistics/Data Analysis software (Stata v14.2, StataCorp, College Station, Texas). For the categorical variables, the Mann-Whitney test was used. The normality of the continuous variables was accessed by the Shapiro-Wilk test, and the Mann-Whitney test was used for non-parametric data. The data collected were subjected to descriptive statistical analysis. Statistical significance was defined as $p<0.05$.

RESULTS

In 2013 and 2014, 52 cases of cervical trauma injuries were treated in our service. The sex ratio was 6.43:1 (45 men and 7 women). The mean age was 35.65 years (± 15.42), distributed with a bimodal peak of incidence, as shown in Figure 1.

The most frequent mechanism of trauma was traffic accident, in 23 cases (44%), followed by falls from height in 14 cases (27%), and diving in shallow water in 7 cases (13%). Other observed trauma mechanisms were fall from own height, direct trauma, sports trauma, and violence, and the distribution of these mechanisms can be seen in Figure 2.

The cervical fractures were classified as high (affecting the first and second cervical vertebrae) or low (occurring between the third and seventh cervical vertebrae), with a frequency of 17% and 96%, respectively. In 8% of the total number of patients concomitant fractures in the high and low cervical spine were identified, and in three of the seven patients with odontoid fracture, associated subaxial fracture was also seen. When we isolated the low cervical fractures and classified them according to the AO classification for low cervical fractures, we found that type C fractures predominated, with 35 cases (70%).

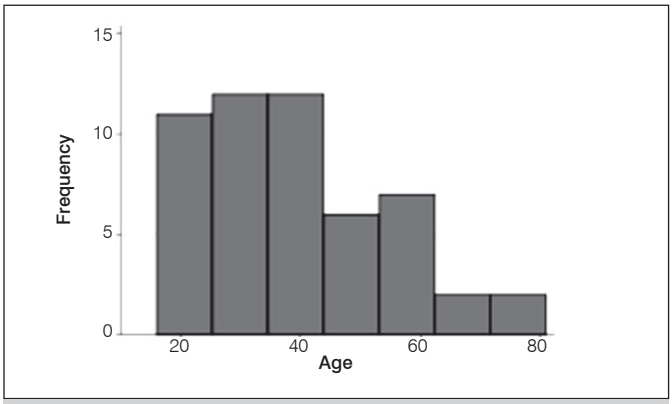

Figure 1. Frequency of fractures by age.

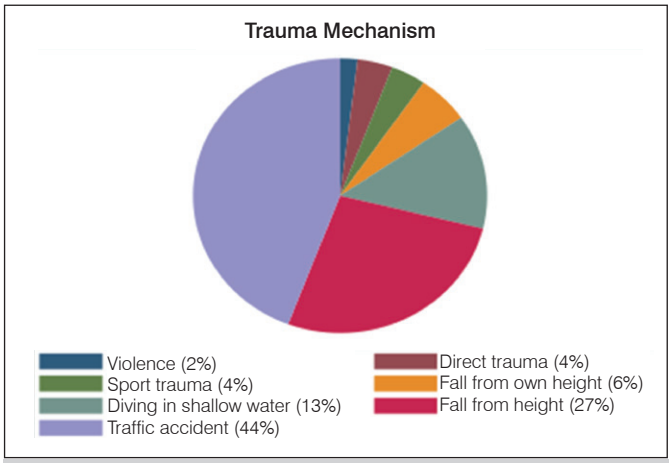

Figure 2. Trauma mechanism.

In the 52 patients comprising our sample, 39 (75%) had isolated injuries in the cervical region, while 12% had concomitant fractures in the lower limbs, 8% in the upper limbs, 8% had cranioencephalic trauma, and 8% had fractures in other segments of the spine.
Most of the patients (63.46%) arrived at our service without neurological deficits, but 8 (15.38%) were initially assessed as Frankel grade D, 6 (11.54%) Frankel C, 4 (7.69%) Frankel B, and only 1 patient (1.92%), who was injured in an automobile accident and had a C4-C5 fracture/dislocation, arrived with a complete deficit. Table 1 correlates the initial Frankel score with type of fracture.
The median length of hospital stay was 17 days (interquartile range: 10 to 36 days). Table 2 correlates hospitalization time with the patient's initial Frankel score.
Another finding related to Frankel score is that when patients classified as Frankel A, B, and C (Group 1) were compared with Frankel D and E patients (Group 2), postoperative complications were more frequent in the first group, at a statistically significant level ($p<0.01$), with the exception of postoperative infection ($p=0.717$). In addition, hospitalization time was significantly greater in Group 1 ($P<0.001$), as shown in Table 3. Another relevant fact is that all five patients who were initially assessed as Frankel grade A or B developed respiratory failure during the course of hospitalization and required ventilator support.
Half of the patients were placed into skeletal traction with a cranial halo in the emergency room, and bloodless reduction was achieved in 42.31% of cases. Complications were not seen in any patients during installation of the cranial halo, and neurological deficit did not worsen in any patient after the procedure. Only one patient presented nystagmus during traction and the procedure was interrupted, which caused immediate improvement of this symptom.
The average time of surgery for the patients included in the study was 230 minutes (±96) (Figure 3). Only three patients (5.7%) required blood transfusion during surgery, but in about 35% of the cases patients went to the intensive care unit (ICU) after surgery, in accordance with criteria defined by the anesthesia team. The surgical route selected for treatment was the anterior approach in 29 patients, posterior in 20 patients, and a combination of both routes in 3 patients.
Of the 19 patients who presented some degree of neurological deficit in the initial evaluation, 10 (52%) improved at least one Frankel grade during follow-up. Of the 52 patients, 6 (11.5%) required additional surgery: 5 (9.6%) to treat postoperative infection, requiring surgical debridement combined with antibiotic therapy, and 2 (3.8%) to extend the arthrodesis. Of the total number of patients, 3 (5.7%) died during hospitalization; all of these had neurological deficit when they initially arrived for treatment.

Table 1. Correlation between fracture type and Frankel score. Fractures (lines) were categorized as high (C1 - C2) and low (AO classification). Frankel score (columns).

Fracture Type vs. Frankel	A	B	C	D	E
High fracture	0	0	0	1	7
A	0	0	0	2	5
B	0	0	3	1	1
C	1	4	0	5	22

Table 2. Days of hospitalization vs. initial Frankel score.

Initial Frankel	Mean	Frequency
A	136	1
B	83 (±24)	4
C	47 (±24)	6
D	33 (±38)	8
E	17 (±11)	33
Total	29	52

Table 3. Comparison of complications among groups - Group 1 (Frankel A, B, and C), Group 2 (Frankel D and E). P value calculated by Fisher's exact test for categorical variables and the Mann-Whitney test for the time of hospitalization (normal distribution of data was not observed according to the Shapiro-Wilk test).

	Group 1	Group 2	p
Total number of patients	11	41	-
Pressure ulcer	6	2	0.001
Acute kidney failure	5	3	0.007
Pneumonia	4	1	0.005
Urinary tract Infection	7	3	<0.001
Postoperative infection	1	4	0.717
Death	3	0	0.007
Time of hospitalization – median, in days	76	15	0.001
Interquartile interval	39-110	10-21	-

Type of Fracture	Mean (minutes)	Frequency
High	235 (±84)	6
A and B	212 (±51)	11
C	235 (±109)	35
Total	230 (±96)	52

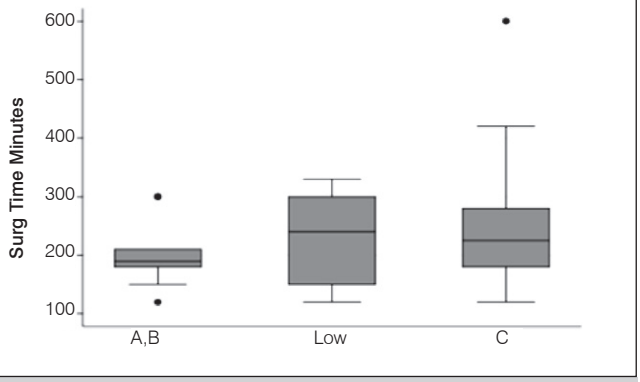

Figure 3. Mean surgical time vs. type of fracture (low fractures were classified by AO classification and type A and B were grouped together).

DISCUSSION

As observed by Kraus et al.,[6] we found a bimodal age distribution in fracture cases (Figure 1); the first and more significant peak occurred between 20 and 35 years of age, and the second peak at around 55 years of age. Fractures predominated significantly in males (86%).
The most frequent mechanism of trauma was traffic accidents (44%), followed by falls from height (27%), and diving in shallow water (13%). Together, these mechanisms corresponded to 84% of the cases in this study, highlighting the need for public policies to reduce car accidents, guidance about the risk of falls from height in the workplace, and warnings about the risks of diving in shallow water in order to prevent these incidents and possibly reduce the costs of healthcare directed toward victims of these accidents.[15,16]
Analysis of the frequency of neurological deficit in patients with high cervical fractures showed that only one was classified as Frankel D among the nine individuals with such fractures, while the other eight did not present any kind of deficit. This finding is consistent

with the literature and can be explained by the difference in the size of the medullary canal between the low and high cervical spine.[16] It is important to emphasize that all patients included in this study who were classified as Frankel A and B developed respiratory failure and required ventilator support. In a systematic review, Berney et al.[17] showed that in patients with neurological deficits, the rate of respiratory complications was 84% in C1 to C4 fractures and 60% in C5 to T1 fractures, with tracheal intubation required in approximately 74% of cases. The findings from this present study as well as the literature therefore recommend that patients with traumatic cervical spine injuries and severe neurological deficits (Frankel A or B) by monitored in the ICU after initial stabilization upon arrival, in order to maintain control of respiratory function and respond quickly if ventilatory function worsens.[17,18]

As shown in Table 3, patients with more severe neurological deficits (Frankel A, B and C) had significantly greater complications and considerably longer hospitalizations than the other group (Frankel D and E). Consequently, health services that provide care for patients with cervical injuries should be prepared for more prolonged hospitalizations and more complications in patients with more severe deficits at the initial evaluation.

Our service has broad experience in initial treatment of cervical fracture/dislocation with the cranial halo, when this is indicated. In many cases, from an institutional point of view it is not possible to provide definitive, urgent surgical treatment for these patients. In these situations, the cranial halo plays an important role in reestablishing the diameter of the spinal canal, providing greater control of neurological prognosis.

In our study, 26 patients received a cranial halo, 23 with AO type C cervical injuries and 3 with the odontoid fractures. In this group of patients there was only one complication related to the cranial halo: one patient developed nystagmus upon reaching 13 kg of traction. At that moment, we chose to gradually reduce the traction, until 6 kg was reached and symptoms resolved completely. This example shows the importance of continuous monitoring by the medical team during weight increase in skeletal traction, through serial examinations and continuous evaluation of vital signs.

Our current practice is to increase traction by 1 kg/hour until reduction of the vertebral dislocation is achieved, or the maximum weight is reached (an initial 5 kg + 2.3 kg per vertebra level up to the level of injury), performing an X-ray each time after weight is added; this is slightly more conservative than the recommendation by Brun et al.[19] to add 1 kg each 30 minutes, but we believe this practice allows patients to better adapt to the progressive increase in weight.

Of the 7 patients with odontoid fractures, 3 (42%) had associated subaxial cervical fractures. This data differs from Burke et al.,[20] who found this combination in only 8% of patients. Among other factors, this difference can be explained by continuous improvements in the quality and definition of diagnostic methods (which identify fractures that previously went unnoticed), the significant difference in sample sizes between our two studies, and finally by the fact that this present study only analyzed cases treated surgically, which tend to result from trauma with greater energy.

CONCLUSIONS

Patients with cervical trauma who present with neurological deficits at hospital admission should receive special attention, since their rates of postoperative complications and hospital stays are significantly greater than for other patients. Furthermore, patients classified as Frankel A and B should be monitored in an ICU because their risk of developing respiratory failure during hospitalization.

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. MACN (0000-0001-9258-483X)* and RGO (0000-0002-9160-9246)* acquired, analyzed, and interpreted the data and wrote the manuscript. IDR (0000-0001-6533-4528)* designed and drafted the article and critically reviewed the content. AFC (0000-0002-7797-5274)* critically reviewed the content. RMM (0000-0001-5958-5646)* designed and drafted the study. TEPBF (0000.000.279697845)* gave final approval of the manuscript version. TEPBF (0000.000.279697845)* gave final approval of the manuscript version. *ORCID (Open Researcher and Contributor ID).

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ORIGINAL ARTICLE

ROLE OF ARTERIOVENOUS VASCULAR LOOPS IN MICROSURGICAL RECONSTRUCTION OF THE EXTREMITIES

PAPEL DA ALÇA VASCULAR NA RECONSTRUÇÃO MICROCIRÚRGICA DOS MEMBROS

Gustavo Bersani Silva[1], Bruno Azevedo Veronesi[1], Luciano Ruiz Torres[1], Raquel Bernardelli Imaguchi[1], Alvaro Baik Cho[1], Hugo Alberto Nakamoto[1]

1. Hand and Microsurgery Group, Instituto de Ortopedia e Traumatologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

ABSTRACT

Objective: To analyze 10 consecutive cases of microsurgical arteriovenous loops created to reconstruct complex injuries from March 2011 to May 2012. Methods: This observational cohort-type study conducted by the Hand and Microsurgery Group at the HC-FMUSP included patients who were candidates for microsurgical reconstruction as a last alternative to amputation of the limb with proven absence of adequate recipient vessels for primary microsurgical anastomosis, in a prospective and consecutive manner. We analyzed 14 variables (epidemiological, clinical, procedure-related, and outcome) in patients who underwent reconstruction using an arteriovenous loop utilizing a single-stage or two-stage procedure. Results: The injuries were mostly traumatic (80%). The success rate of the single-stage procedure was 75%, and 17% for the two-stage procedure. The rate of preservation for the injured limb was 44%. Conclusion: This study reinforces the more recent understanding that the indication for single-stage or two-stage reconstruction should be individualized; our findings favor the single-stage reconstruction. This technique should be used in selected cases, as a last reconstructive alternative before amputation, and further studies are necessary to confirm its safety and efficacy in our practice. ***Level of Evidence IV; Case series.***

Keywords: Arteriovenous fistula. Microsurgery. Upper extremity. Lower extremity.

RESUMO

Objetivo: Analisar dez casos consecutivos de alças vasculares microcirúrgicas realizadas para reconstrução de feridas complexas no período de março de 2011 a maio de 2012. Métodos: Estudo de observação, analítico do tipo coorte, realizado pelo Grupo de Mão e Microcirurgia do Instituto de Ortopedia e Traumatologia do HC-FMUSP. Foram incluídos, prospectivamente e de maneira consecutiva, os pacientes candidatos à reconstrução microcirúrgica como última alternativa à amputação do membro, com comprovada ausência de vasos receptores adequados para anastomose microcirúrgica primária. Foram analisadas 14 variáveis (epidemiológicas, clínicas, relacionadas ao procedimento e resultados) nos pacientes submetidos à reconstrução com alça em tempo único e em dois tempos. Resultados: As lesões foram de etiologia traumática em sua maioria (80%). A taxa de sucesso do procedimento em tempo único foi de 75%, e em dois tempos de 17%. A taxa de manutenção do membro lesado foi de 44%. Conclusão: Este estudo reforça o entendimento mais recente de que a indicação de reconstrução em um ou dois tempos deve ser individualizada, e nossos resultados favorecem a reconstrução em tempo único. A técnica deve ser usada em casos selecionados, como última opção reconstrutiva à amputação, sendo necessários mais estudos para atestar sua segurança e eficácia em nosso meio. ***Nível de Evidência IV; Série de casos.***

Descritores: *Fístula arteriovenosa. Microcirurgia. Extremidade superior. Extremidade inferior.*

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INTRODUCTION

Tissue transfer through reconstructive microsurgery is an important therapeutic option for treating complex injuries resulting from trauma, infection, or cancerous infiltration of the limbs. However, some patients have receiving vessels of very poor quality near the wound area, thus impeding the transference of a free flap to treat the defect. In these cases, the necessity of the flap's vessels to communicate with healthy recipient artery and veins demand techniques which permit the use of receiving vessels far from the wound site, including microsurgical arteriovenous loops.[1,2]

The concept of the microsurgical vascular loop, introduced by Threlfall et al.[3] in 1982 and popularized by Grenga starting in 1987,[1] is a useful and versatile tool for facilitating transfers of tissue to receiving areas which lack adequate vessels for microsurgical anastomosis.

All authors declare no potential conflict of interest related to this article.

Work conducted at the Hand and Microsurgery Group, Instituto de Ortopedia e Traumatologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

Correspondence: Rua Dr. Ovídio Pires de Campos, 333, Cerqueira Cesar, São Paulo, SP, Brazil. 05403-010. gustavo.bersani@hc.fm.usp.br

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The technique involves creating an arteriovenous fistula with a vein graft, usually the great saphenous vein. The midpoint of the fistula, which is located near the area to be reconstructed, is then sectioned to provide vessels for arterial inflow and venous drainage for the microsurgical anastomoses.[1-4] This consequently constructs a system with high flow and low resistance near the injury, offering good quality vessels to obtain free flaps.[5,6]

Two options can be used to extend the receiving vessels of a free flap: interposition of a vein graft or the creation of an arteriovenous loop.[7] Several studies have shown the superiority of the vascular loop over long venous grafts with regard to the risk of thrombosis and need for reinterventions.[8-12]

Despite its proven clinical applicability, some details of the surgical technique are still the subject of controversy, such as creating the free flaps during the same surgery (in one single-stage procedure) or later, after the construction and maturation of the arteriovenous shunt (surgery in two stages at two different times), highlighting the need for better understanding of the different variables involved in this technique.[2,4-7] Currently there are no clear criteria which support the decision to perform surgery in one or two stages, and the severity of the injury and patient characteristics (namely the ability to tolerate major surgery due to comorbidities or difficulty obtaining clinical stabilization) are factors that traditionally guide decision-making.[2] These controversies led us to conduct a prospective analysis of 10 consecutive vascular loops used to reconstruct complex wounds in limbs which did not have receiving vessels.

MATERIALS AND METHODS

From March 2011 to May 2012, 10 microsurgical vascular loops were created in 9 patients evaluated prospectively.

The study was approved by the institutional review board under process number 1083. All patients signed an informed consent form.

The criteria for inclusion in this study were:

- Patients presenting with complex wounds (exposure of the bone, tendon, or vascular-nervous bundle) in the limbs, candidates for microsurgical reconstruction as a last alternative to amputation;
- Imaging exams (computed angiotomography/magnetic resonance angiography) or intraoperative assessment indicating inadequate vessels for microsurgical anastomosis (inadequate flow in arterial trunks near the injury to be rebuilt);
- Minimum follow-up of two months after creation of the loop.

The following variables were assessed: sex, age, comorbidities, etiology of the injury, whether loop involved 1 or 2 stages, number of days between AV loop creation and definitive flap elevation (when loop involved 2 stages), flap used, artery receiving the loop, use of the ipsi- or contralateral saphenous vein, loop success, rate of reoperation, whether the limb was saved or not, which anticoagulant drug was used in the postoperative period, and complications.

The surgical technique employed to create the loops used the contralateral great saphenous vein (8 loops) or the ipsilateral great saphenous vein (2 loops). End-to-side anastomoses to the femoral artery (9 loops) or popliteal artery (1 loop) were employed and end-to-end anastomoses of the contralateral saphenous vein to the ipsilateral vein were used when necessary (contralateral saphenous vein graft). All the loops were anastomosed after filling with a heparin solution (20 IU/mL) and all patients used ASA (200mg/day) and hyperhydration during the postoperative period to prevent clotting and vasospasm, respectively.

For the statistical analysis, we used SPSS version 20.0 software (SPSS Inc, Chicago, IL, USA) and performed descriptive statistical and univariate analysis using Fisher's exact test, comparing the groups of vascular loops created during 1 or 2 procedures. A P-value <0.05 was considered statistically significant. The groups had similar age distribution.

RESULTS

The study included eight men and one women, with ages ranging from 21 to 48 years (mean: 33.7 years). The patients were followed for a mean period of 7.9 months (minimum of 2 and a maximum of 14 months). Most of the injuries were traumatic (7 cases); in the other cases, the etiology was chronic osteomyelitis and tumor (squamous-cell carcinoma) with one case each, respectively. (Figure 1)

Four reconstructions were performed in a single-stage procedure, and six were carried out in two stages. The average time between the time when the loop was created and coverage with the microsurgical flap was 2.6 days in the cases where the two-stage procedure was used. The success rate for the one-stage procedure was 75%, (Figure 2) and 17% for the two-stage procedure. (Figure 3)

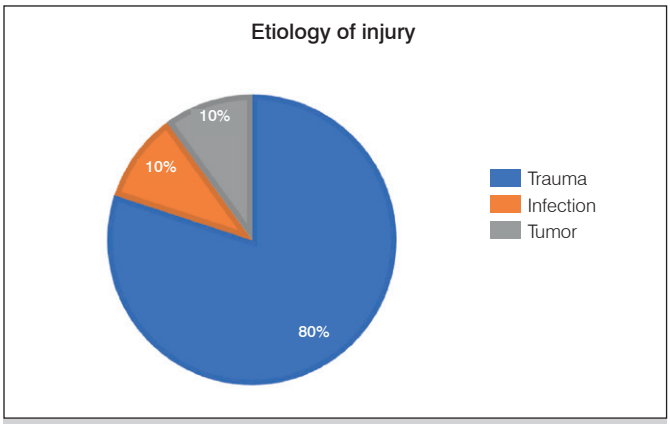


Figure 1. Etiology of injury.

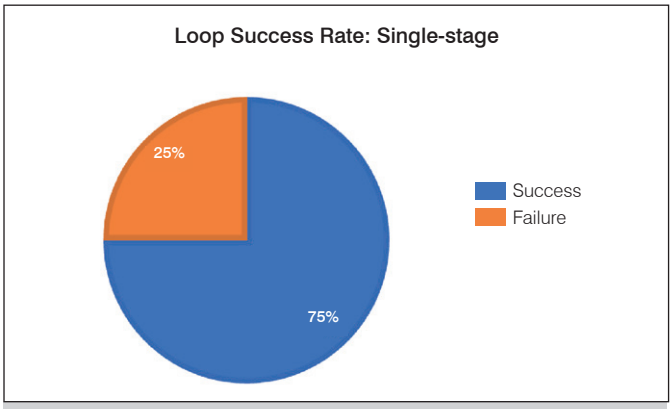


Figure 2. Success rate for loops created in single-stage procedure.

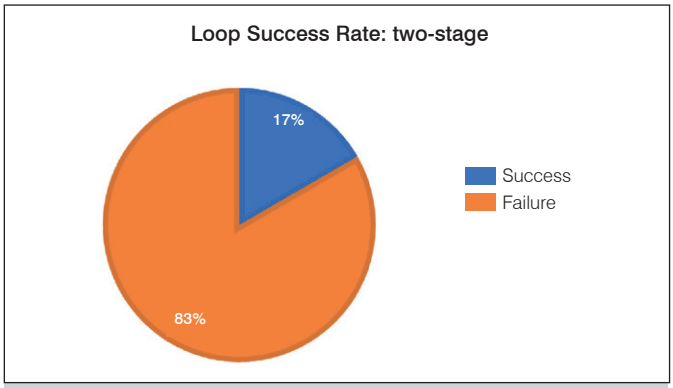


Figure 3. Success rate for loops created in two-stage procedure.

The rate of reoperations after loop reconstruction was 90% (Figure 4), considering re-explorations of the anastomosis, the need for new flaps, or amputation of the limb. The salvage rate for the injured limb was 44% (4/9).
The data are summarized in Table 1.
Figure 5 illustrates one case of reconstruction in two stages, while Figure 6 demonstrates the versatility of using the vascular loop during a single-stage procedure.
No statistically significant difference was observed between the groups with vascular loops made during one or two stages in relation to the flap success rate (p=0.19) or limb salvage rate (p=1.0).

DISCUSSION

In Brazil, as in many developing countries, limb amputation imposes such a severe social stigma and functional limitations due to the lack of suitable prosthesis, that the surgeon is often impelled to manage dramatic cases in which microsurgical reconstruction of a limb lacking good quality recipient vessels is the only suitable treatment alternative. This unique study in the national literature sheds light on this peculiar situation and evaluates the role of the vascular loop as an auxiliary technique in treating these challenging injuries.
Several authors defend creating vascular loops in two stages due to the theoretical advantages obtained after vein arterialization (when there is less chance of collapse and increased vessel diameter) compared to creating the loop and raising the flap in a single stage. They argue that using two stages reduces the chance of complications related to "serial" anastomoses,

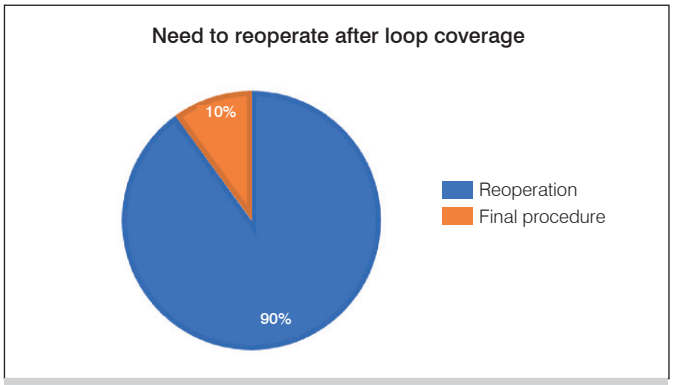
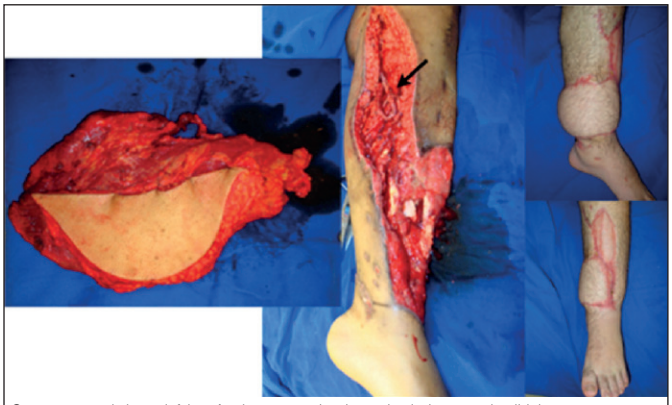
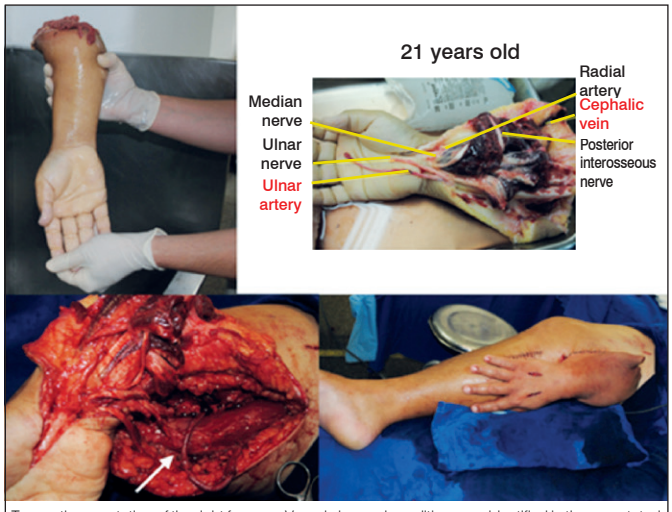


Figure 4. Need to reoperate after surgical skin coverage using vascular loop.



Severe trauma in lower left leg. Angiotomography showed only the posterior tibial artery was patent. Latissimus dorsi flap used to cover the leg injury, rebuilt with vascular loop created in two-stage procedure. Arrow: Vascular loop constructed 2 days prior to coverage with the flap. Right: 12 months after surgery, patient walking normally.

Figure 5. Example of reconstruction using loop created in two-stage procedure.



Traumatic amputation of the right forearm. Vessels in good condition were identified in the amputated portion, but receiving vessels in the arm were not suitable for anastomosis. Construction of an arteriovenous loop with the ipsilateral saphenous vein for ectopic reimplantation of the amputated limb. Arrow: Microsurgical vascular loop. Finalized ectopic reimplantation, with good perfusion.

Figure 6. Example of reconstruction using loop from single-stage procedure.

Table 1. Variables analyzed.

Patient	Sex	Age	Etiology	Comorbidities	Months of follow-up	Time of Loop	Reoperation	Success of Loop	Limb saved	Post-op	Complications	Coverage Used	Recipient Artery	Contralateral saphenous vein
1	M	33	TR		14	2	No	Yes	Yes	ASA		Latissimus dorsi	Femoral	Yes
2	M	24	TR		13	0	Yes	Yes	No	ASA		ALT	Femoral	Yes
3	M	38	TR	HBP	12	5	Yes	No	Yes	ASA		Gastrocnemius M and L	Femoral	Yes
4	M	27	TR		10	0	Yes	No	Yes	ASA		ALT + Cross-leg	Femoral	Yes
5	M	44	TR		9	7	Yes	No	No	ASA		Vacuum dressing	Femoral	Yes
6	M	21	TR		8	0	Yes	Yes	No	ASA		Ectopic reimplantation	Femoral	No
7	M	32	TR		4	6	Yes	No	New loop	ASA		Vacuum dressing	posterior tibial	No
8	M	32	TR		4	5	Yes	No	No	ASA		Vacuum dressing	Femoral	Yes
9	M	38	TU		3	1	Yes	No	No	ASA		Vacuum dressing	Femoral	Yes
10	F	48	I		2	0	Yes	Yes	Yes	ASA		Rectus femoris	Femoral	Yes

M: male; F: female; TR: trauma; TU: tumor; I: infection; HBP: high blood pressure; ASA: acetylsalicylic acid; ALT: anterolateral thigh flap.

permitting complications in the loop to be seen before the flap is transferred.[13] However, recent studies have challenged this concept, and attempt to establish clearer criteria for using a one- or two-stage procedure.[2,14-16]

In our study, the success rate for free flaps using the vascular loop created in one stage was 75% and limb salvage was 50%, better results than those obtained from using a vascular loop created in two stages, which had a flap success rate of 17% and limb salvage rate of 33%. Despite the better results for the single-stage procedure, no statistically significant difference was observed, which may be justified by the small number of cases.

Cavadas[2] rationalized indicating the two-stage procedure in special cases, such as:

- Patients with severe (non-cardiac) comorbidities who cannot tolerate major procedures
- Problems with a loop constructed during a single-stage procedure, such as intraoperative identification of significant atheromatosis of the receiving vessels or thrombosis of the shunt, with the loop created and patient monitored to assess loop patency, creating the flap in ideal conditions.[2]

Prospective analysis of data permitted objective evaluation of 14 variables, studying the behaviour of vascular loops made during one- or two-stage procedures. The correct approach should consider the extent of the injury and the characteristics of the patient, such as their ability to support reconstruction in a single stage, nonetheless intraoperative assessment of the proximal limb vessels and loop conditions are also important, since we would rather abort the reconstruction and perform the procedure in two stages than subject the patient to flap coverage under less than ideal conditions. Besides indication, rigorous implementation of the arteriovenous loop construction techniques also contributes to the success of the procedure. The authors favour AV loops created with an arterial end-to-side anastomosis and end-to-end venous anastomosis when necessary. Special attention should be paid to filling the graft with heparin before starting the anastomoses to prevent twisting of the long vein graft. It is also important to carefully prepare the tissue bed where the loop will rest during the two-stage reconstruction in order to prevent kinking or compression of the loop in the subcutaneous tissue and consequent thrombosis.

CONCLUSIONS

This study reinforces the more recent understanding that indication for single-stage or two-stage reconstruction should be individualised, and our results favour single-stage reconstruction. The technique should be used in selected cases, as a last reconstructive option to amputation, but more studies are needed to attest to its safety and efficacy.

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. GBS (0000-0002-8684-4479)*: wrote, updated, and reviewed the article, and performed surgeries. BAV (0000-0002-4694-6112)*: wrote, updated, and revised the manuscript. LRT (0000-0002-6608-4062)* and ABC (0000-0002-3099-4750)*: performed surgeries and revised the article. RBI (0000-0002-8965-5147)*: performed surgeries, conducted the statistical analysis, and reviewed the article. HAN (0000-0002-7301-4329)*: performed surgeries, conceived the project, and revised the manuscript. All authors contributed to the intellectual concept of the study and approved the final version of the manuscript. *ORCID (Open Researcher and Contributor ID).

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USE OF MAGNETIC RESONANCE IMAGING TO DIAGNOSE BRACHIAL PLEXUS INJURIES

USO DA RESSONÂNCIA MAGNÉTICA PARA O DIAGNÓSTICO DAS LESÕES DO PLEXO BRAQUIAL

Bruno Azevedo Veronesi[1], Marcelo Bordalo Rodrigues[2], Marina Tommasini Carrara de Sambuy[1], Rodrigo Sousa Macedo[1], Álvaro Baik Cho[1], Marcelo Rosa de Rezende[1]

1. Hand and Microsurgery Group, Instituto de Ortopedia e Traumatologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.
2. Radiology Department, Instituto de Ortopedia e Traumatologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

ABSTRACT

Objective: To compare magnetic resonance imaging and intraoperative findings in patients diagnosed with traumatic injury to the brachial plexus. Methods: Patients with a diagnosis of traumatic injury to the brachial plexus admitted to the hand and microsurgery outpatient consult of the Hospital das Clínicas at the University of São Paulo were selected during December 2016. A total of three adult patients with up to six months of injury who underwent surgical treatment were included in the study. A diffusion-weighted sequence magnetic resonance protocol and fluid-sensitive volumetric reformatting sequence were applied. The magnetic resonance results were compared with the diagnoses obtained from the injuries observed during the surgery. The study was double-blind (surgeon and radiologist). Results: A descriptive correlation was found between the magnetic resonance imaging results and the diagnostic findings from the surgeries, for both pre- and post-ganglionic injuries. Conclusion: Magnetic resonance imaging has shown to be a promising diagnostic method in preoperative assessment of brachial plexus lesions; it is less invasive than other common methods, showing not only avulsion lesions but also localized postganglionic lesions in the supra- and infraclavicular region. ***Level of Evidence III; Diagnostic studies – Investigating a diagnostic test.***

Keywords: Brachial plexus/injuries. Brachial plexus neuropathies/diagnosis. Magnetic resonance imaging.

RESUMO

Objetivo: Comparar resultados de ressonância magnética e achados intraoperatórios de pacientes com diagnóstico de lesão traumática do plexo braquial. Métodos: Foram selecionados pacientes com diagnóstico de lesão traumática do plexo braquial admitidos no ambulatório de mão e microcirurgia do Hospital das Clínicas de São Paulo no mês de dezembro de 2016. Foram incluídos pacientes adultos com até seis meses de lesão que seriam submetidos a tratamento cirúrgico, totalizando três para o estudo. Foi aplicado um protocolo de ressonância magnética com sequência ponderada em difusão e sequência com reformatação volumétrica fluido-sensível. Os resultados da ressonância magnética foram comparados com os diagnósticos das lesões obtidos na cirurgia. O estudo foi duplo-cego (cirurgião e radiologista). Resultados: Houve correlação em termos descritivos entre os laudos das ressonâncias magnéticas e os achados diagnósticos das cirurgias, tanto para as lesões pré como pós-ganglionares. Conclusão: A ressonância magnética mostrou ser um método diagnóstico promissor na avaliação pré-operatória das lesões do plexo braquial, sendo menos invasiva que os outros métodos mais utilizados, permitindo o estudo não somente das lesões por avulsão, mas também das lesões pós-ganglionares localizadas na região supra e infraclavicular. ***Nível de Evidência III; Estudos diagnósticos – Investigação de um exame para diagnóstico.***

Descritores: *Plexo braquial/lesões. Neuropatias do plexo braquial/diagnóstico. Imagem por ressonância magnética.*

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INTRODUCTION

Brachial plexus injury is considered the most serious neural alteration of the limbs, and is a significant challenge for those who treat it.[1] Traumatic injuries in adults are mostly caused by traction on the neck and shoulder in high-energy accidents.[2] The exponential increase in cases of brachial plexus injury in Brazil, especially in large cities, is associated with car and motorcycle accidents, which correspond to 80-90% of cases.[2,3]

Several classifications have been proposed for traumatic injuries to the brachial plexus. For decision-making and prognosis, they are commonly classified into three categories according to anatomical parameters: pre-ganglionic (root avulsion), post-ganglionic (rupture or injury in the continuity of the nerve), or a combination of both.[4,5] In this context, electrodiagnostic and imaging tests have become important tools in anatomical location of these injuries. Currently,

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Work conducted at the Hand and Microsurgery Group, Instituto de Ortopedia e Traumatologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.
Correspondence: Rua Dr. Ovídio Pires de Campos, 333, Cerqueira Cesar, São Paulo, SP, Brazil. 05403-010. brunoazevedoveronesi@hotmail.com

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the most commonly used imaging methods are myelography, computerized myelotomography, and magnetic resonance imaging (MRI).[5-10] The first two have the disadvantage of being invasive examinations involving considerable risk due to radiation exposure and potential adverse reaction to the contrast material, as well as poor differentiation of the tissues adjacent to the neural injury.[11,12] Specifically in relation to the brachial plexus, MRI should be performed according to a specific protocol to obtain slices and images that can be used to stage the injuries. One differential sequencing technique is diffusion-weighted MRI of the brachial plexus, also called diffusion-weighted neurography. This sequence permits greater contrast between the nerve structures and surrounding tissue, enhancing the image of long stretches of the brachial plexus nerves, revealing both the morphological characteristics of the structures involved (caliber, continuity, and relationship with adjacent bone and muscle structures) and the pathological characteristics of the nerves (fibrosis, inflammation, and edema). When several planes are combined, the high contrast of diffusion-weighted neurography can provide a three-dimensional evaluation, permitting better location of the lesions.[13-17]

The objective of this study is to conduct a comparative assessment between preoperative diagnosis using MRI with a specific technique for the brachial plexus and intraoperative findings.

MATERIALS AND METHODS

The study protocol was approved in advance by the institutional review board (process 10612/13).

Patients included in the study were adults (above 18 years) with clinical diagnosis of brachial plexus injury with traumatic etiology who were admitted to the outpatient hand and microsurgery clinic at the Institute of Orthopedics and Traumatology in the Hospital das Clínicas de São Paulo during December 2016, with up to six months of injury and indication for surgical treatment. The exclusion criteria were patients requiring sedation or with contraindications to MRI. Three patients were included, all men with an average age of 30.66 years, all victims of motorcycle accidents. All patients signed an informed consent form.

In addition to the preoperative clinical evaluation, the patients underwent MRI to obtain brachial plexus imagery using a specific diffusion-weighted sequencing protocol and sequencing with fluid-sensitive volumetric reformatting. The examinations were performed using a GE HDXT 1.5-Tesla device (GE Medical Systems, Milwaukee, Wisconsin, USA), 12.0 version software, and 33mT/min gradients.

The surgeries were performed by the same team, and the dissection stages followed a standard sequence. Dissection was performed using the supra-clavicular transverse approach (two centimeters above the clavicle), where the roots and trunks are easily accessed. After making the incision in the skin and subcutaneous tissue, the omohyoid muscle was dissected and sectioned, providing an important anatomical landmark of the topography of the proximal brachial plexus and providing access to the plane of the roots and trunks. Generally, the first element of the brachial plexus that is seen is the upper trunk. The C5 root is smaller, vertical, above and to the side of the C6 root. The C7 root is below the transverse cervical artery, more horizontal than C6. The C8 root is located just above and behind the subclavian artery, which lies directly above the T1 root.

The intraoperative evaluation was meant to diagnose and classify the lesions as avulsion (solution of complete continuity of a pre-ganglionic root), rupture (solution of complete continuity of a post-ganglionic segment), or lesion in continuity (focal thickening, without solution of macroscopic continuity of the nerve).

Intraoperative decisions related to the treatment of brachial plexus lesions were not influenced by the study.

The study was conducted in a double-blind manner: the surgeons did not have access to the preoperative MRI imaging, and the radiologists had no access to the surgical findings.

A brachial plexus inventory was created and completed by the surgeon and the radiologist. These data were compared to establish the degree of correlation between them.

RESULTS

A close descriptive correlation was seen between the MRI reports using the technique in question and the diagnostic findings from the surgeries of the three patients.

Patient 1

intraoperative findings: C5 and C6 roots and neuroma were identified in the continuity of the upper trunk. (Figure 1)

Description of MRI: Thickening and increased signal in the C5 and C6 roots extending to the upper trunk, compatible with post-ganglionic lesion in continuity. No signs of pre-ganglionic lesions. (Figure 2)

Patient 2

intraoperative findings: Neuroma identified in the continuity of the upper trunk. (Figure 3)

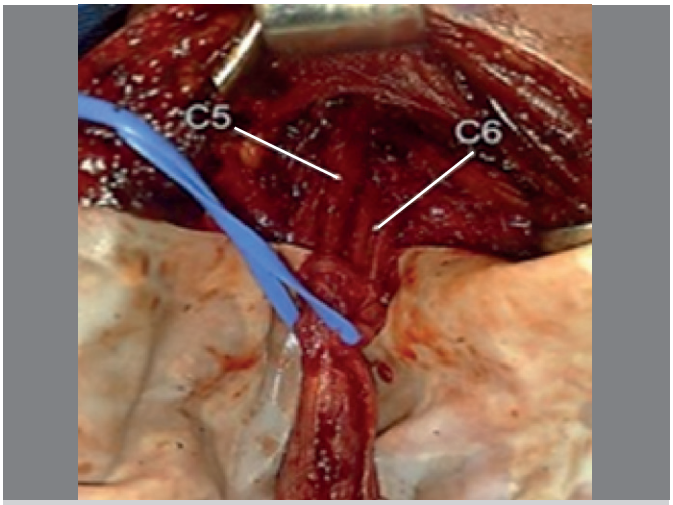

Figure 1. Intraoperative photo, patient 1. Identification of C5 and C6 roots forming the upper trunk, where neuroma in continuity was observed.

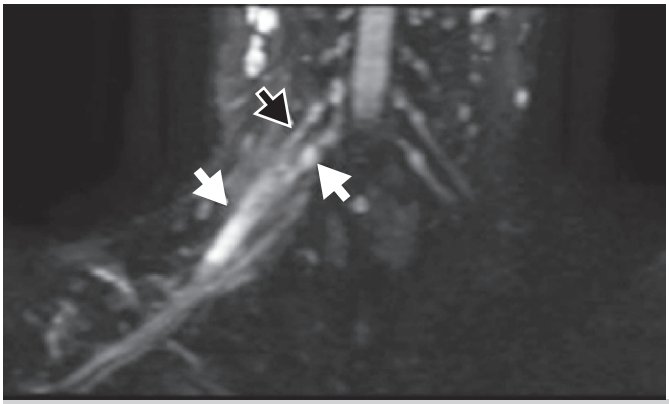

Figure 2. Magnetic resonance imaging, patient 1. Diffusion-weighted neurography - reconstruction in the coronal plane: Thickening and increased signal of the C5 roots (black arrow) and C6 roots (tip of arrow) and upper trunk (white arrow), corresponding to the lesion in continuity.

Description of MRI: Thickening and increased signal in the C5 and C6 roots extending to the upper trunk, compatible with post-ganglionic lesion in continuity. (Figure 4)

Patient 3

Intraoperative findings: Post-ganglionic neuroma-type C5 lesion in continuity; avulsion of the C6 and C7 roots; post-ganglionic lesion at the level of the division of the lower trunk, neuroma-type in continuity. (Figure 5)
Description of MRI: Thickening and increased signal in the C5 root and region of the division of the lower trunk. Formation of pseudo-meningocele in the emergence of the C6 and C7 roots, suggestive of avulsion (pre-ganglionic lesion). (Figure 6)

DISCUSSION

The incidence of traumatic brachial plexus injuries is increasing in Brazil, mainly due to the increase in motorcycle accidents.[3] Consequently, it is important to identify tests which permit earlier and more accurate diagnosis to improve decision-making related to nerve reconstruction and consequently improve prognosis.
The earlier surgical reconstruction of the brachial plexus is performed (when this is indicated), the better the prognosis. In patients with symptoms suggesting favorable neuropraxis or partial lesions, watchful treatment may be an option if additional high-accuracy tests are not available to stage the lesions. In these cases, it is possible to wait for clinical improvement over time, avoiding an unnecessary surgical procedure. But in lesions with unfavorable prognoses (axonotmesis and neurotmesis), time is a decisive factor in surgical reconstruction. In these cases, earlier staging of lesions and indication for surgery provides better reconstructive planning and prognosis.[4]
Topographic knowledge of the lesions prior to surgery is important to avoid unnecessary dissections. Consequently, if the type and location of the lesions have not been precisely determined before surgery, supra- and infraclavicular approaches may be performed for this purpose, increasing morbidity and surgical time.
Currently, the most commonly used imaging exams are myelography, computerized myelotomography, and MRI using the conventional technique. The first two are more accurate in diagnosing root avulsion, but do not offer good definition of the brachial plexus as a whole. Furthermore, these tests present higher morbidity because of the use of intrathecal contrast. Conventional MRI, in turn, does not provides images with the definition needed for correct staging of the lesions.[11]

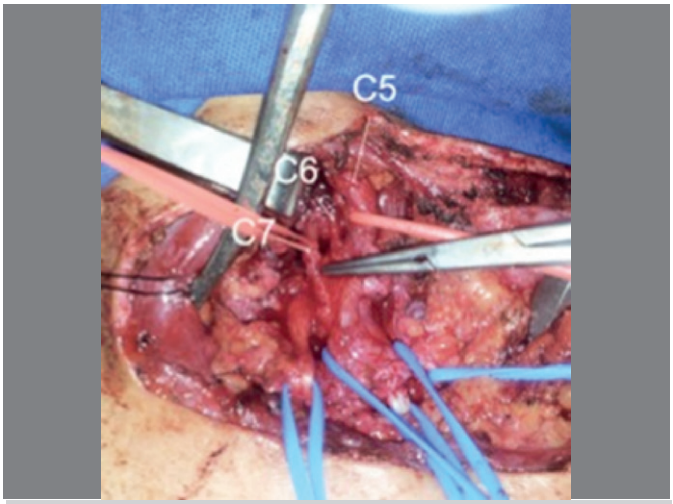

Figure 5. Intraoperative photo, patient 3. Neuroma in post-ganglionic region of C5 root; avulsion-type lesion of the C6 and C7 roots; neuroma in continuity at the level of the division of the lower trunk.

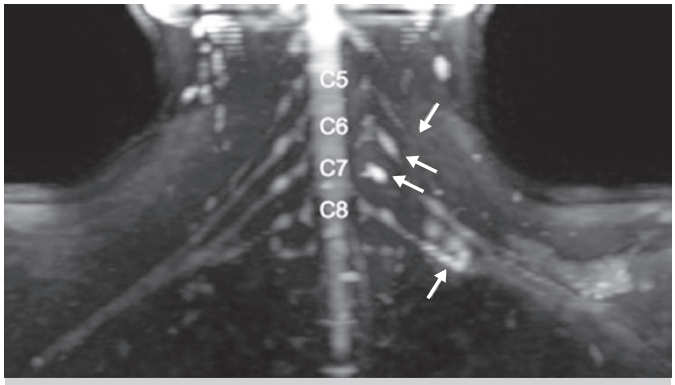

Figure 6. Magnetic resonance imaging, patient 3. Diffusion-weighted neurography - reconstruction in the coronal plane: Thickening and increased signal in the C5 root and region of the division of the lower trunk. Formation of pseudo-meningocele in the emergence of the C6 and C7 roots, suggestive of avulsion (pre-ganglionic lesion).

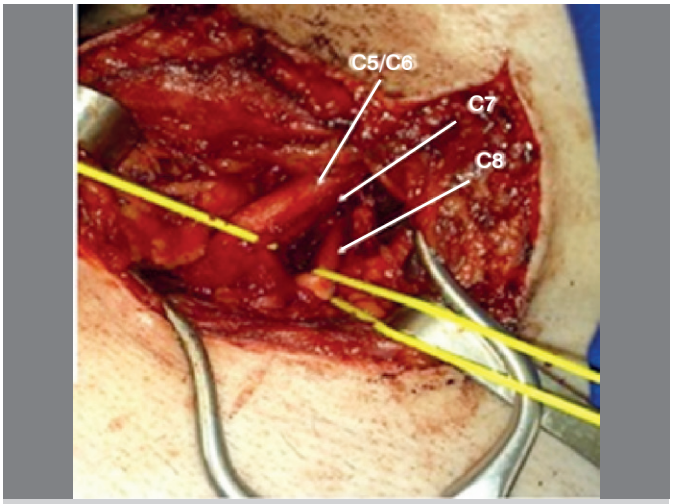

Figure 3. Intraoperative photo, patient 2. Visualization of C5, C6, C7, and C8 roots. Neuroma observed in the continuity of the upper trunk.

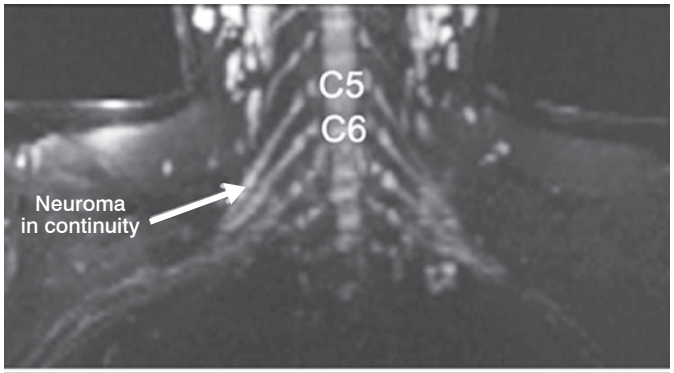

Figure 4. Magnetic resonance imaging, patient 2. Diffusion-weighted neurography - reconstruction in the coronal plane: Thickening and increased signal in the C5 and C6 roots extending to the upper trunk, corresponding to lesion in continuity.

Therefore, when MRI with diffusion-weighted sequences and volumetric reformatting of fluid-sensitive sequences is applied to traumatic lesions of the brachial plexus it provides new diagnostic perspectives, with sensitivity and specificity similar to those of computerized myelotomography for diagnosing pre-ganglionic lesions (avulsion) and greater accuracy for post-ganglionic lesions.[11] This technique provides greater contrast between the nerves and adjacent tissues, improving the image of the nerve pathways in the brachial plexus. Adding this sequence does not extend the examination excessively, only by approximately 5 minutes. When combined with the other sequences and planes of conventional MRI of the brachial plexus, this examination can provide a more accurate assessment without increasing morbidity.

In this study, we used a macroscopic classification of neural injury to compare with the MRI findings. Among the classifications, lesions in continuity (considered when neural thickening is observed during the surgery and when thickening and high signal are seen in MRI) may not have a good functional correlation and may exhibit varying degrees of axonal involvement ranging from neuropraxis to neurotmesis.

This is a preliminary study carried out over a short period of time, which explains the low number of patients evaluated. Studies with larger numbers of patients should be performed in order to confirm these data.

The study showed that the MRI technique described has good accuracy in diagnosing lesions of the brachial plexus throughout its entire extension, allied with lower morbidity.

CONCLUSIONS

The specific MRI technique described herein is a promising diagnostic method for brachial plexus lesions, and provides good accuracy in identifying the type of lesion and topography. Unlike other imaging methods, it not only permits visualization of whether avulsion is present, but also studies the entire length of the brachial plexus. It can consequently help the medical team select treatment (conservative or surgical), make decisions about the most appropriate time to operate, and select the surgical technique, reducing operative time and thus allowing better prognosis for these patients.

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. BAV (0000-0002-4694-6112)*: wrote the article, MBR (0000-0003-4747-5081)*: conceived the project and revised the article, MTCS (0000-0003-4493-4879)*: revised the article, RSM (0000-0002-5025-4338)*: collected the data and structured the article, ABC (0000-0002-3099-4750)*: performed the surgeries and reviewed the article, MRR (0000-0003-3441-8117)*: performed the surgeries, conceived the project, and revised the article. All authors contributed to the intellectual concept of the study and approved the final version of the manuscript. *ORCID (Open Researcher and Contributor ID).

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WEIGHT-BEARING COMPUTED TOMOGRAPHY OF THE FOOT AND ANKLE: AN UPDATE AND FUTURE DIRECTIONS

TOMOGRAFIA COMPUTADORIZADA COM CARGA DO TORNOZELO E PÉ: ATUALIZAÇÃO E PERSPECTIVAS FUTURAS

*Alexandre Leme Godoy-Santos[1], Cesar de Cesar Netto[2]; Weight-bearing CT International Study Group**

1. Instituto de Ortopedia e Traumatologia, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, SP, Brazil.
2. Department of Orthopedics, Hospital for Special Surgery, New York, NY, USA.

ABSTRACT

Spatial understanding of osteoarticular deformities of the foot and ankle is vital to correct diagnosis and therapeutic decision making. Poor reproducibility in conventional standing radiography in three orthogonal views has driven the development of weight-bearing computed tomography (WBCT) technology over the last decade. We analyzed the available literature on WBCT imaging in patients with foot and ankle disorders by performing a literature review of relevant clinical studies in multiple databases including PubMed, MedLine, and Scopus from January 1999 to October 2017. WBCT imaging allows correct evaluation of foot and ankle anatomy with the patient in a standing position, providing images with high spatial resolution, short image acquisition time, low dose of radiation, and costs which are similar to other available imaging technologies. This diagnostic tool can be used for decision making in the treatment of deformities of the ankle, hindfoot, midfoot, and forefoot. ***Level of Evidence III; Systematic review of level III studies.***

Keywords: Ankle. Foot. Weight-bearing. Tomography, x-ray computed/methods.

RESUMO

Na topografia do tornozelo e do pé é fundamental o entendimento espacial das deformidades osteoarticulares para correto diagnóstico e decisão terapêutica. A dificuldade de reprodução da avaliação com radiografias convencionais em posição ortostática em três dimensões impulsionou, na última década, o desenvolvimento da tecnologia de tomografia computadoriza com carga. Analisamos a literatura relacionada com o tema tomografia computadorizada com carga em pacientes com distúrbios do pé e do tornozelo. Para fazer isso, realizamos uma revisão da literatura de estudos clínicos relevantes nas bases de bancos eletrônicos, incluindo PubMed, MedLine e Scopus, de janeiro de 1999 a outubro de 2017. A tomografia computadorizada com carga permite a avaliação da anatomia na posição ortostática fisiológica, com imagens de alta resolução espacial, pequeno tempo de aquisição de imagens, baixa dose de radiação e custos similares a outras tecnologias atualmente disponíveis. Ela pode ser usada para tomada de decisão terapêutica em deformidades do tornozelo, retropé, mesopé e antepé. ***Nível de Evidência III; Revisão sistemática de estudos de nível III.***

Descritores: *Tornozelo. Pé. Suporte de carga. Tomografia computadorizada, imagem/métodos.*

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INTRODUCTION

In the area of ankle and foot performance, imaging studies are fundamentally important aids in diagnosis, therapeutic decision-making, and evaluation of functional results. The most commonly used resources are conventional X-rays with load, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI).[1]

The initial diagnostic investigation often uses conventional X-rays with load to more accurately reproduce the three-dimensional bone relationships in the ankle and foot. However, in many situations the information acquired from this method is limited (especially in relation to the different planes of the ankle and foot) and usually needs to be complemented for correct therapeutic decision making.[1]

The choice of complementary image study is based on certain criteria such as availability, sensitivity, and specificity of the method, cost, and adverse effects/safety, including exposure to radiation.[1]

In this scenario, computed tomography (CT) allows acquisition of high-resolution images in different axes of the ankle and foot, and is usually used to evaluate fractures, degenerative changes,

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Correspondence: Instituto de Ortopedia e Traumatologia, Universidade de São Paulo. Rua Dr. Ovídio Pires de Campos, 333, Cerqueira Cesar, São Paulo, SP, Brazil. 5403-010. alexandrelemegodoy@gmail.com

**** Weight-bearing Computed Tomography International Study Group:***
Martinus Richter - Department of Foot and Ankle Surgery in Rummelsberg and Nuremberg, Germany; Francois Lintz - Clinique de L'Union in Toulouse, France; Arne Burssens - Ghent University Hospital, Gent, Belgium; Alexej Barg - University of Utah, USA; Shadpour Demehri – Johns Hopkins University, Baltimore-MD, USA.

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bone healing, and surgical planning for osteotomies, arthrodeses and arthroplasties.[2]

However, a major limit of conventional CT is its inability to reproduce images of feet and ankles subjected to body weight load. In the absence of support for the patient's body weight, true alignment is not measured correctly. Therefore, this imaging resource is limited, particularly in scenarios related to axial deviations and osteoarticular degeneration such as acquired flatfooted valgus, pes cavus, Charcot's neuroarthropathy, osteoarticular deformities, diabetic foot, and dynamic ligament instability.[2]

Many researchers have made efforts to develop auxiliary methods to simulate body weight support by the ankle and foot, using different strategies. These authors recognized that the deficiencies in simulated weight support conditions unfortunately did not resolve the limitation of conventional CT.[3-10] Additionally, the devices that simulate body weight load generally utilize passive application of force, have a low standard of reproducibility, and do not permit the active muscle forces that act during orthostatic physiological positioning.[11-13]

In this sense, the concept of visualizing the relative alignment of the bones in the ankle and foot using weight-bearing computed tomography (WBCT) is not new. Over the last decade, the cone beam computed tomography with load technique (WBCT) proved feasible and to have high reproducibility of the real situation of the ankle and foot with regard to body weight.[2,14]

The advantages of this new technology include: the ability to obtain images with the patient in an orthostatic position, high resolution, possibility of reconstruction in three dimensions, rapid image acquisition, low rate of radiation exposure, small device size, and low cost in relation to conventional CT.[15]

This article presents a review of this important technological innovation in patients with foot and ankle disorders.

Exposure to radiation and its effects on humans

Radiation is energy in the form of electromagnetic waves, which can be ionizing or non-ionizing. X-rays are located on the spectrum of ionizing radiation.[16,17] (Figure 1)

The energy produced by X-rays is measured in rems, and the energy deposited in inert materials is measured in grays (Gy), with 1 Gy equivalent to 1 Joule/kg. The energy deposited in living tissue (equivalent dose) is measured in Sieverts (Sv), and 1 Sv is the equivalent of 1 Joule/kg, which reflects the biological effects of ionizing energy.[16]

The somatic and cumulative effects (not determined by dose) of ionizing radiation can result in cancer, genetic mutations, and teratological malformations (at the beginning of pregnancy).[17]

Table 1 shows different sources of ionizing radiation and their respective doses deposited in human tissue in Sieverts.

STUDIES CONDUCTED PRIOR TO WBCT, USING CT WITH SIMULATED LOAD

Method using 75 Newton (N) axial force plate, in supine position

In a case-control study with 12 patients (8 with flatfoot valgus and four asymptomatic), Ananthakrisnan et al.[3] demonstrated less subtalar joint contact in patients with posterior tibial tendon dysfunction (PTTD).

In a case-control study with 24 patients (19 with flatfoot valgus and 5 asymptomatic), Malicky et al.[4] observed a higher prevalence of lateral impact in the subtalar joint within the tarsal sinus (92% vs. 0%) and calcaneal-fibular joint (66 vs. 5%) in comparison with controls. Greisberg et al.,[5] in a case series with 37 patients with PTTD, demonstrated increased deformities in these patients when evaluating the

Table 1. Dose of radiation in living tissue by type of human exposure.

Radiation from high-altitude flights	0.001-0.01 mSv/hour
Radiation from natural lighting	0.01 mSv/day
Radiation from simple X-ray of the thorax (anteroposterior)	0.02 mSv
Radiation from simple X-ray of the foot (single exposure)	0.001 mSv
Radiation from surgical radioscopy	0.0375 mSv/3 months
Radiation from surgical radioscopy	0.21 mSv/3 months
Radiation from conventional CT, cranium	1.5 mSv
Radiation from conventional CT, ankle	0.07 mSv
Radiation from conventional CT, full body	9.9 mSv
Weight-bearing CT (WBCT) of the foot/ankle	

Abbreviations: CT, computed tomography; mSV = millisievert.

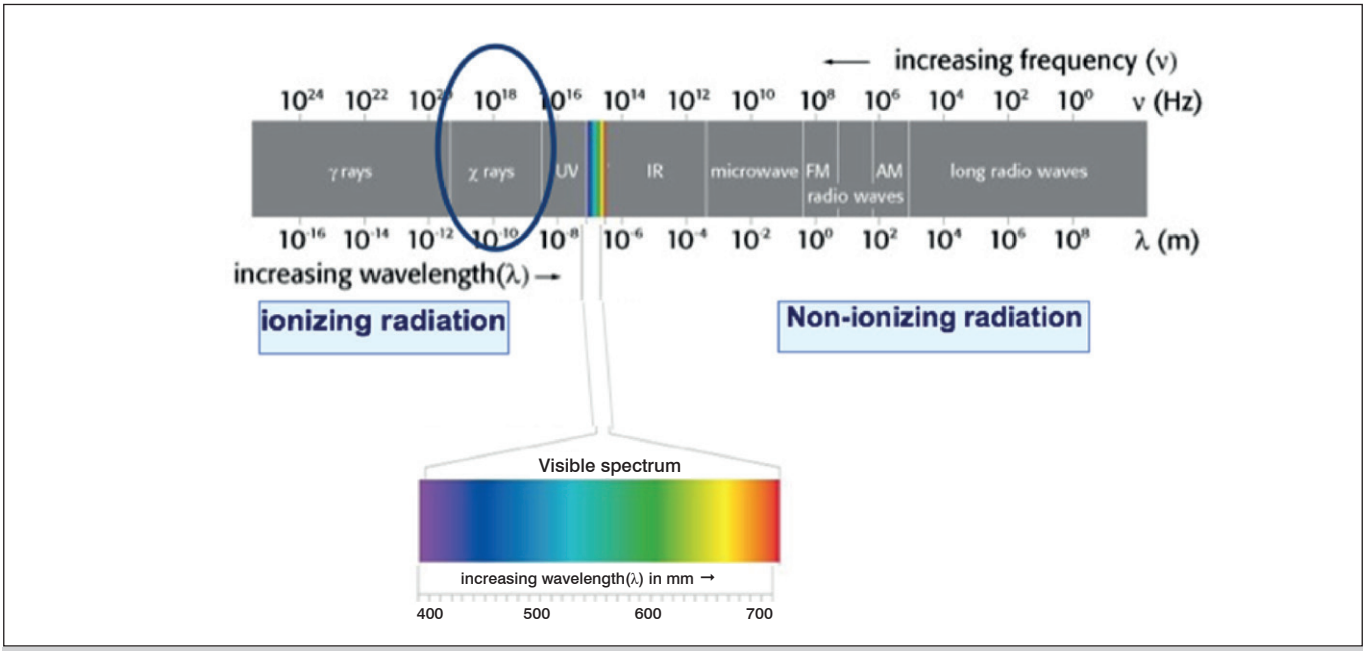

Figure 1. Graph representing the spectra of potential radiation according to frequency in Hertz (Hz) and wave size in Lambda (λ).

talo-navicular and navicular cuneiform joints, and subluxation of the first tarsal-metatarsal joint.

Apostle et al.,[6] in a case-control study with 40 patients (20 with peritalar subluxation and 20 healthy volunteers), demonstrated that the subtalar joint axis presents greater valgus in patients with peritalar subluxation.

Computed tomography using total body weight support platform, in supine position

Geng et al.,[7] in a case-control study with 20 patients (10 with hallux valgus and 10 healthy volunteers) showed greater dorsiflexion and supination of the first tarsal-metatarsal joint in patients with hallux valgus.

Kido et al.,[8] in another case-control study with 42 patients (21 with flatfoot valgus and 21 healthy volunteers), observed that patients in the case group had greater plantar talus flexion, navicular abduction in the talo-navicular joint, and calcaneal dorsiflexion and eversion in the subtalar joint when compared to the controls.

Kimura et al.,[9] in a case-control study with 20 patients (10 with hallux valgus and 10 healthy volunteers) showed greater dorsiflexion in the talo-navicular and first tarsal-metatarsal joints in patients with hallux valgus.

Kido et al.,[10] in a case-control study with 44 patients (20 with valgus flat foot and 24 healthy volunteers) demonstrated greater dorsiflexion of the first metatarsal, greater eversion of the navicular and the calcaneus, and greater rotation in the talo-navicular joint.

Van Bergeyk et al.,[11] in a case-control study with 23 patients (11 with chronic lateral instability of the ankle and 12 healthy controls), observed a significantly different hindfoot alignment angle between the groups: $6.4° \pm 4°$ varus in the instability group and $2.7° \pm 5°$ varus in the controls.

Yoshioka et al.,[12] in a case-control study with 20 patients (10 with flatfoot valgus and 10 healthy volunteers) identified greater forefoot supination in patients with flatfoot valgus.

Zhang et al.,[13] in a case-control study with 30 patients (15 with flatfoot valgus and 15 healthy volunteers) identified significant differences with regard to the position of the talus, navicular, and calcaneal joint between the groups.

Studies with WBCT in normal asymptomatic volunteers

Lepojärvi et al.[18] evaluated the normal anatomy and rotational dynamics of the distal tibiofibular joint in 32 asymptomatic individuals under physiological conditions. Images were acquired at for three different ankle rotations: neutral, internal and external. Four parameters were measured: 1) sagittal translation of the fibula, 2) anterior and posterior width of the syndesmosis, 3) tibiofibular free space, and 4) rotation of the fibula. With the ankle in neutral position, the fibula was seen to be located anterior to the tibial notch in 88% of the volunteers during all the measurements. During rotational movement of the ankle, the mean anteroposterior movement was 1.5 mm and the average rotation of the fibula was 3 degrees.[18] In the same population, these authors also assessed the rotational dynamics of the talus within the upper section of the ankle joint between the lateral and medial malleoli. When the ankle was turned with strength equivalent to 30 Nm, a 10° rotation was observed without a substantial increase in free medial space.[19]

Cody et al.[20] performed WBCT in 59 volunteers without a history of previous disease or foot/ankle injury to describe their findings in the subtalar joint. The orientation of the posterior facet of the subtalar joint was measured in three different coronal planes (at the center of the subtalar joint, and 5 mm anterior and posterior to the center). These authors observed a concave posterior facet in 88% of the volunteers and flat facet in the other 12%. In the coronal plane, the posterior facet was in valgus in 90% of the images and in varus in the other 10%. They also found greater valgus angulation in positions more posterior to the subtalar joint.

WBCT studies in patients with deformities

A total of 12 studies published between 2001 and 2017 were selected: two case reports, five prospective studies, and five retrospective studies. The levels of evidence ranged from II to IV, with two level II studies, six level III studies, and four level IV studies.

CASE REPORTS

Welck and Meyerson[21] described an unusual case of bilateral atraumatic erosive subtalar osteoarthritis with unilateral subtalar collapse, and used WBCT for surgical planning and postoperative evaluation. These authors emphasized the value of this method in pre-surgical planning, since it allowed the relevant angles to be measured precisely in three dimensions, exactly determining the presence of posterior osteophytes and anterior and lateral impact in the ankle. They also emphasized its use in postoperative follow-up, permitting a functional and anatomically correct assessment of the correction performed.

Using Kaplan's analysis, these same authors described their findings from a study using WBCT in three cases of Muller-Weiss disease.[22]

CASE REPORTS

Burssens et al.[15] described a clinically reproducible method for measuring hindfoot alignment using WBCT. In a prospective case series with 60 patients divided into two groups (30 patients with varus alignment and 30 patients with valgus hindfoot alignment), these authors observed a positive correlation between the hindfoot alignment angles measured and concluded that WBCT can be used objectively for this measurement.

Tomography studies with partial load

Kim et al.[23] used CT with partial load to evaluate preoperative alignment of the forefoot in 138 patients (166 feet) with hallux valgus deformities and compared their results with a control group of 19 patients (19 feet). These authors evaluated the angle α (pronation angle of the first metatarsal) and the relative position of the sesamoids. Angle α and subluxation of the sesamoids differed significantly between the study group and the control group. The authors suggested that the use of CT with partial load might be useful in assessing the deformity of the forefoot in the coronal plane and guiding the choice of treatment of patients with hallux valgus.

Case-control studies using CT with load

Cody et al.[20] used WBCT to analyze the anatomy of the talus and the alignment of the subtalar joint in 45 patients with adult type II acquired flatfoot and 17 volunteer controls. The subtalar alignment was assessed using the angles between the bottom facet of the talus and the ground and the angle between the upper and lower facets of the talus. Both of these angles were seen to differ significantly between the study groups. The researchers concluded that patients with flatfoot valgus deformity presented greater innate valgus in their talar anatomy and greater alignment of the subtalar joint in valgus. They emphasized that these measures can be used to identify patients with higher risk of progressive deformity and subtalar joint degeneration.

Krähenbühl et al.[24] analyzed subtalar orientation using WBCT in 40 patients with tibiotalar osteoarthritis and 20 healthy controls. Subtalar alignment was assessed through the angle between a line perpendicular to the ground and the posterior facet of the subtalar joint. When they compared the joints in varus and valgus, the authors observed significant differences when compared to healthy controls. They concluded that the orientation of the subtalar joint could be a determinant factor in the development of ankle osteoarthritis.

Lintz et al.[25] described a new three-dimensional biometric tool for WBCT to evaluate hindfoot alignment, using the concept of

the biomechanical tripod formed by the head of the first and fifth metatarsals and the farthest point of the calcaneal tuberosity in relation to the positioning of the center of the ankle joint, represented by the point closest to the domus talar. This relationship is represented by the foot-angle offset (FAO). The data set from the population studied was analyzed (57 volunteers with normal hindfoot alignment, 38 volunteers with varus alignment, and 40 volunteers with valgus alignment), and the authors observed FAO of 2.3% ± 2.9% in the controls, -11.6% ± 6.9% in the patients with varus of the hindfoot, and 11.4% ± 5.7% in patients with hindfoot valgus. They concluded that the method described was feasible and reproducible for measuring foot-ankle offset and hindfoot alignment.[25]

In a prospective study of 50 patients with symptomatic hallux rigidus and 50 controls who underwent CT with load assessed by two examiners in relation to the difference in length between the first and second metatarsals, intermetatarsal angle between the first and second metatarsals (IMA), and hallux valgus angle (HVA), Cheung et al. observed a smaller difference in length, smaller IMA, and smaller HVA in the patients with hallux rigidus than in the controls.[26]

Studies comparing CT with load and pedobarography

In a prospective study, Richter et al.[27] evaluated 50 patients who simultaneously underwent WBCT and pedobarography. The authors mapped the alignment of the hindfoot and midfoot, and the relationship between the head of the first metatarsal/sesamoids and the heads of the lateral metatarsals (2nd, 3rd, 4th, and 5th) and with all the toes (1st-5th). These authors found no significant correlation between bone alignment measurements in WBCT and the distribution values for plantar pressure in pedobarography.

Studies comparing CT with load and simple X-ray with load

Kim et al.[14] evaluated conventional X-rays with load and WBCT for 96 patients with osteoarthritis (OA) of the ankle, divided into groups with moderate OA (50 patients) and severe OA (46 patients). These authors documented the presence of abnormal internal rotation of the talus in patients with osteoarthritis in varus, which was more frequently observed in the group with severe OA than those with moderate OA. They emphasized that this rotation could not be noted in conventional X-rays since axial images cannot be acquired.

Studies comparing CT with and without load

Collan et al.[28] compared the alignment of the first metatarsal in 10 patients with hallux valgus with five asymptomatic controls using CT with and without load; these authors observed an increase in medial deviation of the first metatarsal and pronation of the first toe on images with load in patients with hallux valgus.

Hirschmann et al.[29] performed a prospective evaluation of multiple alignment measurements in 22 volunteers using CT with and without load. These authors found significant differences for most measurements: distance between fibula and calcaneum, lateral subtalar joint space, talus-calcaneus overlap, and calcaneus-navicular distance. They found no difference between the hindfoot alignment angle and distance between the tibia and calcaneus when comparing images from the group with load and without load. The hindfoot alignment angle was comparable when measured with and without load (21.0° ± 7.9° vs. 19.0° ± 9.0°). The authors suggested using WBCT in assessing fibular impact and talus-calcaneus overlap.

Richter et al.[30] prospectively evaluated foot and hindfoot alignment in 30 patients using WBCT, CT without load, and conventional X-rays with load. They found significant differences in angles measured using different imaging methods. The hindfoot alignment angle in the WBCT was 10.1° ± 7.16, 5.4°±5.6° in CT without load, and 2.4°±6.9° in conventional X-ray with load.

de Cesar Netto et al.[2] prospectively evaluated multiple parameters used in measuring adult valgus flatfoot deformity, comparing CT images with and without load from 20 patients diagnosed with flexible deformity. These authors demonstrated that WBTC produced similar measurements to those traditionally obtained from conventional X-ray imaging to stage adult valgus flatfoot deformity. They also noted that the measures, which indicate the severity of the deformity, are more pronounced in images obtained with load than those obtained without load.

FINAL CONSIDERATIONS

Computed tomography with load is available to investigate osteoarticular deformities of the ankle and foot. This method allows more suitable and reliable assessment of the anatomy in a physiological position with load, closer to the mechanical demands of normal gait. This technique provides images with high spatial resolution, with rapid image acquisition, low radiation dose, and costs similar to other technologies available. WBCT may be used for therapeutic decision making in deformities of the ankle, hindfoot, forefoot, and midfoot, to help determine more accurate surgical planning.

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. ALGS (0000-0002-6672-1869)*: designed the study and drafted the article. CCN (0000-0001-6037-0685)* and SD (0000-0001-5991-5924)*: interpreted the data and performed the critical review. AB (0000-0003-0682-1961)*, MR (0000-0002-7934-6551)*, and FL (0000-0002-0163-6516)*: acquired, analyzed, and interpreted the data. AB (0000-0002-8602-100X)*: contributed to the concept and design of the study. All authors contributed to the intellectual concept of the study and approved the final version of the manuscript. *ORCID (Open Researcher and Contributor ID).

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Review Article

CONTRALATERAL PATELLAR TENDON AUTOGRAFT IN ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

TENDÃO PATELAR CONTRALATERAL COMO ENXERTO EM RECONSTRUÇÃO DO LIGAMENTO CRUZADO ANTERIOR

Paulo Lobo Júnior[1], Eugênio dos Santos Neto[1], José Humberto de Souza Borges[1], Luana Junqueira Resende Volpe Dias[1], Ronny de Souza Machado[1], Anderson Freitas[1]

1. IPE-HOME, Hospital Ortopédico e Medicina Especializada, Brasília, DF, Brazil.

ABSTRACT

Objective: To conduct a systematic review of literature about the use of contralateral patellar tendon autograft in anterior cruciate ligament reconstructions and present the results. Methods: The LILACS, MEDLINE, Cochrane, PubMed, Scielo and Google Scholar databases were searched without date restrictions for the keywords "anterior cruciate ligament reconstruction" combined with "contralateral" in the article title. After the studies were identified, two independent evaluators collected the qualitative characteristics of the studies and classified them according to clinical outcomes of these grafts as positive, neutral, or negative. Results: A total of 755 articles were found initially, and after detailed evaluation of all references, followed by a screening process and assessment of quality, a total of 11 studies were determined to be eligible for inclusion in this systematic review. Of these, 72.72% were level II studies, the most common level of evidence among the results. Positive results for this type of graft were found in 63.63% of the studies. Conclusion: Based on the literature review, most of the included articles (63.63%) presented positive results for the use of contralateral patellar tendon grafts. ***Level of Evidence III; Systematic review.***

Keywords: Anterior cruciate ligament. Patellar ligament. Knee joint. Tendons/transplantation.

RESUMO

Objetivo: Realizar uma revisão sistemática da literatura abordando o uso do tendão patelar contralateral como enxerto nas reconstruções do ligamento cruzado anterior e apresentar seus resultados. Métodos: Foi realizado um levantamento nas bases de dados LILACS, MEDLINE, Cochrane, PubMed, Scielo e Google acadêmico sem restrição de data e utilizando como descritores as palavras: "anterior cruciate ligament reconstruction" combinadas com "contralateral" no título do artigo. Após a identificação dos estudos, dois avaliadores independentes coletaram características qualitativas dos estudos, as quais foram classificadas de acordo com os resultados clínicos como positivas, indiferentes e negativas para o uso desse enxerto. Resultados: Foram encontrados, inicialmente 755 artigos e após uma avaliação detalhada de todas as referências, seguida de processo de triagem e avaliação da qualidade, um total de 11 estudos foram determinados como elegíveis para inclusão nesta revisão sistemática, sendo que 72,72% deles apresentaram nível de evidência II, sendo este o maior nível encontrado; 63,63% apresentaram resultado positivo para esse tipo de enxerto. Conclusão: Com base na revisão da literatura, a maioria dos artigos avaliados (63,63%) apresenta resultados positivos para o uso do enxerto do tendão patelar contralateral. ***Nível de Evidência III; Revisão sistemática.***

Descritores: *Ligamento cruzado anterior. Ligamento patelar. Articulação do joelho. Tendões/transplante.*

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INTRODUCTION

The anterior cruciate ligament (ACL) plays a very important role in knee biomechanics; it is the primary stabilizer against anterior tibial translation, and acts as a secondary stabilizer in excessive internal rotation and in stress in valgus and varus. Because of the high incidence of ACL injuries in the population, this ligament has been the subject of many contemporary studies. Considering the instability ACL injuries cause, and potential comorbidities resulting from ACL rupture (such as meniscal and chondral injury and possibly early osteoarthrosis), the recommended treatment is surgical and involves ligament reconstruction.[1,2]

An improved surgical technique for reconstructing this ligament has made it less invasive, and when combined with early rehabilitation leads to joint stability and decreases the time patients need to return to their normal activities (not only professional sports, but particularly to work in ordinary patients), which has greatly increased the number of surgical reconstructions in recent years.[3]

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Work conducted at the Hospital Ortopédico e Medicina Especializada, Brasília, DF, Brazil.
Correspondence: Eugênio dos Santos Neto. QI 6, Lote1280, Residencial Encanto, 301-B, Setor de Indústrias. Gama Leste. 72445-060. Brasília, DF, Brazil. eugeniosneto@hotmail.com

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Despite the frequency of ACL reconstruction surgery, extensive experience among orthopedic surgeons, and increasing advancement in surgical techniques, the choice of graft to be used in ligament reconstruction remains a main topic of debate in the literature.[2,4] Currently, several graft sources have been shown effective in ACL reconstruction; the choice of the ideal graft is tailored to the patient profile and the injury, and also is affected by the surgeon's personal experience. Grafts derived from the quadriceps tendon and the flexors have emerged as an option for patellar grafting, following studies on anterior knee pain and morbidity of the donor site.[4]

With increasing numbers of revision procedures after ACL reconstruction surgery, there was a need for grafts from other sites such as the contralateral patellar tendon. Clinical observations by surgeons choosing this new site produced results equaling or even exceeding those of the primary surgery, raising the possibility that this site could be a good donor candidate for primary reconstructions.[5-7] Because of the importance and scarcity of scientific studies on the use of the contralateral patellar tendon as a graft in reconstructing the ACL, the authors conducted this review, which is principally intended to present the results of studies that used this graft in primary reconstructions of the ACL of the knee.

MATERIALS AND METHODS

A systematic review of the literature in the LILACS, MEDLINE, Cochrane, Scielo, PubMed and Google Scholar databases was conducted. The search was not limited to any date range because of the need for a historical delineation. The text keywords we used were: "anterior cruciate ligament reconstruction" combined with "contralateral", and we always searched for these terms in the article title.

The selection criteria for studies included in this review were:

a. articles written in English or Portuguese;
b. theoretical studies matching the objectives of this analysis;
c. cross-sectional studies comparing graft types including contralateral patellar tendon grafts;
d. correlation studies involving the use of the contralateral patellar tendon as a graft;
e. controlled clinical trials verifying outcomes from the use of the contralateral patellar tendon as a graft.

Exclusion criteria were:

a. articles in languages other than English or Portuguese;
b. articles with deficiencies in their methodology section, principally with regard to selection and sample power, as well as materials used;
c. studies which did not involve the use of the contralateral patellar tendon as a graft;
d. case reports or case series involving fewer than five patients;
e. letters to the editor or expert opinions.

Data were collected from May 2017 to August 2017. The main author of this study evaluated all the articles and applied the inclusion and exclusion criteria. Each relevant study was obtained and reviewed in its entirety. The studies were identified electronically, based on the abstracts and full texts in the databases. After the studies were identified, two evaluators independently collected the qualitative characteristics and results of the studies, grouping them as positive, negative, or neutral. Any doubts related to selecting the articles or their results were resolved by consensus between the two researchers. When questions remained, a third reviewer was consulted to achieve a majority opinion.

This level of evidence has been determined in accordance with the Oxford Levels of Evidence Classification System produced by the Oxford Center for Evidence-Based Medicine.[8]

RESULTS

Searching for the terms "anterior cruciate ligament reconstruction" combined with "contralateral" in the article titles, we initially identified 755 articles from the electronic databases consulted. (Table 1) After detailed evaluation of all references followed by a screening process and quality assessment, a total of 11 studies were determined eligible for inclusion in this systematic review, as shown in Figure 1. Table 2 presents the lead author, year of publication, article title, most important findings presented in the article, level of evidence, and clinical outcome. The highest level of evidence found was level II, which was also the most frequent, with 72.72% of studies (8). Level III was found in 27.28% studies (3); no articles were found with level I, and studies with levels IV and V were excluded from this

Table 1. Number of articles found on May 1, 2017 according to database.

Database	Number of articles
Pubmed	22
Bireme	557
Lilacs	26
Google Scholar	68
Cochrane	67
Scielo	15
Total	755

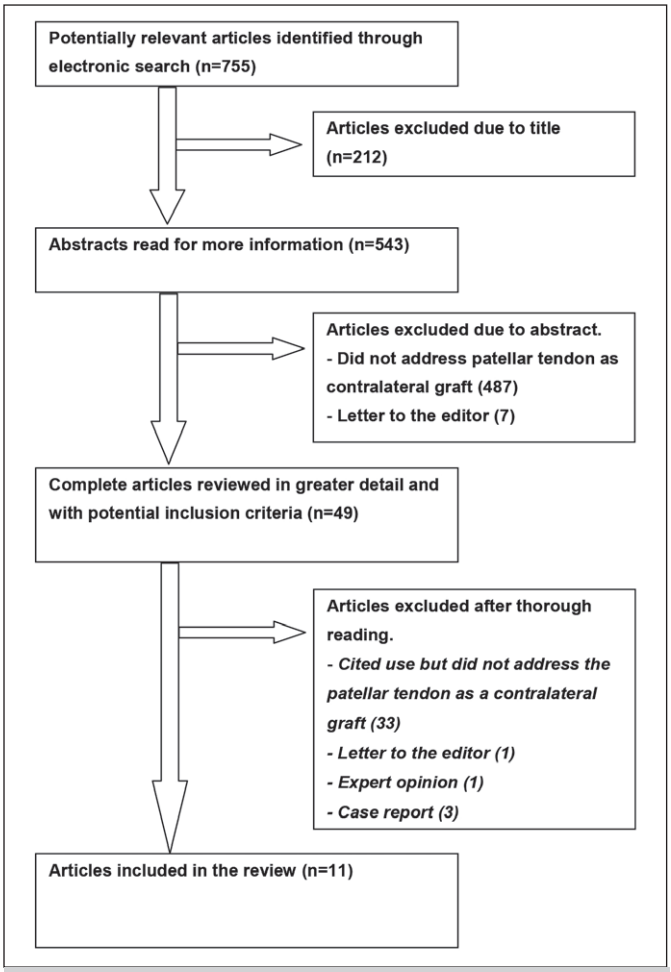

Figure 1. Flowchart of study selection.

Table 2. Reference, title, conclusion, level of evidence, and results for each study selected for bibiliographic review.

Reference	Title	Conclusion	Level of Evidence	Result
Rubinstein et al.[5], 1994.	Isolated autogenous bone-patellar tendon-bone graft site morbidity	The morbidity from collecting contralateral patellar tendon grafts seems to be of short duration and largely reversible.	2C	P
Uribe et al.[6], 1996.	Revision anterior cruciate ligament surgery: experience from Miami.	Collection of the contralateral patellar tendon was not found to produce adverse effects in the long term. Learning several anterior cruciate ligament reconstruction techniques and avoiding tunnels and pre-existing implants facilitate surgical revision. Correct placement of the graft and addressing secondary constraints are essential for a successful revision surgery.	2C	I
Kartus et al.[9], 1998.	Ipsi- or contralateral patellar tendon graft in anterior cruciate ligament revision surgery. A comparison of two methods.	Recovery after anterior cruciate ligament reconstruction using the ipsilateral patellar tendon resulted in lower functional scores and a greater rate of complications than revision with the contralateral patellar tendon.	2B.	P
Bruck et al.[10],1998.	Morbidity after contralateral transplantation of the patellar ligament for cruciate ligament replacement	There was no radiographic evidence of low patella. Use of contralateral patellar tendon graft for anterior cruciate ligament reconstruction does not involve severe morbidity.	2C	P
Shelbourne et al.[11], 2000.	Primary anterior cruciate ligament reconstruction using the contralateral autogenous patellar tendon.	The contralateral patellar tendon may be used to restore range of motion and muscle strength earlier than ipsilateral patellar tendon graft. Patients may also return to full capacity in sports more quickly without compromising maximum stability.	2A	P
Shelbourne et al.[12], 2005.	Contralateral patellar tendon and the Shelbourne experience Part 2. Results of Revision Anterior Cruciate Ligament Reconstruction	The objectives of ACL reconstruction revision should be similar to those of primary surgery, restoring stability, movement, and function. Suggests using the contralateral patellar tendon graft and mini-arthrotomy technique Provides similar results to the primary procedure and has consequently become the method of choice for primary ACL reconstruction.	2B	P
Zink et al.[13], 2005.	Gender comparison of knee strength recovery following ACL reconstruction with contralateral patellar tendon graft.	Since strength recovery after surgery is not identical in men and women, specific rehabilitation protocols for each sex may be justified.	2C	I
Mastrokalos et al.[14], 2005.	Donor site morbidity and return to the preinjury activity level after anterior cruciate ligament reconstruction using ipsilateral and contralateral patellar tendon autograft: a retrospective, nonrandomized study	Contralateral patellar tendon graft appears to offer no advantages over ipsilateral grafts, because all symptoms related to morbidity of the donor site are transferred to the healthy knee, and patients do not return to activity earlier.	2A	N
Benner et al.[15], 2011.	Infections and patellar tendon ruptures after anterior cruciate ligament reconstruction A comparison of ipsilateral and contralateral patellar tendon autografts	There were no significant differences in the incidence of infection or patellar tendon rupture between the ipsilateral and contralateral groups. Patients with complications after ACL reconstruction using an autogenous patellar tendon graft may have less difficulty achieving complete knee movement when the graft is collected from the contralateral knee.	3A	P
Dauty et al.[16], 2014.	Muscular isokinetic strength recovery after knee anterior cruciate ligament reconstruction revision: Preliminary study	Deficits in isokinetic muscle strength after ACL revision seem similar to those observed after primary ACL reconstruction using the same surgical technique and patellar, ipsilateral ischiotibial, and contralateral patellar grafts.	3A	I
Shelbourne et al.[17], 2015.	Anterior cruciate ligament reconstruction with contralateral autogenous patellar tendon graft: evaluation of donor site strength and subjective results.	After ACL reconstruction using a contralateral patellar graft, patients can achieve symmetrical force in the legs without adverse subjective symptoms after graft collection. Additionally, there may be more return with a contralateral graft than with an ipsilateral graft.	3A	P

P= positive; N=negative; I=neutral.

review. This review also found that 63.63% of studies (7) presented positive results for the use of the contralateral patellar tendon as a graft, 27.27% studies (3) contained neutral results, and 9.09% of studies (1) presented negative results for use of this graft.

DISCUSSION

Over the last 40 years, the therapeutic approach to ACL injury has undergone significant alterations, returning to the 1939 technique which used the patellar tendon to replace the ruptured ACL. This return to the old technique was only possible through advances in anatomy and biomechanics, along with arthroscopy using new tools and fixation techniques which provide earlier rehabilitation and better results.[18]

Besides good fixation, the current goal is anatomical reconstruction of the ACL in order to reestablish the structural and biomechanical properties of the knee, mainly with regard to rotational instability. The items that contribute to satisfactory progress after this procedure are adequate choice of surgical technique for each patient, the condition of the secondary restrictors (meniscus and ligaments), post-operative analgesia, and early and safe rehabilitation. Improvements and innovations in ACL reconstruction techniques have produced satisfactory results for instability control and early return to sports.[3,18]

Since it is a surgical procedure, ACL reconstruction presents complications inherent to any intervention, such as healing problems, deep venous thrombosis, infection, and hemorrhage. However, there are specific complications arising from the use of different graft types.[1,2]

During the study period, several types of grafts were used: autologous, allografts, and synthetic. Currently, the tendency is to use a strong biological graft; autologous grafts from the patellar and ischiotibial tendons (semitendinosus and gracilis tendons) are the most frequently discussed. One of the complications which have been most widely studied with regard to the use of patellar tendon graft is patellar fracture. When the ischiotibial tendons are used, a possible complication is that patients may present some deficit of knee flexion in the donor knee.[11,12]

Among the most frequent complications of ACL reconstruction, pain in the anterior face of the knee and loss in residual muscle strength seem to be linked to the choice of donor source. The studies are controversial in defining whether these comorbidities (such as anterior knee pain, patellofemoral symptoms, and weakness of the quadriceps muscle) are related to the graft harvest, a rehabilitation program, or the reduction in movement. However, complications such as fracture of the patella or the proximal portion of the tibia and patellar tendon rupture are clearly attributed to the process of collecting the patellar graft.[15]

As the number of primary ACL reconstructions grows, the need for revision surgery has increased significantly, and while the ideal graft choice continues to be unresolved, the contralateral patellar tendon has emerged as an option. Studies on ACL injury revision procedures and the use of this graft type found no adverse effects over the long term, and also showed a potentially more rapid post-operative recovery, with better functional scores and an even lower rate of complications.[6,9]

However, because collection of the patellar tendon graft leads to some degree of morbidity to the donor site, such as decreased sensitivity, difficulty kneeling, and quadriceps muscle weakness, orthopedic surgeons tend to choose other graft sources as their first option.[17]

In 1994, a study by Rubinstein reported the results of using contralateral patellar tendon grafts in ACL reconstruction revision procedures and proposed the use of this tendon in primary reconstruction based on the results obtained in patients related to recovery of knee range of motion, muscular strength of the quadriceps in both knees, in both the reconstructed and the donor knees. In another study in 1998, Bruck found good results for the use of this graft in ACL reconstructions, with low donor site morbidity.[5,10]

Other subsequent articles showed that the contralateral patellar tendon could be used in primary ACL reconstructions, restoring range of motion and muscle strength as early as an ipsilateral patellar tendon graft, and consequently could offer a faster full-capacity return to sports without compromising maximum stability, since after proper post-surgical rehabilitation there was no loss of strength or subjective symptoms that were not resolved.[11,17]

On the other hand, one study showed that the losses in isokinetic muscle strength after ACL revision seem similar to those observed after primary reconstruction of this ligament using the same surgical technique and grafts of the ipsilateral patellar tendon, ipsilateral ischiotibial tendons, and contralateral patellar tendon. Additionally, contralateral patellar tendon graft appeared to offer no advantages over the ipsilateral graft, because all the symptoms related to morbidity in the donor site are transferred to the healthy knee, and return to sports or professional activities is not faster.[14,16]

This present study shows that the contralateral patellar tendon graft has been used for at least twenty years, and studies are still recent. Of the 11 articles included in this review, no study used evidence level I, and studies with levels IV and V were discarded according to the exclusion criteria. Eight articles were at level II and 3 at level III. Therefore, this review demonstrates a lack of articles with a high evidence levels and A-level recommendation which compared the contralateral patellar tendon to other graft types.

Despite the lack of these studies with higher levels of evidence, it is important to emphasize that there are cohort studies with a large number of patients, most notably by Shelbourne, who authored or co-authored 5 of the articles in this review (45.45%), all of which presented positive results for the use of contralateral patellar tendon grafts. This author also has some bibliographic reviews and texts classified as expert opinions, indicating that he is a major scholar and proponent of this type of graft. Besides these 5 articles, another 2 articles reported positive results for the use of this graft, 3 articles presented neutral results, and only 1 study indicated negative results. However, this latter case was a cohort study with evidence level II.

This literature review encountered some obstacles, such as a small number of articles addressing the use of the contralateral patellar tendon as a graft; broader descriptors were required to find more studies and then develop inclusion and exclusion criteria as well as exclusion methods involving only reading the title and abstract.

CONCLUSIONS

A review of studies describing the use of the contralateral patellar tendon as a graft in ACL reconstruction surgeries provides information and parameters required for decision-making. According to the literature studied, most of the articles (63.63%) presented positive results for the use of contralateral patellar tendon grafts.

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