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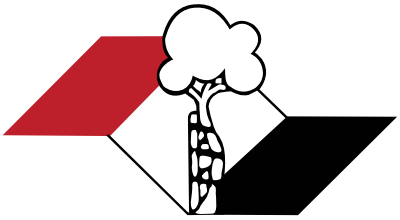

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Acta Ortopédica Brasileira

Volume 25 – Number 2 – Year 2017

CHEGOU

FOXIS
CELECOXIBE

Eficácia, segurança e preço acessível no tratamento anti-inflamatório.[1-4]

- **Melhora significante** dos sinais e sintomas de osteoartrite.[6]
- **Eficaz** no tratamento de dor aguda.*[7]
- Inibidor da COX-2 **mais utilizado no mundo.**[5]

* Devido a entorse de tornozelo em 24 horas após o início do tratamento.

Referências bibliográficas: 1. SIMON, L.S. et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: A randomized controlled trial. JAMA, v. 282, n. 20, 1999. **2.** ESSEX, M.N; BHADRA, P; SANDS, G.H. Efficacy and tolerability of celecoxib versus naproxen in patients with osteoarthritis of the knee: a randomized, double-blind, double-dummy trial. The journal of international medical research, v. 40, p. 1357-1370, 2012. **3.** LÉRIAS, J.R. Celecoxibe e rofecoxibe: eficácia e segurança dos inibidores selectivos da Cox-2 comparativamente aos AINEs não selectivos. Rev Port Clin Geral, v. 20, p. 47-64, 2004. **4.** Kairos Web Brasil. Disponível em: <http://brasil.kairosweb.com>. Acesso em: Fev. 2017.**5.** SOLOMON, S.D. et al. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: The cross trial safety analysis. Circulation, v. 117, p. 2104-2113, 2008.2008. **6.** BENSEN, W.G. et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: A randomized controlled trial. Mayo ClinProc, v. 74, p. 1095-1105, 1999. **7.** CARDENAS-ESTRADA, E. et al. Efficacy and Safety of Celecoxib in the Treatment of Acute Pain due to Ankle Sprain in a Latin American and Middle Eastern Population. The Journal of International MedicalResearch, v. 37, p. 1937-1951, 2009. **8.** Internal report. **9.** Bula do produto FOXIS: cápsulas. Farmacêutica Responsável: Gabriela Mallmann. Guarulhos, SP. Aché Laboratórios Farmacêuticos S.A.

FOXIS - celecoxibe. Cápsulas. 200 mg. USO ORAL. USO ADULTO. Indicações: Tratamento dos sinais e sintomas da osteoartrite e da artrite reumatoide; alívio dos sinais e sintomas da espondilite anquilosante; alívio da dor aguda (principalmente no pós-operatório de cirurgia ortopédica ou dental e em afecções musculoesqueléticas), alívio dos sintomas da dismenorreia primária e da lombalgia. **Contraindicações:** Não deve ser usado por pacientes: que tenham tido crise de asma, urticária ou reações alérgicas após uso de ácido acetilsalicílico ou outros anti-inflamatórios; com doença hepática e/ou com insuficiência renal grave; que tenham dor relacionada à cirurgia de revascularização do miocárdio; com hipersensibilidade ao celecoxibe ou a qualquer componente da fórmula. **Cuidados e advertências:** O uso de AINEs pode retardar ou inibir a ovulação, o que pode estar associado com a infertilidade reversível em algumas mulheres. Não deve ser usado por grávidas sem orientação e seguimento médico; especialmente durante o primeiro e segundo trimestres. O uso de celecoxibe durante a gravidez requer que se pesem os potenciais benefícios para a mãe e riscos para a criança. **Celecoxibe é um medicamento classificado na categoria C de risco de gravidez.** Embora reduza o risco de desenvolvimento de complicações gastrintestinais associadas ao uso de anti-inflamatórios, esse risco não está eliminado pelo uso de celecoxibe, sendo maior em maiores de 65 anos, consumo de bebidas alcoólicas ou com história anterior de perfuração, úlcera ou sangramento gastrintestinal. Celecoxibe deve ser usado com cautela em pacientes com: hipertensão, pois pode piorá-la; portadores de insuficiência renal, alterações da função hepática em idosos; portadores das alterações das enzimas metabolizadoras CYP2C9. Celecoxibe deve ser descontinuado ao aparecimento de rash cutâneo, lesões nas mucosas ou outros sinais de alergias.**Interação medicamentosa:** anticoagulantes; anti-hipertensivos das classes dos inibidores da enzima conversora de angiotensina (ECA) e/ou antagonistas da angiotensina II diuréticos e betabloqueadores podem ter seu efeito reduzido; em pacientes idosos, com desidratação (incluindo aqueles em tratamento com diuréticos) ou com função renal comprometida, a coadministração de antiinflamatórios, incluindo os inibidores específicos da COX-2, com inibidores da ECA, pode resultar no comprometimento da função renal, incluindo possível insuficiência renal aguda; fluconazol pode aumentar os níveis sanguíneos de celecoxibe; lítio pode ter seu nível sanguíneo aumentado; medicamentos anti-inflamatórios podem aumentar o risco de toxicidade no rim associada à ciclosporina; a administração concomitante de dextrometorfano ou metoprolol com celecoxibe 200 mg duas vezes ao dia resultou em aumento de 2,6 vezes e 1,5 vezes das concentrações no sangue de dextrometorfano e metoprolol, respectivamente; fosinopril administrado concomitante com celecoxibe pode não controlar a pressão alta. **Foxis 200 mg: Este produto contém o corante amarelo de TARTRAZINA que pode causar reações de natureza alérgica, entre as quais asma brônquica, especialmente em pessoas alérgicas ao ácido acetilsalicílico. Atenção: Este medicamento contém Açúcar, portanto, deve ser usado com cautela em portadores de Diabetes. Reações adversas: Comuns** (ocorre entre 1% e 10% dos pacientes) inflamação dos brônquios e seios da face, infecção do trato respiratório superior, infecção urinária, insônia, tontura, hipertensão e piora da hipertensão, tosse, vômito, dor abdominal, dispepsia, flatulência, prurido, rash, edema periférico. Incomuns (ocorre entre 0,1% e 1% dos pacientes): faringite; rinite, anemia, hipersensibilidade, ansiedade, hipertonia, sonolência, visão borrada, zumbido; palpitação, úlceras no estômago; doenças dentárias; aumento da quantidade de enzimas hepáticas, urticária, equimose, edema facial, doença semelhante à gripe, lesão. Infecção pela bactéria Heliocobacter, pelo vírus Herpes zoster, infecções na pele, em feridas e gengiva, labirintite, infecção por bactéria, lipoma, distúrbio do sono, infarto cerebral, hemorragia conjuntival, depósitos no humor vítreo, hipoacusia, angina instável, insuficiência da valva aórtica; aterosclerose da artéria coronária; bradicardia sinusal, hipertrofia ventricular; trombose venosa profunda; hematoma; disfonia, sangramento da hemorróida; evacuações frequentes; ulceração da boca; estomatite; dermatite alérgica; cisto sinovial, noctúria, cisto ovariano, sintomas da menopausa; sensibilidade nas mamas; dismenorreia; aumento da quantidade de potássio e sódio no sangue, redução da testosterona no sangue; redução do hematócrito, aumento nos níveis de hemoglobina, fraturas, epicondilite, ruptura do tendão. Posologia: Celecoxibe deve ser engolido com ou sem alimentos. Para o tratamento de dor aguda e dismenorreia primária: 400 mg na primeira dose, seguidos de uma dose de 200 mg por via oral após 12 horas, seguido de 200 mg a cada 12 horas nos dias seguintes conforme necessário. Uso para o tratamento de dor crônica: menor dose diária eficaz durante o menor período possível. As doses sugeridas de celecoxibe para essas doenças são as seguintes: Osteoartrite e Espondilite anquilosante: 200 mg em dose única ou 100 mg duas vezes; Artrite reumatóide: 100 ou 200 mg duas vezes ao dia; Lombalgia: 200 mg ou 400 mg em dose única ou dividida em duas vezes de 100 mg ou 200 mg. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. **VENDA SOB PRESCRIÇÃO MÉDICA. SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA. MS - 1.0573.0491. MB 02 VP_SAP 4591400_SAP 4585100. *Material técnico científico de distribuição exclusiva a profissionais de saúde habilitados à prescrição e/ou dispensação de medicamentos.**

CONTRAINDICAÇÕES: Não deve ser usado por pacientes: que tenham tido crise de asma, urticária ou reações alérgicas após uso de ácido acetilsalicílico ou outros anti-inflamatórios; com doença hepática e/ou com insuficiência renal grave; que tenham dor relacionada à cirurgia de revascularização do miocárdio; com hipersensibilidade ao celecoxibe ou a qualquer componente da fórmula. INTERAÇÕES MEDICAMENTOSAS: Anticoagulantes; anti-hipertensivos das classes dos inibidores da enzima conversora de angiotensina (ECA) e/ou antagonistas da angiotensina II diuréticos e betabloqueadores podem ter seu efeito reduzido; em pacientes idosos,) ou com função renal comprometida, a coadministração de anti-inflamatórios, incluindo os inibidores específicos da COX-2, com inibidores da ECA, pode resultar no comprometimento da função renal, incluindo possível insuficiência renal aguda; fluconazol pode aumentar os níveis sanguíneos de celecoxibe; medicamentos anti-inflamatórios podem aumentar o risco de toxicidade no rim associada à ciclosporina.

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ACTA ORTOPÉDICA BRASILEIRA

INSTRUCTIONS TO AUTHORS

(Reviewed January 2016)

The journal *Acta Ortopédica Brasileira*, official organ of the Department of Orthopedics and Traumatology, Faculdade de Medicina da Universidade de São Paulo (DOT/FMUSP), is published bimonthly in six issues per year (Jan/Feb, Mar/Apr, May/Jun, Jul/ Aug, Sep/Oct, and Nov/Dec) with Portuguese and English printed and online versions. *Acta* is distributed to orthopedists and leading educational and research institutions in Brazil. The publication follows entirely the international standard of the International Committee of Medical Journal Editors (ICMJE) - Vancouver Convention - and its uniform requirements [http://www.icmje.org/]. Submitted papers are sent for double-blind peer review evaluation to decide whether they should be published or not, suggesting improvements, asking the authors for clarification and making recommendations to the Editor-in Chief. The concepts and statements contained in the papers are the sole responsibility of the authors.

We ask authors to observe the following instructions for publication.

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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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ORGANIZING THE ELECTRONIC FILE: All parts of the manuscript should be included in a single file. It should be formed by the cover page, then the text, references, figures (with their captions) and finally, tables and charts (with their respective captions).

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d) The place where the work was performed;
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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.

ACKNOWLEDGEMENTS

When applicable, briefly acknowledge the people who have contributed intellectually or technically to the study, but whose contribution does not justify co-authorship. The author must ensure that people agree to have their names and institutions disclosed. Financial support for the research and fellowships should be acknowledged in this section (funding agency and project number).

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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

VOLUME 25–Nº 2–2017

Original Articles

SPINE

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OSTEOBAN
ibandronato de sódio

Segurança na prevenção e tratamento da Osteoporose.[1,2]

Detalhes que fazem a diferença no combate à Osteoporose[1,5,6,7]

Prevenção:
- **34% de redução de risco** de fraturas não vertebrais.*[3]
- **Redução de risco** de fraturas vertebrais.*[4]

Eficácia:
Melhora da **densidade mineral óssea** em mulheres com osteopenia e osteoporose.[5]

Comodidade:
Posologia cômoda: **1x ao mês.**[1]

* Refere-se ao ibandronato de tratamento diário

CUIDADOS PELA VIDA | Benefícios para uma vida melhor.

Referências Bibliográficas:1) Bula do produto OSTEOBAN: comprimido revestido. Farmacêutica Responsável: Gabriela Mallmann. Guarulhos, SP. Aché Laboratórios Farmacêuticos S.A. 2) BUMBASIREVIC, M. et al. Prospective clinical study of monthly ibandronate in the treatmetn of osteoporosis and prevention of fractures in postmenopausal women: ORPHEUM study. Srp Arh Celok Lek, v. 139, n. 11-12, p. 790-7694, 2011. 3) MILLER, P. D. et al Efficacy of monthly oral ibandronate is sustained over 5 years: the MOBILE long-term extension study. Osteoporos Int, v. 23, n. 6, 2012. 4) HARRIS, S. T. et al. Ibandronate and the risk of nonvertebral and clinical fractures in women with postmenopausal osteoporosis: results of a metaanalysis of phase III studies. Curr Med Res Opin, v. 24, n. 1, p. 237-245, 2008. 5) BOCK, O. et al. Impact of oral ibandronate 150 mg once monthly on bone structure and density in post-menopausal osteoporosis or osteopenia derived from in vivo ?CT. Bone, v. 50, p. 317-324, 2012. 6) Kairos Web Brasil. Disponível em: < http:// brasil.kairosweb.com>. Acesso em: Jul/ 2016. 7) Programa Cuidados pela Vida (O Programa Cuidados pela Vida pode alterar ou interromper esta campanha sem aviso prévio. Desconto calculado sobre o Preço Máximo ao Consumidor).

Interação Medicamentosa: Os pacientes devem esperar 60 minutos após ingerir OSTEOBAN, antes de tomarem outros medicamentos orais. Contraindicação: OSTEOBAN é contraindicado a pacientes que não conseguem ficar em pé ou sentados durante, pelo menos, 60 minutos.

Osteoban. ibandrônato de sódio 150mg comprimido revestido. USO ORAL USO ADULTO. Indicações: OSTEOBAN é indicado para o tratamento da osteoporose pós-menopausa, com a finalidade de reduzir o risco de fraturas vertebrais. Em um subgrupo de pacientes de risco, com escore T < -3,0 DP no colo do fêmur, ibandronato de sódio também demonstrou reduzir o risco de fraturas não vertebrais. **Contraindicações**: **OSTEOBAN é contraindicado a pacientes com hipersensibilidade ao ibandronato de sódio ou aos demais componentes da fórmula e a pacientes com hipocalcemia não corrigida; pacientes com anormalidades do esôfago, como demora no esvaziamento esofágico, estenose ou acalasia; pacientes que não conseguem ficar em pé ou sentados durante, pelo menos, 60 minutos. Precauções e advertências: OSTEOBAN é contraindicado a pacientes com hipocalcemia não corrigida. Bisfosfonatos administrados por via oral podem causar irritação local da mucosa gastrintestinal superior. O risco de experiências adversas esofágicas graves parece ser maior para pacientes que não seguem as instruções de uso e/ou que continuaram a tomar bisfosfonatos por via oral após desenvolver sintomas sugestivos de irritação esofágica. Os pacientes devem prestar especial atenção e serem capazes de cumprir as instruções de administração. Considerando-se que anti-inflamatórios não esteróides e bisfosfonatos associam-se, ambos, à irritação gastrintestinal, recomenda-se cautela durante a administração concomitante de anti-inflamatórios não esteroides e ibandronato de sódio. Osteonecrose de mandíbula foi relatada em pacientes tratados com bisfosfonatos. A maioria dos casos em pacientes oncológicos submetidos a procedimentos dentários, mas alguns casos ocorreram em pacientes em tratamento para osteoporose pós-menopausa e outros diagnósticos. Fatores de risco conhecidos para osteonecrose de mandíbula: câncer, terapias concomitantes (ex: quimioterapia, radioterapia e corticosteroides) e distúrbios concomitantes (ex: anemia, coagulopatia, infecção e doença dentária pré-existente). A maioria dos casos foi relatada em pacientes tratados com bisfosfonatos de administração intravenosa, mas também em alguns pacientes tratados com bisfosfonatos orais.Relatos na literatura médica indicam que os bisfosfonatos podem estar associados à inflamação ocular, como uveíte e esclerite. Não foram realizados estudos sobre os efeitos de ibandronato de sódio sobre a capacidade de dirigir veículos e operar máquinas. Gestação e lactação: Categoria de risco na gravidez: B. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista.** Não há experiência sobre o uso clínico de ibandronato de sódio em mulheres durante a gestação. OSTEOBAN não deve ser utilizado por mulheres que estejam amamentando sem orientação médica ou do cirurgião dentista. **Atenção diabéticos: contém açúcar (lactose). Interações medicamentosas:** é provável que suplementos à base de cálcio, antiácidos e alguns medicamentos orais que contenham cátions multivalentes (tais como alumínio, magnésio e ferro) interfiram na absorção de ibandronato de sódio. Os pacientes devem esperar 60 min após ingerir OSTEOBAN, antes de tomarem outros medicamentos orais. Foi demonstrada, em estudo de interação farmacocinética em mulheres na pós-menopausa, a ausência de qualquer interação potencial com tamoxifeno ou tratamentos de reposição hormonal (estrogênio). Não se observou interferência quando ibandronato de sódio foi administrado concomitantemente com melfalano / prednisolona em pacientes com mieloma múltiplo. **Interações com alimentos:** a ingestão de alimentos deve ser postergada em 60 min após a administração oral de ibandronato de sódio. **Reações adversas: reações adversas comuns (> 1/100 e ≤ 1/10): doença do refluxo gastroesofágico, diarreia, dor abdominal, dispepsia, náusea, flatulência, cefaleia, síndrome influenza-like, fadiga, artralgia, mialgia, exantema. Reação incomum (>1/1.000 e <1/100):** distúrbios gastrintestinais (gastrite, esofagite, incluindo ulcerações esofágicas ou estenose, vômitos e disfagia), distúrbios do sistema nervoso (tonturas), distúrbios musculoesqueléticos e do tecido conjuntivo (dor nas costas). **Reação rara (>1/10.000 e <1/1.000):** distúrbios gastrintestinais (duodenite), distúrbios do sistema imunológico (reações de hipersensibilidade), distúrbios da pele e do tecido subcutâneo (angioedema, edema facial e urticária). **Posologia** deve ser administrado em jejum, 60 min antes da ingestão do primeiro alimento ou bebida do dia (exceto água) e antes da administração de qualquer outro medicamento ou suplemento, inclusive cálcio. Os comprimidos devem ser deglutidos inteiros, com um copo cheio de água filtrada (180 a 240 mL). O paciente não deverá deitar-se nos 60 min seguintes após tomar o medicamento; A dose recomendada de OSTEOBAN é um comprimido de 150 mg, **uma vez por mês. Pacientes idosos:** não é necessário ajuste de dose. **Pacientes com insuficiência renal:** não é necessário ajuste de dose para pacientes com insuficiência renal leve a moderada e com depuração de creatinina ≥ 30 mL/min. Em pacientes com depuração de creatinina < 30 mL/min, a decisão de administrar OSTEOBAN deve ser baseada na avaliação individual da relação risco / benefício. **Pacientes com insuficiência hepática:** não há necessidade de ajuste de dose para pacientes com insuficiência hepática. "SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO." **VENDA SOB PRESCRIÇÃO MÉDICA**. MS - 1.0573.0422. **"Material técnico científico de distribuição exclusiva a profissionais de saúde habilitados à precrição e/ou dispensação de medicamentos"**. Para informações completas, consultar a bula na íntegra através da Central de Atendimento ao Cliente. MB 02-SAP. 4408302.

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osteo muscular

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MOTORE
Curcuma longa 250 mg

O ANTI-INFLAMATÓRIO
COMPROVADAMENTE[3] EFICAZ E SEGURO
A LONGO PRAZO[1]

EXTRATO DE CURCUMINA COMPLEXADO
TECNOLOGIA **EXCLUSIVA**[3,4]

posologia

CURCUMINA[1]

CÁPSULA GELATINOSA[1]

Exclusivo complexo curcumina-fosfatidilcolina (fitossomo):
18X mais biodisponível
em comparação à curcumina não complexada.[3]

Cientificamente comprovado
Curcumina principal fração (curcuminoide) com ação anti-inflamatória amplamente estudada.[3]

Referências Bibliográficas: 1) BELCARO, G et al: Efficacy and Safety of Meriva®, a Curcumin-phosphatidylcholine Complex,during Extended Administration in Osteoarthritis Patients. Alternative Medicine Review 15(4):337-344,2010. 2) BOSI,PL: saúde baseada em evidências. disponível em: http://disciplinas.nucleoead.com.br/pdf/Livro_SaudeBaseadaemEvidencias.pdf. Acesso em 11/2015. 3) JURENKA, S. J. Anti-inflammatory properties of Curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Alternative Medicine Review, v.14, n.2, p. 141-153, 2009. 4) CUOMO, J. et al. Comparative absorption of a standardized curcuminoid mixture and its lecithin formulation. J Nat Prod, v.74, p.664-669, 2011. 5) Bula do produto MOTORE: cápsulas. Responsável Técnico: Gabriela Mallmann. Guarulhos, SP. Aché Laboratórios Farmacêuticos S.A.

Contraindicações: contraindicado em caso de alergia à curcumina, açafrão *(Curcuma longa)* ou a qualquer outro componente da fórmula. É contraindicado em pacientes que estejam em tratamento com medicações que alterem as características de coagulação como antiagregantes plaquetários, anticoagulantes, heparina de baixo peso molecular e agentes trombolíticos. É também contraindicado em casos onde haja risco de obstrução de vias biliares ou casos de cálculos biliares, úlceras estomacais e hiperacidez do estômago.

MOTORE curcuma longa Extrato seco. **Cápsulas 250 mg. USO ORAL. USO ADULTO. Indicações**: medicamento fitoterápico destinado ao tratamento da osteoartrite e artrite reumatóide, e tem ação antiinflamatória e antioxidante. **Cuidados e advertências: a curcumina é muito bem tolerada em seu uso por via oral pela grande maioria dos pacientes, sendo raros os relatos de efeitos prejudiciais. Raramente podem ocorrer queixas como desconforto gástrico leve e movimentos intestinais mais frequentes. Precauções e advertências: o uso da curcumina por via oral mostrou ser bem tolerada pela maioria dos pacientes. Em casos esporádicos foram relatados episódios de menor gravidade como desconforto gastrointestinal. Não há relatos de overdose ou efeito tóxico grave. Em caso de ocorrência de reação de hipersensibilidade, a medicação deve ser imediatamente descontinuada e os sintomas avaliados pelo médico. Motore deve ser tomado apenas por via oral. Os riscos do uso por via de administração não recomendada são a não obtenção do efeito desejado e a ocorrência de reações adversas indesejadas. Não há dados de segurança relativo ao uso da curcumina em portadores de insuficiência hepática e/ou renal, não sendo recomendável o uso da medicação em pacientes nessas condições. As doses de tratamento recomendadas não devem ser excedidas. Informe ao seu médico ou cirurgião-dentista se você está fazendo uso de algum outro medicamento. Não use medicamento sem o conhecimento do seu médico. Pode ser perigoso para a sua saúde. Gravidez e lactação:** apesar de não haver estudos conclusivos em humanos que mostrem efeito negativo na fertilidade humana, alguns estudos realizados em animais sinalizaram efeito negativo na implantação de embriões após uso injetável de altas doses de extrato etanol da curcuma. Desta maneira sugere-se evitar o uso da curcumina em pacientes com intenção de engravidar ou em gestantes. Mulheres em fase de lactação também devem evitar o uso desta medicação. Categoria de risco na gravidez C: Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. **Interações medicamentosas: é contraindicado para uso em pacientes que estejam fazendo uso de medicações que alterem as características de coagulação como antiagregantes plaquetários, anticoagulantes, heparina de baixo peso molecular e agentes trombolíticos, pois, pode haver aumento no risco de casos de sangramento. Reações adversas: o uso da curcumina por via oral mostrou ser bem tolerada pela maioria dos pacientes. Em casos esporádicos foram relatados episódios de menor gravidade como desconforto gastrointestinal. Não há relatos de overdose ou efeito tóxico grave.** Em caso de ocorrência de reação de hipersensibilidade, a medicação deve ser imediatamente descontinuada e os sintomas avaliados pelo médico. Motore deve ser tomado apenas por via oral. Os riscos do uso por via de administração não recomendada são a não obtenção do efeito desejado e a ocorrência de reações adversas indesejadas. Não há dados de segurança relativo ao uso da curcumina em portadores de insuficiência hepática e/ou renal, não sendo recomendável o uso da medicação em pacientes nessas condições. As doses de tratamento recomendadas não devem ser excedidas. **Posologia:** Motore deve ser ingerido por via oral, com um pouco de água. A dose habitual para adultos é de 2 cápsulas a cada 12 (doze) horas, ou seja, duas tomadas diárias, totalizando 500mg de medicação a cada tomada. "SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO." **VENDA SOB PRESCRIÇÃO MÉDICA.** MS - 1.0573.0442. **MB 03 SAP 4437701.**

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CONTRAINDICAÇÕES: OSTEOTRAT está contraindicado em pacientes com hipersensibilidade a qualquer componente da fórmula, com hipocalcemia, durante a gravidez, lactação e para pacientes com insuficiência renal severa ("clearance" de creatinina < 30 mL/min). INTERAÇÕES MEDICAMENTOSAS: Não foram realizados estudos formais de interação medicamentosa, entretanto, durante os estudos clínicos não foi observada qualquer interação clinicamente relevante com outros medicamentos.

OSTEOTRAT. risedronato sódico 35 mg. comprimidos revestidos. USO ORAL. USO ADULTO. Indicações: tratamento e prevenção da osteoporose em mulheres no período pós-menopausa para reduzir o risco de fraturas vertebrais e não vertebrais. Tratamento da osteoporose em homens com alto risco de fraturas. **Contraindicações: hipersensibilidade a qualquer componente da fórmula, hipocalcemia, gravidez e lactação e para pacientes com insuficiência renal severa ("clearance" de creatinina <30 mL/min), Precauções e advertências: Alimentos, bebidas (exceto água) e drogas contendo cátions polivalentes (tais como: cálcio, magnésio, ferro e alumínio) podem interferir na absorção dos bisfosfonatos e não devem ser administrados concomitantemente. Em mulheres mais idosas (> 80 anos), a evidência de manutenção da eficácia de risedronato sódico, é limitada. Alguns bisfosfonatos foram relacionados a esofagites e ulcerações esofágicas. Em pacientes que apresentam antecedentes de alteração esofágica que retardam o trânsito ou o esvaziamento esofágico (ex. estenosose ou acalasia), ou que são incapazes de permanecerem em posição ereta por pelo menos 30 minutos após a ingestão do comprimido, o risedronato deve ser utilizado com especial cautela. Os prescritores devem enfatizar a importância das instruções posológicas para pacientes que apresentam antecedentes de alterações esofágicas. A hipocalcemia deve ser tratada antes do início do tratamento com OSTEOTRAT. Outras alterações ósseas e do metabolismo devem ser tratadas quando iniciada a terapia com OSTEOTRAT.** Osteonecrose de mandíbula, geralmente associada com extração dentária e/ou infecção local foi relatada em pacientes com câncer em regimes de tratamento com bisfosfonatos, principalmente, na administração intravenosa. Osteonecrose de mandíbula também foi relatada em pacientes com osteoporose recebendo bisfosfonatos orais. Este medicamento contém lactose. Pacientes com problemas hereditários raros de intolerância à galactose, a deficiência da Lapp lactaseou má absorção da glucose-galactose, não devem tomar esse medicamento. Gravidez e lactação: O risco potencial para humanos é desconhecido. Risedronato sódico só deve ser utilizado durante a gravidez, se o risco benefício justificar o potencial risco para a mãe e o feto. A decisão de descontinuar a amamentação ou o produto deve considerar a importância do medicamento para mãe. Interações medicamentosas: Se considerado apropriado, OSTEOTRAT pode ser utilizado concomitantemente com a terapia de reposição hormonal. A ingestão concomitante de medicamentos contendo cátions polivalentes (ex. cálcio, magnésio, ferro e alumínio) irá interferir na absorção de OSTEOTRAT. O uso concomitante de antiácidos pode reduzir a absorção de risedronato. OSTEOTRAT não é metabolizado sistemicamente, não induz as enzimas do citocromo P450 e apresenta baixa ligação protéica. **Reações adversas: Estão listadas a seguir de acordo com a seguinte convenção: muito comum (>1/10); comum (>1/100; <1/10); incomum (>1/1000; <1/100); raro (>1/10000; <1/1000); muito raro (<1/10000). Comuns: dor de cabeça, constipação, dispepsia, náusea, dor abdominal, diarréia, dor musculoesquelética. Incomuns: gastrite, esofagite, disfagia, duodenite, úlcera esofágica Raros: glossite, estenose esofágica. Muito raramente foram observadas reações como: uveíte, irite, osteonecrose de mandíbula, hipersensibilidade e reações cutâneas, incluindo angioedema, rachaduras generalizadas e reações bolhosas de pele, algumas severas. Raramente observaram-se anormalidades nos testes de função hepática. Relatos laboratoriais: foram observados em alguns pacientes discreta diminuição nos níveis de cálcio sérico e fosfato, as quais foram precoces, transitórias e assintomáticas. Posologia:** A dose recomendada nos adultos é de 1 comprimido de 35 mg uma vez por semana, por via oral. Deve ser administrado no mínimo 30 minutos antes da primeira refeição, outra medicação ou bebida (exceto água) do dia. Os comprimidos devem ser engolidos inteiros, sem deixá-los dissolvendo na boca ou mastigá-los. Os pacientes devem utilizar OSTEOTRAT enquanto estiverem na posição vertical, com um copo de água (120 mL) para auxiliar a chegada ao estômago. Os pacientes não devem deitar por 30 minutos após ingestão de OSTEOTRAT. O comprimido de Osteotrat deve ser tomado no mesmo dia de cada semana, não devem ingeridos dois comprimidos no mesmo dia. Nenhum ajuste de dose é necessário para pacientes com insuficiência renal leve a moderada. O uso do risedronato sódico é contraindicado em pacientes com insuficiência renal severa ("clearance" de creatinina menor que 30 mL/min.) "SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO." VENDA SOB PRESCRIÇÃO MÉDICA. MS - 1.0573.0418. 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NISULID D
nimesulida

DISPERSÍVEL
DILUÍDO EM ÁGUA
ou deglutido inteiro[4]

nimesulida
Suíça[9]

A eficácia da nimesulida. [1,2,3]

- Reduz a dor em 15 minutos[1]
- Medicamento referência[5]
- Reduz significativamente sinais e sintomas inflamatórios em doenças ORL[2,3]
- Boa tolerabilidade gástrica[6,7]
- Eficaz no controle dos sintomas da dismenorreia[8]

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Contraindicação: crianças menores de 12 anos. Interação medicamentosa: Não se aconselha usar medicamentos que provoquem irritação no estômago durante o tratamento com NISULID® (nimesulida).

NISULID. nimesulida. 100 mg comprimidos. 100 mg comprimidos dispersíveis. 100 mg / envelope granulado. 50 mg/ml gotas. 10 mg/ml suspensão oral. uso oral. 100 mg supositórios. uso retal. uso adulto e pediátrico. MS – 1.0573.0301. INDICAÇÕES: Indicado em condições clínicas que requeiram atividade anti-inflamatória, analgésica e antipirética. CONTRAINDICAÇÕES: **Hipersensibilidade à nimesulida ou a qualquer outro componente do medicamento; história de hipersensibilidade ao ácido acetilsalicílico ou a outros AINEs. Pacientes com úlcera péptica em fase ativa, ulcerações recorrentes ou com hemorragia gastrintestinal; paciente com distúrbios de coagulação grave; pacientes com insuficiência cardíaca grave; pacientes com disfunção renal grave; pacientes com disfunção hepática; crianças menores de 12 anos. A nimesulida não deve ser administrada durante a gravidez ou em mulheres que estejam amamentando.** CUIDADOS E ADVERTÊNCIAS: Raramente nimesulida foi relatada estar associada com reações hepáticas sérias, incluindo casos fatais. Pacientes que apresentaram sintomas compatíveis com dano hepático durante o tratamento com nimesulida (por exemplo, anorexia, náusea, vômitos, dor abdominal, fadiga, urina escura ou ictericia) devem ser cuidadosamente monitorados. A administração concomitante com drogas hepatotóxicas conhecidas e abuso de álcool, devem ser evitados durante o tratamento com nimesulida. Pacientes que apresentaram testes de função hepática anormais devem descontinuar o tratamento e não devem reiniciar o tratamento com a nimesulida. Em raras situações, onde ulcerações ou sangramentos gastrintestinais ocorrem em pacientes tratados com nimesulida, o medicamento deve ser suspenso. Em pacientes com insuficiência renal ou cardíaca, cuidado é requerido, pois o uso de AINES pode resultar em deterioração da função renal. Pacientes idosos são particularmente sensíveis às reações adversas dos AINES, incluindo hemorragia e perfuração gastrintestinal, dano das funções renal, cardíaca e hepática. O uso prolongado de AINES em idosos não é recomendado. A nimesulida deve ser usada com atenção em pacientes com história de ulceração péptica ou inflamações intestinais. Como os AINES podem interferir na função plaquetária, eles devem ser usados com cuidado em pacientes com hemorragia intracraniana e alterações da coagulação, como por exemplo, hemofilia e predisposição a sangramento. As drogas antiinflamatórias não-esteroidais podem mascarar a febre relacionada a uma infecção bacteriana subjacente. Com relação ao uso da nimesulida em crianças, foram relatadas algumas reações graves, incluindo raros casos compatíveis com síndrome de Reye. O uso concomitante de outros anti-inflamatórios não-esteroidais durante a terapia com nimesulida não é recomendado. Como os outros anti-inflamatórios não-esteroidais, a nimesulida deve ser usada com cuidado em pacientes com insuficiência cardíaca congestiva, hipertensão, prejuízo da função renal ou depleção do volume extracelular, que são altamente suscetíveis a uma redução no fluxo sanguíneo renal. Por ser a eliminação do fármaco predominantemente renal, o produto deve ser administrado com cuidado a pacientes com prejuízo da função hepática ou renal. Em pacientes com clearance de creatinina de 30-80 ml/min, não há necessidade de ajuste de dose. Em caso de disfunção renal grave o medicamento é contra-indicado. Em pacientes com história de perturbações oculares devido a outros AINES, o tratamento deve ser suspenso e realizado exames oftalmológicos caso ocorram distúrbios visuais durante o uso da nimesulida. Pacientes com asma toleram bem a nimesulida, mas a possibilidade de precipitação de broncoespasmo não pode ser inteiramente excluída. Os riscos de uso por via de administração não-recomendada são: a não-obtenção do efeito desejado e ocorrência de reações adversas. Atenção diabéticos: contém açúcar (nas apresentações da suspensão oral (300 mg/ml), granulado (1,774 g por envelope) e gotas (300 mg/ml)). GRAVIDEZ E LACTAÇÃO: Categoria de risco de gravidez C: este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. INTERAÇÕES MEDICAMENTOSAS: A potencial interação com glibenclamida, teofilina, varfarina, digoxina, cimetidina e uma preparação antiácida (ou seja, uma combinação de hidróxido de magnésio e alumínio) foram estudadas in vivo. Nenhuma interação clínica significante foi observada. A nimesulida pode antagonizar os efeitos dos diuréticos e em particular bloquear o aumento da atividade da renina plasmática induzida pela furosemida. O uso concomitante de furosemida e nimesulida requer cautela em pacientes renais ou cardíacos susceptíveis. A administração concomitante de nimesulida com anticoagulantes (varfarina) ou ácido acetilsalicílico pode causar efeitos aditivos (aumento do risco de complicações de sangramento). Portanto, esta combinação não é recomendada e é contra-indicada em pacientes com distúrbios de coagulação graves. Se a combinação não puder ser evitada, a atividade anticoagulante deve ser cuidadosamente monitorada. Se nimesulida for prescrita para um paciente sob terapia com lítio, os níveis de lítio devem ser monitorados cuidadosamente. Deve-se ter cuidado com pacientes que apresentem anormalidades hepáticas, particularmente se houver intenção de administrar nimesulida em combinação com outras drogas potencialmente hepatotóxicas. Não há evidência de que a nimesulida afete a glicemia em jejum ou a tolerância à glicose em pacientes diabéticos tratados com sulfoniluréias. Pode haver potencialização da ação da fenitoína. Embora não tenham sido relatados especificamente com a nimesulida, foram documentadas interações entre antiinflamatórios não-esteroidais e lítio, metotrexato, probenecida e nimesulida. Portanto, recomenda-se cuidado na administração concomitante de nimesulida com qualquer uma destas drogas, devido ao aumento do risco de hemorragias gastrintestinais. Devido ao seu efeito sobre as prostaglandinas renais, os inibidores da prostaglandina-sintetase como a nimesulida podem aumentar a nefrotoxicidade das ciclosporinas. Recomenda-se tomar NISULID após as refeições. Não se aconselha a ingestão de bebidas alcoólicas durante o tratamento. REAÇÕES ADVERSAS: **Pele e tecidos subcutâneos: prurido, rash e sudorese aumentada. Gastrintestinais: diarréia, náusea e vômito. Hepatobiliar: alterações dos parâmetros hepáticos (transaminases), geralmente transitórias e reversíveis. Casos isolados de hepatite aguda, falência hepática fulminante (algumas fatalidades foram relatadas), icterícia e colestase. Sistema nervoso: tonturas e vertigens. Sistemas visual e auditivo: raramente visão borrada. Sistema cardiovascular: hipertensão. Renais: raramente: disúria, hematúria e retenção urinária. Sistema sanguíneo e linfático: raramente: anemia e eosinofilia. Sistema imunológico: raramente hipersensibilidade. Sistema endócrino: raramente hiperglicemia. Respiratórios: casos isolados de reações anafiláticas como dispnéia, asma e broncoespasmo, principalmente em pacientes com histórico de alergia ao ácido acetilsalicílico e a outros AINES. Distúrbios gerais: edema.** POSOLOGIA: USO PARA ADULTOS E CRIANÇAS ACIMA DE 12 ANOS. Comprimidos: 50 - 100mg (1/2 a 1 comprimido tomado com 1/2 copo de água) duas vezes ao dia, podendo alcançar até 200 mg duas vezes ao dia. A administração é por via oral. Comprimidos dispersíveis: 100mg (1 comprimido) duas vezes ao dia, podendo alcançar até 200 mg duas vezes ao dia. Dissolver o comprimido em 1/2 copo de água (100 mL) ou, se preferir, o comprimido poderá ser deglutido inteiro, sem a necessidade de dissolução prévia. A administração é por via oral. Granulado: 50 a 100mg (1/2 a 1 envelope dissolvido em um pouco de água ou suco) duas vezes ao dia, podendo alcançar até 200mg duas vezes ao dia. A administração é por via oral. Supositórios: 1 supositório de 100mg duas vezes ao dia, podendo alcançar até 200mg (2 supositórios de 100mg) duas vezes ao dia. Aplicar o supositório por via retal. Gotas: administrar 1 gota (2,5mg) por kg de peso, duas vezes ao dia, diretamente na boca da criança ou se preferir diluída em um pouco de água açucarada. Lembramos que cada gota contém 2,5mg de nimesulida e cada mL de NISULID contém 50mg de nimesulida. Cada mL do produto contém 20 gotas. Suspensão: a posologia recomendada é de 5mg/kg/dia - fracionada a critério médico em duas administrações. Agitar antes de usar. Colocar a dose recomendada no copo-medida que acompanha o produto e pedir para a criança tomar pela boca (1mL da suspensão contém 10mg de nimesulida). Pacientes com insuficiência da função renal: não há necessidade de ajuste de dose em pacientes com insuficiência renal moderada. Em casos de insuficiência renal grave o medicamento é contra-indicado. Pacientes com insuficiência hepática: contra-indicado em pacientes com insuficiência hepática. VENDA SOB PRESCRIÇÃO MÉDICA. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. Material técnico científico de distribuição exclusiva à classe médica - Documentação Científica e informações adicionais estão à disposição da classe médica, mediante solicitação. MB_05 SAP4094207(A)09/09.

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CLINICAL APPLICATION OF A DRILL GUIDE TEMPLATE FOR PEDICLE SCREW PLACEMENT IN SEVERE SCOLIOSIS

APLICAÇÃO CLÍNICA DE MATRIZ DE GUIA DE BROCA PARA COLOCAÇÃO DE PARAFUSO PEDICULAR EM ESCOLIOSE GRAVE

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ABSTRACT

Objective: To evaluate the accuracy and the effect of drill guide template for pedicle screw placement in severe scoliosis. Method: Eight patients with rigid scoliosis were enrolled, five males and three females, ranging from nine to 23 years old. A three-dimensional CT scan of the spine was performed and saved as a DICOM file type. The multi-level template was designed by Mimics software and manufactured according to the part of the most severe deformity. The drill template was placed on the corresponding vertebral surface. Pedicle screws were carefully inserted across the trajectory of the template. Postoperatively, the positions of the pedicle screws were evaluated by CT scan and graded for validation. Results: No spinal cord injury or nerve damage occurred. All patients had satisfactory outcomes. The abnormalities and the measures observed during operation were the same as those found in the preoperative period. The position of the pedicle screws was accurate, according to the postoperative X-ray and CT scan. The rate of scoliosis correction was 60%. Compared with controls, surgery time, blood loss and radiation were significantly lower. Conclusion: With the application of multi-level template, the placement of pedicle screws shows high accuracy in scoliosis with shorter surgical time, less blood loss and less radiation exposure. ***Level of Evidence III, Retrospective Comparative Study.***

Keywords: Scoliosis. Pedicle screws. Surgery, computer-assisted/methods. Imaging, three-dimensional. Prosthesis design. Printing, three-dimensional.

RESUMO

Objetivo: Avaliar a precisão e o efeito da matriz de guia de broca para colocação de parafuso pedicular em escoliose grave. Método: Oito pacientes com escoliose rígida foram selecionados, sendo cinco homens e três mulheres na faixa etária de nove a 23 anos. Foi realizada TC tridimensional da coluna, gravada no formato DICOM. A matriz multinível foi desenhada pelo software Mimics e fabricada de acordo com a parte da deformidade mais grave. A matriz da broca foi colocada na superfície vertebral correspondente. Os parafusos pediculares foram cuidadosamente inseridos ao longo da trajetória da matriz. No pós-operatório, as posições dos parafusos pediculares foram avaliadas por TC e classificadas para validação. Resultados: Não ocorreu nenhuma lesão da medula espinhal nem lesão de nervos. Todos os pacientes tiveram desfechos satisfatórios. As anormalidades e as medidas observadas durante a operação foram as mesmas encontradas no pré-operatório. A posição dos parafusos pediculares foi precisa, de acordo com a radiografia e a TC pós-operatórias. A taxa de correção de escoliose foi de 60%. Em comparação com os controles, o tempo de cirurgia, a perda de sangue e a radiação foram significantemente menores. Conclusão: Com a aplicação da matriz multinível, a colocação dos parafusos pediculares mostra alta precisão na escoliose, com menor tempo cirúrgico, menos perda de sangue e menor exposição à radiação. ***Nível de Evidência III, Estudo Retrospectivo Comparativo.***

Descritores: *Escoliose. Parafusos pediculares. Cirurgia assistida por computador/métodos. Imagem tridimensional. Desenho de prótese. Impressão tridimensional.*

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INTRODUCTION

Computer-aided rapid prototyping (RP) using Mimics medical imaging software can be simulated in a computer-based operation using an operational design and planning scheme which displays the results of the procedure. This method also permits rapid input on a digital machine which can copy the real structure for an entity model and allow the surgeon to simulate and evaluate intraoperative references and guides for positioning and navigation prior to the procedure. Rapid prototyping has been widely applied in the medical field in China and abroad in recent years; this technology is used in the fields of complex fractures, spine and extremity deformities, joint replacement, plastic surgery, cranial and facial tumors, nasal

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Work conducted at the Department of Orthopedics, Beijing Ditan hospital, Capital Medical University
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reconstruction, dental implants and prosthesis engineering,[1-6] as well as for planning procedures in clinical medicine. Biological manufacturing provides a more effective solution and means of production. The aim of this study is to investigate the use of a RP technique to construct a pedicle drill template as well as to assess and evaluate the outcomes.

MATERIALS AND METHODS

This study was approved by the institutional review board of Beijing Ditan Hospital at Capital Medical University under number 1501/2009. Written informed consent was obtained from all patients prior to enrollment in the study. From June 2006 to October 2009, 8 patients (5 males and 3 females) with scoliosis were evaluated; the participants ranged in age from 9 to 23 (average age: 18). Five subjects had congenital scoliosis and 3 had idiopathic scoliosis; 4 patients underwent a repeat operation. Preoperatively, the average Cobb angle was 91° (70°~125°), and the average kyphosis Cobb angle was 65° (45°~95°). The preoperative Frankel scores were as follows: 1 case with C, 1 case with D, and 6 cases with E, including 1 case with bladder sphincter dysfunction. Five cases had serious thoracolumbar back pain. During the preoperative period, the patients underwent plain film X-rays, MRI scans, and three-dimensional reconstruction of spiral CT. All patients had different degrees of spina bifida, butterfly vertebra, congenital fusion of the ribs, spinal bone ridge, posterior fusion, and severe vertebral rotation. At the same time, 8 severe scoliosis patients who did not undergo spinal modeling were selected at random to comprise the control group.

Preoperatively, all the patients underwent full spine enhanced CT scanning with a 1 mm slice thickness. We collected the original CT data and used a DICOM format input computer and Mimics 6.3 software (Materialise N.V., Haasrode, Belgium) for three-dimensional reconstruction of the digital display as well as to measure the spinal data. We used the CT data to perform the operation, reconstruct the surgical region, define placement, diameter, and depth direction of the pedicle screws using the software design of the virtual pin tract, avoid neurovascular organs, and ensure that the pedicle screws designed prior to the procedure were in the pedicle to avoid breaking through the bone. (Figure 1) We identified the best screw trajectory and location based on the RP spine pedicle screw placement in the real model. We also made the drill guide template, designed the surgical plan, simulated the procedure in models, and ensured that pedicle screw placement was more intuitive and accurate. We also attached the three-dimensional reconstruction of the vertebral model template to the back of the vertebrae and rotated the model in each direction, observing the positioning guide hole and the accuracy of pedicle placement. (Figure 2)

The rapid prototyping guide template was managed by low temperature plasma sterilizer. All patients received general anesthesia prior to surgery to correct the posterior deformity utilizing the pedicle screw fixation technique, intraoperative findings, and preoperative three-dimensional reconstruction. The RP model showed that the results were consistent and that the navigation template and deformity were a close fit. The preoperative design permitted successful correction of the deformity via placement of pedicle screws, and intraoperative fluoroscopy showed that the pedicle implant was well-positioned and that the template fit well. (Figure 3) There were 5 cases of complete vertebral osteotomy and 3 cases of simple internal fixation. Excision of the ribs and vertebrae and bone allograft were routinely performed. Four cases involved autologous blood transfusion. Surgical time, volume of blood lost, and fluoroscopy frequency data were recorded.

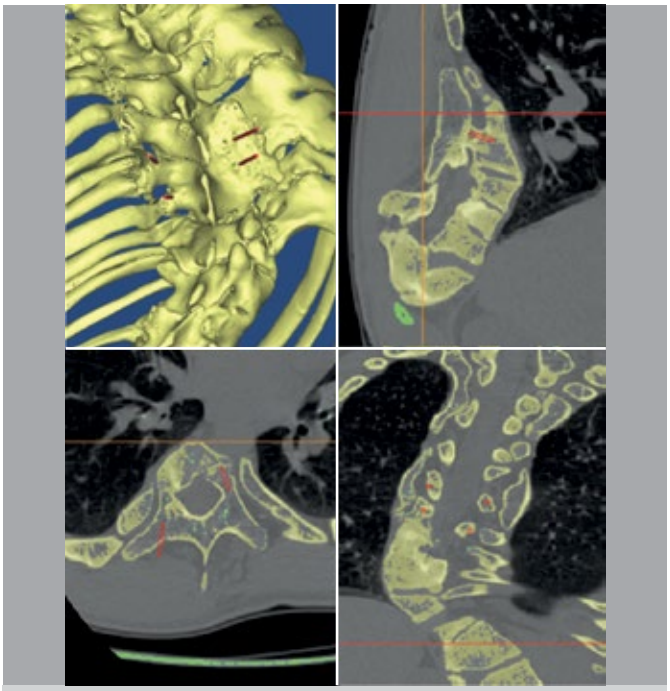

Figure 1. Placement, diameter, and depth direction of the pedicle screw defined using Mimics software with the three-dimensional reconstruction data.

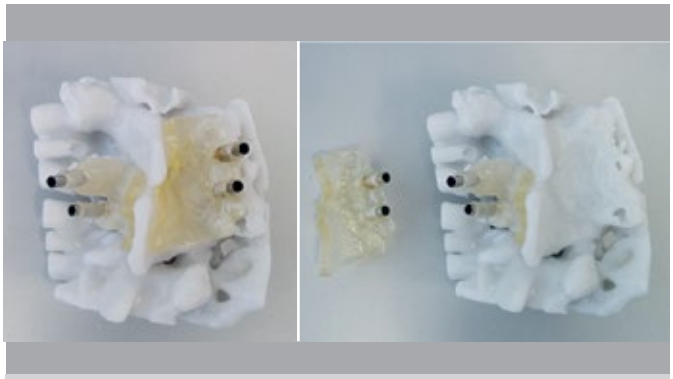

Figure 2. Attaching the pedicle drill navigation template to the back of the vertebrae and rotating the model in each direction to observe the positioning guide hole and accuracy of pedicle placement.

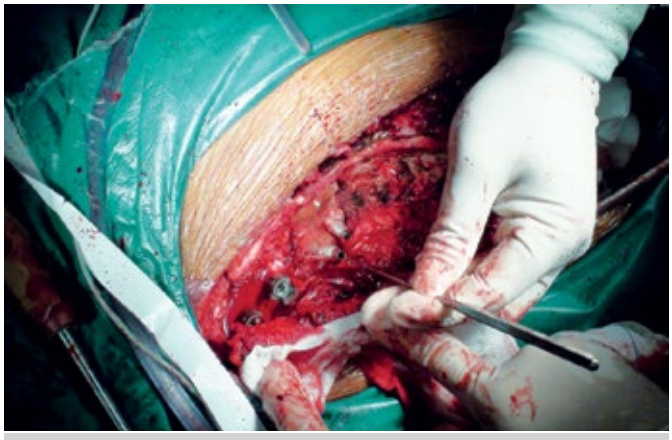

Figure 3. The intraoperative view was the same as the three-dimensional reconstruction and rapid prototyping model. The navigation template and deformity were a close fit. Needle passage using the navigation template was correct and safe.

RESULTS

All 8 patients underwent digital reconstruction of the skeleton, which allowed us to observe a case of severe congenital scoliosis from any direction by constructing a spinal model. This model in turn allowed us to measure the extent of the deformity, understand the range and shape of the spina bifida, and to understand the scope and shape divided by intraspinal osseous lesions as well as the relationship between the spinal cord and the configuration of the spinal canal. A RP spine model design for surgery was created for all cases. The intraoperative findings and preoperative 3D reconstruction results were completely consistent. Eight patients were scheduled for the procedure; in these cases, we could clearly identify the anatomical structure of the spinal deformity and pedicle screw positioning was adequate. All cases healed well without wound infection, spinal cord injury, cerebrospinal fluid leakage, or complications such as pneumothorax, and the patients obtained good postoperative results. Additionally, the findings from the surgical procedure and the preoperative three-dimensional reconstruction of the digital model for abnormal findings and measurement results were completely consistent. Postoperative X-ray and CT demonstrated that adequate positioning of the pedicle screws. The scoliosis correction rate was 60%, and the average surgical time was 186 min. Average blood loss was 460 ml, and C-arm fluoroscopy was used 4 times. Using guide navigation in the patient group, the average surgical time was 225 minutes, average blood loss was 550 ml, and fluoroscopy was used approximately 30 times.

DISCUSSION

Modern computer technology allowed the development of a digital model of the human skeleton and RP technology in the late twentieth century, providing new technologies for use in clinical medicine. Human CT scan data are processed with a computer to create three-dimensional digital images of structures in the human body, including lesion sites, and DICOM data are acquired using a computer. This technique also uses CAD, Mimics 6.3, and 3D View 3.5 software for three-dimensional reconstruction and measurement display. The laser stacking method has been used for RP in plastic surgery.[1-6] The field of orthopedics has seen revolutionary developments, and this methodology is currently used in orthopedic reconstructions. Additionally, this positioning technology has been widely applied in more invasive orthopedics operations to improve accuracy.[2,6-8] As the difficulty of these operations has increased, doctors no longer depend on the patient's medical history alone; instead, images are required for the surgeon to determine the surgical plan. Consequently, surgeons should be able to use surgical planning software, establish a three-dimensional anatomical model of the target site, and design the procedure on the computer screen in order to achieve the best surgical plan. These skills will be required of clinicians in the twenty-first century.[6]

The anatomy of the spine is very complex, and the complex morphologic structure of scoliosis has several associated variations, including kyphosis, vertebral rotation, wedge, spondylolisthesis deformities, spinal deformities, severe thoracic spinal deformation with a small, irregular vertebral arch root, and deformation of the spinal cord, nerve root, adjacent lung, esophagus, aorta, inferior vena cava, and other important organs and large vessels. Consequently, congenital scoliosis with pedicle screw placement has presented a challenge to surgeons for some time, particularly in patients with spina bifida, butterfly vertebrae, and congenital posterior fusion. Such patients are treated with an anterior approach, but the posterior or anterior and posterior approach for correction can encounter many difficulties. Accurate understanding of the specific malformations well in advance of surgical planning and the procedure itself is essential.[2] However, it can be difficult to fully and clearly view the deformities in specific circumstances due to scoliosis, vertebral rotation, and overlapping morphological variation in images, even with the use of conventional X-ray plain films, CT, or two-dimensional MRI tomography. Even with preoperative three-dimensional reconstruction, it can be difficult to acquire a visible and tangible three-dimensional view and spine model. However, RP of the spine uses a human skeleton as the reconstruction of the spine. It is the same size as the patient's bones but does not present any trauma when used for surgical planning and simulation and the procedure. In cases of severe spine deformity, the spinal and morphology and anatomical landmarks can undergo tremendous changes and be difficult to recognize. Scoliosis can substantially alter the vertebral morphology, and judging the screw entrance point can be a major challenge in clinical work. The navigation guide plate was recently developed based on the digital spine model in pedicle screw placement, and may present a solution for this challenge.[3,4,9,10] Preoperatively, computerized surgical plans have been used to select the correct screw entry point and suitable pedicle screws. Additionally, the RP spine model has been used to produce the pedicle navigation guide and to avoid surgical errors, save time, reduce the use of intraoperative fluoroscopy, and alleviate patient pain.

The free hand technique is still the most commonly used clinical placement method, intraoperative C-arm fluoroscopy, and computer-aided navigation. The acts technique is still the most commonly used clinical placement method.[3,4,11] Generally, when the surgeon has sufficient experience in spinal surgery, the spinal deformity is not serious and the anatomic landmarks are clearly defined, the accuracy of freehand pedicle screw placement can be assured using a pedicle probe. Some studies have reported that the rate of pedicular cortical perforation ranges from 6.2% to 72.4%; rates of neural, vascular and visceral injuries as well as other complications range from 0% to 0.9%.[12-17] Intraoperative C-arm fluoroscopic X-ray can increase the accuracy of pedicle screw placement, but extended surgical time, increased intraoperative fluoroscopy, and repeated adjustment of pedicle screw placement direction can also cause screw loosening or failure. Complex vertebral malformations make it difficult to place the screw in the correct position; blind placement can cause injuries to the spinal cord, nerves, blood vessels, and adjacent viscera. Computer-assisted navigation technology can be used to increase the accuracy of pedicle screw placement. However, complex vertebral malformations make it difficult to place screws in the correct position, and the procedure is complicated, time-consuming and laborious. Additionally, navigation devices are expensive, accuracy is low, there is a high learning curve, and there are other shortcomings; furthermore, they have not been used in Chinese hospitals.

As pedicle screw fixation technology has developed and matured, these techniques have been widely used in the treatment of adult spinal trauma and degeneration, orthopedic surgery, and tumor resection.[1-6] Severe vertebral rotation may be present in these cases, or patients may require multiple operations, and surgeons often have doubts about how to replace the pedicle screw because the allowable deviation range is small, especially in the thoracic spine, and risk increases. In the past, these surgeries relied on the surgeon's experience and repeated C-arm X-rays to adjust the position of the pedicle screw; this procedure largely depends on the surgeon's experience and luck. If all goes well, the screw can be inserted smoothly, but in some cases a loose screw may need repeated adjustments, may not be placed, or may cause injury. In severe cases, mistakes can cause disability or death, and the risk is high. Spinal surgeons are paying greater attention to the accuracy of thoracic pedicle screw placement

and safety.[11-15] To improve accuracy of pedicle screw placement, we used RP technology to making a drill guide template for pedicle navigation, which made placement of pedicle screw as a safe and feasible method for congenital scoliosis. Reverse engineering and RP technology[15] were the keys of design. We used reverse engineering software to extract the lamina surface from the posterior vertebral anatomy, then established optimal pedicle screws trajectory. The drill guide templates were designed according to these data, so that its placement can be consistent with the posterior vertebral. And RP technology can produce the dill guide template for personalized individuals. In the operation, template and corresponding thoracic posterior bony structure fit well. Made position and channels along the drill of template can be ensure each screw placed correctly. The fluoroscopy and postoperative CT confirmed adequate pedicle screw placement. The template was made to fit the bone closely according to the anatomical structure, allowing more stable fixation; in theory, greater contact between the template and bone provides greater stability. However, it is important that the template not be too large or it may reduce the motion of the intervertebral spinal segment. In our experience, it is best to not manipulate more than two segments of the vertebral plate and facet joint. A 3-5 centimeter guide sleeve is advisable; if the sleeve is too short, accuracy will also be affected. During the procedure, the spinous process, laminectomy, and facet joint are fully exposed so that the guide plate and corresponding segment of the spinal bone can fit fully. Next, the cannula is used to open, drill, sound, and remove the guide; detection of the pedicle bone is complete at this time, permitting evaluation of tapping and the pedicle screw. Additionally, the navigation template for screw preparation (preferably using a drill or drills) can reduce shaking with the borehole. This allows the screw channel to be prepared as exactly as possible according to the direction of the guiding channel, and the surgeon can strive to follow the template design of the navigation positioning. To reduce error and increase the precision of the guide, a CT scan is best in patients prone to spinal operation bed frame defects because CT is closer to the patient's intraoperative position and is as far as possible from postural changes that may influence the guide's accuracy. To ensure that the operation is not in danger of failing, pedicle screw placement is completed with the assistance of a C-arm X-ray check.

In short, RP guide navigation technology can quickly produce the desired prototype without requiring substantial experience with the procedure, and can also simulate the surgical process and possible problems, allowing prior consideration of remediative and preventive measures. The use of an operation navigation guide plate in severe scoliosis procedures improves safety, shortens surgical time, reduces surgical trauma, and reduces bleeding as well as intraoperative fluoroscopy. It is safe, accurate, and minimally invasive.[3,4,15] In addition to ensuring speed and accuracy (and in turn, reducing patient suffering and postoperative complications), this method can relieve the economic burden on patients and produce positive economic and social benefits.

CONCLUSION

The RP pedicle drill template is a new method for precise insertion of pedicle screws in operations. This method is highly accurate and safe in scoliosis spinal procedures. Utilizing the pedicle drill template navigation procedure is simple, and does not require extensive specific experience on the part of the surgeon. This method can shorten surgical time and reduce blood loss, and the surgeon's exposure to radiation can be reduced or avoided with this technique.

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QUANTITATIVE EVALUATION OF EXPERIMENTAL BONE REGENERATION USING INDENTATION TESTS

AVALIAÇÃO QUANTITATIVA DE REGENERAÇÃO ÓSSEA EXPERIMENTAL USANDO TESTES DE INDENTAÇÃO

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ABSTRACT

Objectives: To determine whether the macroindentation test can be applied to quantitatively assess bone regeneration. Methods: A 3.2 mm diameter transverse monocortical defect was created on the medial aspect of both proximal metaphyses of the tibia of male Unib-WH rats. For the macroindentation tests, we used 5.00 mm diameter indenters with a 3.2 mm tip. Defect testing was performed 1 to 12 weeks following the surgical procedures to compare the hardness of the newly developed tissue over the 12-week study period. Additional histological, morphological and physical/chemical data were obtained by optical and electronic microscopy, Raman, and energy dispersive x-ray spectrometry (EDS). Results: The mean indentation forces increased in a time-dependent manner from 4 to 12 weeks ($p<0.001$). Tests performed with the 5.0 mm diameter tip were not able to measure the indentation forces in the first week after the procedure. Moreover, in the second postoperative week indentation forces and the newly formed tissue within the spinal canal were greater than those measured in the fourth and eighth weeks. Conclusions: The macroindentation test can be used to quantitatively assess bone regeneration in experimental studies. The choice of indenter tip diameter should consider the study design. ***Level of Evidence II, Diagnostic Studies.***

Keywords: Bone regeneration. Hardness tests. Animal experimentation.

RESUMO

Objetivos: Determinar se o teste de macroendentação pode ser aplicado para avaliar quantitativamente a regeneração óssea. Métodos: Foi criado um defeito monocortical transversal com 3,2 mm de diâmetro na face medial de ambas as metáfises proximais da tíbia de ratos Wistar machos. Para os testes de macroendentação, empregou-se endentador com ponta de 3,2 mm e 5,0 mm de diâmetro. O teste dos defeitos foi realizado em 1 a 12 semanas depois dos procedimentos cirúrgicos, de modo que a dureza do tecido recém-formado foi comparada no período de 12 semanas do estudo. Os dados histológicos, morfológicos e físico-químicos adicionais foram obtidos por microscopia óptica e eletrônica, espectrometria Raman e EDS (espectrometria com dispersão de energia). Resultados: As forças médias de endentação aumentaram de modo dependente do tempo de 4 a 12 semanas ($p < 0,001$). Os testes realizados com a ponta de 5 mm de diâmetro não foram capazes de medir as forças de endentação na primeira semana depois do procedimento. Além disso, na segunda semana, as forças de endentação e o tecido recém-formado no interior do canal medular foram superiores aos da quarta e oitava semanas. Conclusões: O teste de macroendentação pode ser utilizado em estudos experimentais para avaliar quantitativamente a regeneração óssea. A escolha do diâmetro da ponta do endentador deve considerar o desenho do estudo. ***Nível de Evidência II, Estudos Diagnósticos.***

Descritores: Regeneração óssea. Testes de dureza. Experimentação animal.

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INTRODUCTION

In 5–10% of fractures, bone healing takes longer than expected and bone consolidation is not achieved.[1] This fact highlights the importance of developing novel therapeutic, clinical or surgical strategies to accelerate bone healing and avoid nonunion. Consequently, biomechanical tests to quantitatively assess bone repair are important tools to evaluate the efficiency of these strategies. Many biomechanical tests are used in animal models to evaluate implant performance, bone repair, and the quality of the newly formed bone, such as tensile, bending and torsion tests.[2-7]

The indentation test is used in mechanical engineering to determine the hardness of a material to deformation, and this test can also be used to quantify the hardness of newly developed tissue on bone surfaces. As the hardness of this new tissue gradually equals the hardness of intact bone, bone repair is likely to be successful. Micro and nanoindentation tests are commonly used for this purpose, but

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Study conducted at the Universidade de Campinas (UNICAMP), Faculdade de Ciências Médicas, Laboratório de Biomateriais em Ortopedia, Campinas, SP, Brazil.
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few studies can be found in the literature on the macroindentation test.[8-11] To determine the efficacy of the macroindentation test in quantitatively assessing bone repair, we examined the 12-week follow-up of histological, morphological, and biomechanical findings in newly developed tissue in the tibias of rats which were subjected to monocortical perforation.

MATERIALS AND METHODS

Because of the lack of knowledge about the statistical distribution of results which would be obtained in the tests, samples were initially chosen from four animals for each indentation test group and two animals for the histology/EDS/ERS/Raman groups. Preliminary processing of the results showed that some sample sizes needed to be increased, resulting in the use of one hundred and two male Unib: WH rats (*Rattus novergicus albinus,* Rodentia mammalia), 10(±2) weeks old, with a body mass of 350(±20) g. The animals were obtained from the Centro Multidisciplinar para Investigação Biológica na Área de Ciência em Animais de Laboratório (CEMIB) of the Universidade de Campinas (UNICAMP). All procedures were approved by the institutional review board (record 2497-1). The animals were randomly allocated in groups as described in Table 1. Following trichotomy and antisepsis of both hindlimbs, 88 animals were anesthetized via intravenous tail injection of ketamine (70 mg/kg) and xylazine (5 mg/kg), and placed in a supine position on a surgical stand. Using an anterior longitudinal knee approach, the proximal anteromedial metaphysis of both tibias was exposed and a 3.2-mm transverse monocortical defect was created with a low-speed (130 rpm) electrical hand drilling machine. A 1.5-mm length stop device avoided over-penetration and perforation of the opposite cortical surface. Next, the skin was sutured with 3.0 nylon line. The animals were maintained in a plastic cage with wood shaving bedding, food pellets, and water at 25°C with 12h:12h light-dark cycles. They received Paracetamol solution (25 mg/kg) during the first 48 postoperative hours for analgesia. Full weight-bearing on the hindlimbs was immediately permitted. After a period of 1, 2, 4, 8, and 12 weeks, the animals were euthanized with a sodium pentobarbital overdose, and their tibias were harvested for biomechanical, histological, and morphological examination. Fourteen animals were not subjected to the surgical procedure and served as a control group. (Table 1)

The tibias were carefully placed on a molded bed made of plaster of Paris to maintain the surface of the defect parallel to the ground. The macroindentation test was performed using a EMIC universal testing machine. The indenter, which was attached to a 100 N load cell, was centered on the defect axis and positioned just above the surface of the newly formed tissue. Next, the indenter was lowered to a depth of 0.6 mm (t = 0.6 mm) at a speed of 0.1 mm/s. The tests were performed using either a 3.2-mm diameter or a 5.0-mm diameter spherical Brinell indenter. Curves for applied load vs. indenter penetration depth were plotted using test data which were continuously registered by the test machine software (TESC 3.04). The applied force for t = 0.5 mm ($F_{0.5}$) of each curve was determined.

Table 1. Allocation of the animals according to test groups.

Test		Follow-up time (weeks)						Total
		Control	1	2	4	8	12	
Indentation	3.2 mm indenter	4	5	7	6	4	4	30
	5.0 mm indenter	4	3	7	6	4	5	29
Histology	Transverse sections	2	2	3	3	2	2	14
	Longitudinal sections	2	3	3	3	2	2	15
EDS/ERS/Raman	-	2	2	3	3	2	2	14
Total								102

Two-way analysis of variance (ANOVA) was used to compare the mean values of $F_{0.5}$ between groups. Pairwise comparison was performed using the Scheffe test, and a significance level of 5% ($\alpha = 0.05$) was considered.

The pair of tibias from 29 animals (a total of 58 tibias) was assigned to histological analysis. (Table 1) Samples were fixed (using 10% buffered formalin), decalcified (using tetrasodium EDTA), and stained with hematoxylin and eosin (HE) for optic microscopic examination (using a Leica DMLB device). Next, the microscopic images were captured (using a Leica DC 300 F device) and analyzed using IMAGE-PRO PLUS 4.5 software. Newly developed tissues were classified as granulation tissue, cartilaginous bone, newly formed bone, and bone.

The samples were then dehydrated (from 70% to 100% alcohol), embedded in polyester resin, and cut with a precision sectioning diamond saw (Bühler Isomet). The samples were excited with an argon laser (λ = 514.5 nm wavelength, ~6 mW), and their spectra were acquired using a Raman microscope (inVia model, Renishaw). Scanning electron microscopy (SEM) was performed to study the topography of the newly developed tissue surface. Additionally, energy dispersive X-ray spectroscopy (EDS) (using a Zeiss EVO LS15 model coupled with an EDS system) was used to determine the chemical composition of the newly developed tissue within the defect.

RESULTS

Of the total 118 tibias (pairs of tibias from 59 animals), 4 were discarded due to fractures, and consequently 114 tibias underwent macroindentation testing. Indentation force increased in a time-dependent manner for both 3.2-mm and 5.0-mm diameter indenters. (Figures 1 and 2, and Table 2)

Nevertheless, data from samples taken from the 1-week follow-up could not be obtained with the 5.0-mm diameter indenter. Because the newly developed tissue was fragile, the indenter easily penetrated into the defect and reached its margins, invalidating the test.

Histological examination revealed progressive primary bone regeneration within the monocortical tibial defect. At the 1-week follow-up we observed high-cellularity connective tissue composed predominantly of undifferentiated, spindle-shaped mesenchymal cells within the medullary canal. The initial stage of bone formation was also observed at the margins of the defect, where multiple ossification centers composed of osteoid (secreted by osteoblasts) and initial trabecular formation could be seen one week after tibial perforation. (Figure 3)

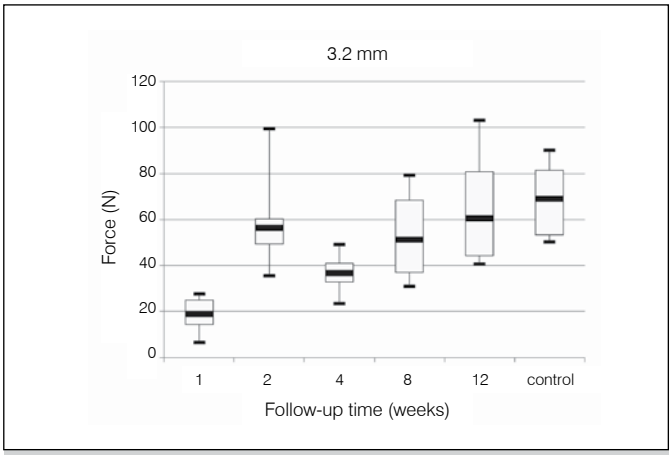

Figure 1. Penetration force achieved at 0.5 mm of a 3.2 mm indenter as a function of follow-up time.

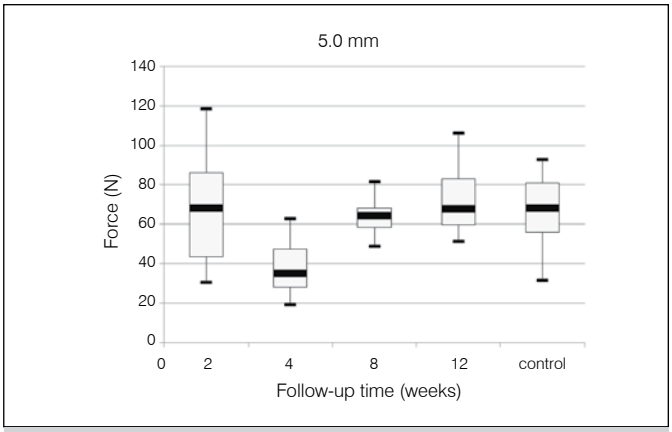

Figure 2. Penetration force achieved at 0.5 mm of a 5.0 mm indenter as a function of follow-up time.

Table 2. Scheffe contrast between pairs of follow-up time means according to indenter diameter ($\alpha = 0.05$, critical value = 2.519).

Indenter diameter (mm)	Follow-up times (weeks)	FS	Significant?
3.2	4 – 8	2.27	No
	4 – 12	3.80	Yes
	8 – 12	1.42	No
5.0	4 – 8	3.74	Yes
	4 – 12	5.14	Yes
	8 – 12	1.07	No

Two weeks after surgery, the defect site was filled with woven bone. Intense osteoblastic activity and dense connective tissue were observed within the intertrabecular space of the medullary canal. (Figure 3)

Four weeks after the procedure, a uniform pattern of osteogenesis could already be seen. Furthermore, the granulation tissue was completely resorbed, the woven bone was differentiated into cortical bone, and the medullary canal was remodeled. (Figure 3)

At 8 and 12 weeks post-procedure, the osteocytes reorganized into Haversian systems and complete remodeling of cortical and medullary bones was achieved. (Figure 3)

Raman spectra obtained from the surface of the cortical bone and medullary canal defects showed time-dependent decreases in phosphate apatite, amide III, and hydrocarbon (CH) side chain elements. (Figures 4 and 5)

Images obtained with SEM are shown in Figures 6 to 10. In distinct areas of each sample, 4 to 6 points (center and margins of the defect and the medullary canal) were chosen to examine the chemical composition and mineral phase components using EDS. Table 3 indicates the proportion of calcium content at each point according to follow-up period.

DISCUSSION

Micro or nanoindentation tests are commonly used for mechanical evaluation of bone,[8-11] but macroindentation testing is not common.[12] This study describes a macroindentation test developed from the Brinell hardness test. Advantages of the Brinell hardness test include the fact that it can be performed using equipment which is easy to handle and its singular status as the only test used and accepted for materials with heterogeneous structural composition (such as bone).[13]

Instead of using the original method, we adapted the Brinell hardness test because it is difficult to determine the imprinted diameter on the bone, and it because a low magnitude force F would be required

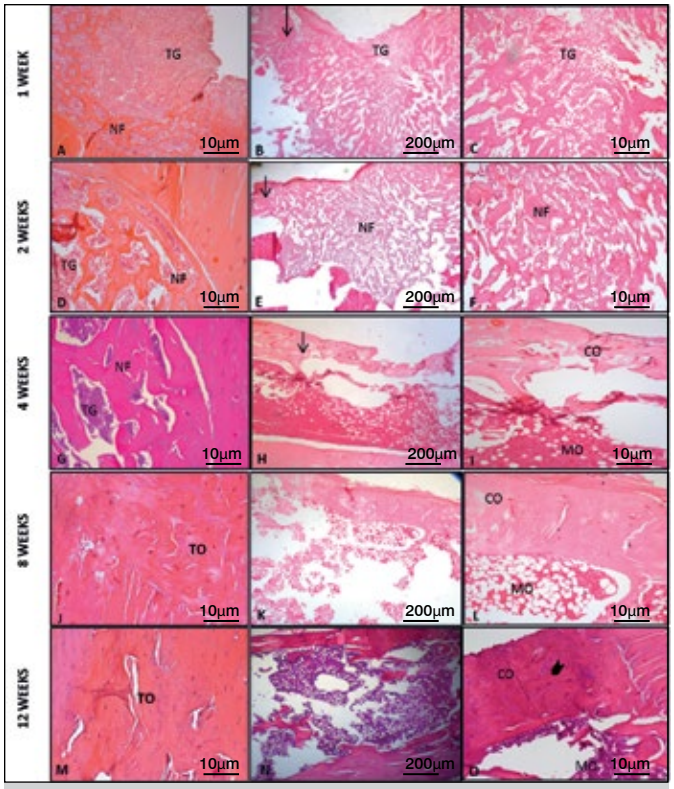

Figure 3. Transverse (A , D, G, J and M) and longitudinal sections (B, C, E, F, H, I, K, L, N and O) of the bone defect area after 1, 2, 4, 8 and 12 weeks (arrow: original-defect bone interface), with granulation tissue (GT), newly formed bone (NF), tissue in the cortical bone (CO) and medullar canal (MO), and osteocytes arranged concentrically around the central (Haversian) canals (lower arrowhead).

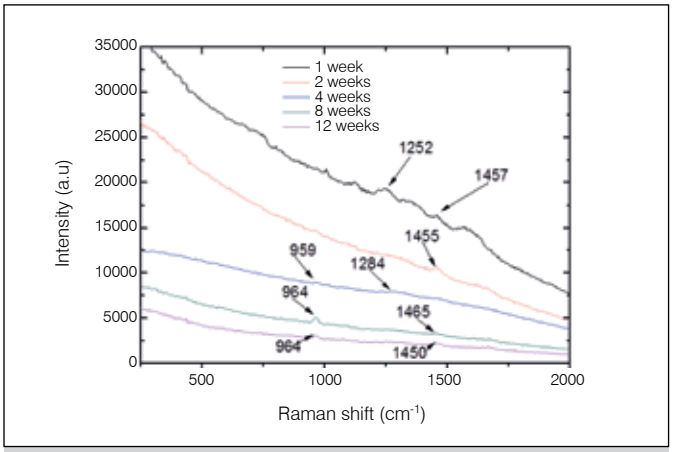

Figure 4. Raman spectra of the center of bone healing (cortical region of the defect). The bands indicate phosphate apatite (~960 cm-1), amide III (1200-1300 cm-1), and CH side chains (1450-1470 cm-1).

to avoid harming the newly formed and fragile tissue. Moreover, this force F would not allow the indenter to penetrate sufficiently, and would not yield reliable results.[14]

A 3.2 mm monocortical defect was chosen because it behaves like a bone fracture, which heals by primary intention when anatomically reduced and internally fixed.[15,16] Furthermore, two diameters of indenter tips were evaluated (3.2 mm and 5.0 mm). Each indenter penetrated no more than 0.6 mm into the newly formed tissue. By penetrating 0.6 mm, the 3.2-mm diameter indenter produced an indentation with a diameter of 2.5 mm, and the 5.0-mm diameter

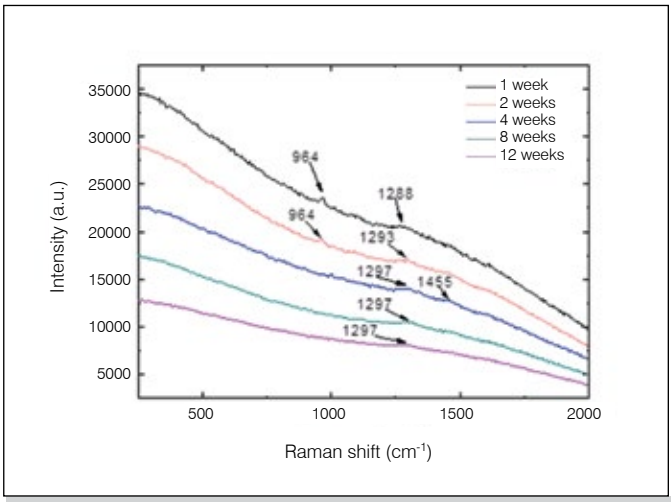

Figure 5. Raman spectra of the center of bone healing (medullar region). The bands indicate a) phosphate apatite (~960 cm-1), amide III (1200-1300 cm-1), and CH side chains (1450-1470 cm-1).

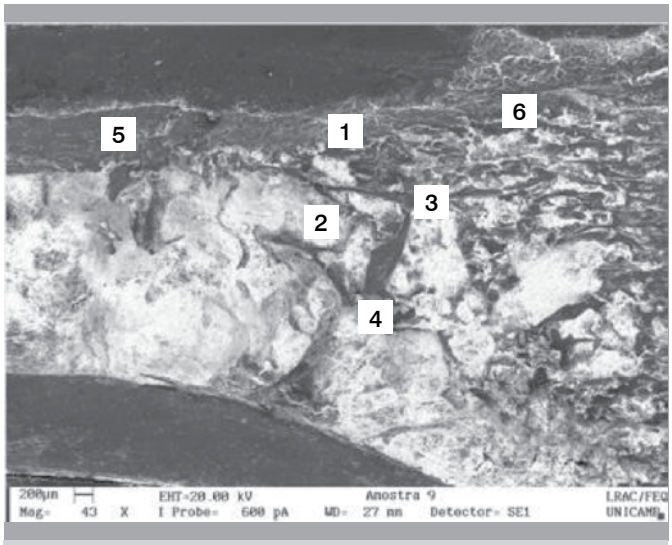

Figure 8. Longitudinal section of the defect at 4 weeks post-procedure.

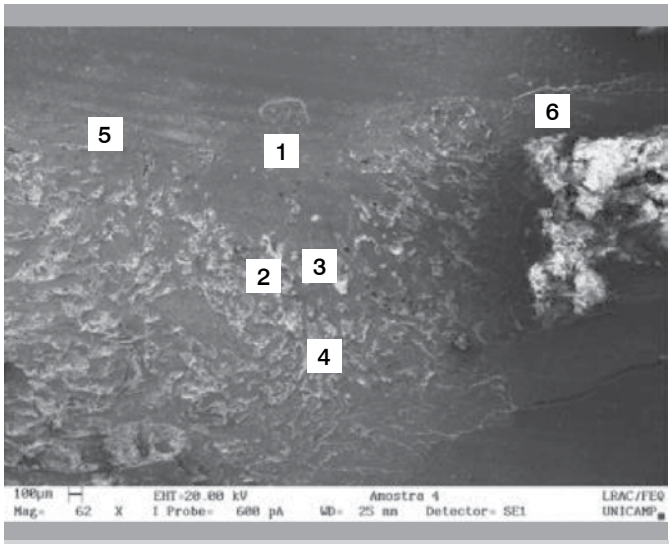

Figure 6. Longitudinal section of the defect at 1 week post-procedure.

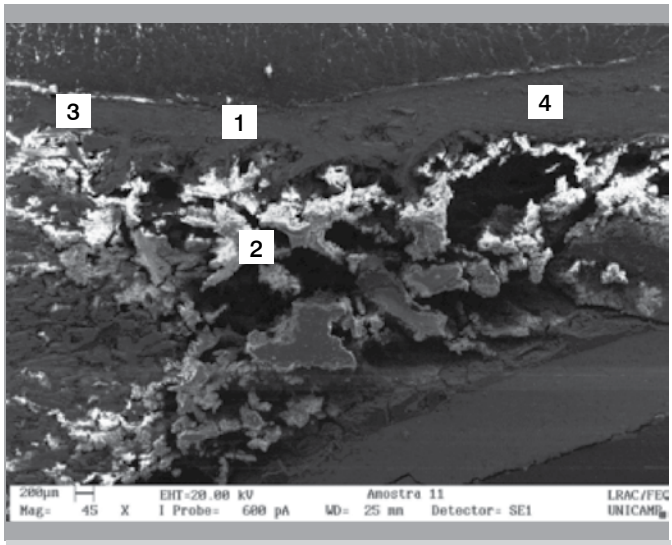

Figure 9. Longitudinal section of the defect at 8 weeks post-procedure.

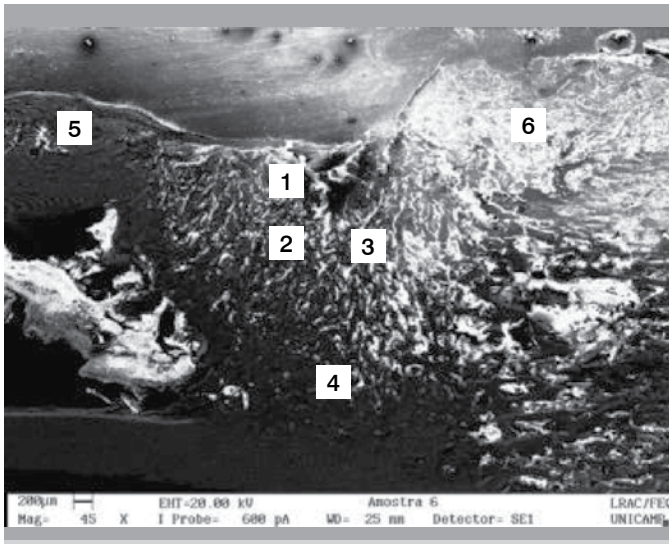

Figure 7. Longitudinal section of the defect at 2 weeks post-procedure.

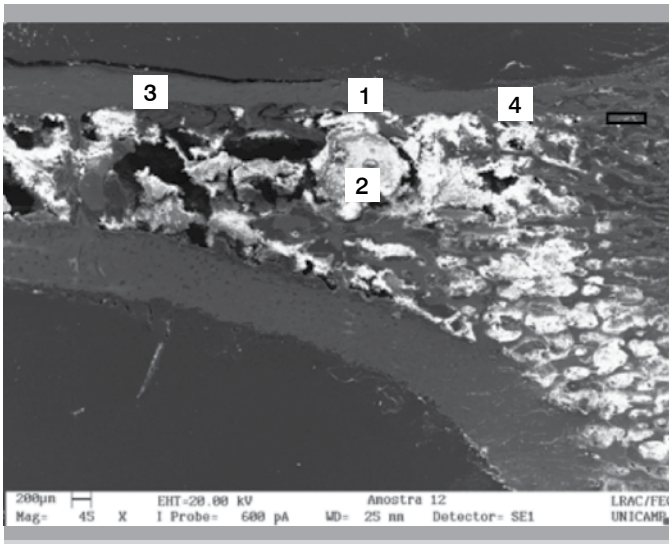

Figure 10. Longitudinal section of the defect at 12 weeks post-procedure.

Table 3. Calcium content obtained by EDS in different points of the samples according to follow-up time.

	Follow-up (weeks)				
Point	1	2	4	8	12
1	3.07	25.10	28.81	32,28	32.55
2	19.47	29.88	7.19	6.81	7.63
3	18.45	26.81	28.26	-	-
4	23.04	32.13	5.41	-	-
5	32.03	34.86	30.41	28.90	33.54
6	32.73	22.35	26.29	33.81	30.08

indenter produced an indentation with a 3.2 mm diameter. Since the 5.0-mm diameter indenter covered a larger indentation area, it was more sensitive to positioning errors than the 3.2-mm diameter indenter. Table 2 confirms our expectation that from 4 to 12 weeks postoperatively the 5.0-mm diameter indenter applied greater force than the 3.2-mm diameter indenter. Since bone maturation occurs from margin to center, and the 5.0-mm diameter indenter reaches an area closer to the margin (i.e. resulting in greater strength at the margin than at the center of the defect), we expected the 5.0-mm diameter indenter to require greater force to penetrate 0.5 mm.

Also as expected, for most results $F_{0.5}$ increased in a time-dependent manner. Surprisingly, samples obtained 2 weeks after the procedure revealed higher mean values than samples obtained 4 and 8 weeks later. (Figures 1 and 2) To explain those conflicting results, histological analyses were performed, and massive formation of tissue was seen within the medullary canal 2 weeks post-procedure. Furthermore, newly formed tissue remodeled at postoperative weeks 4 and 8. This leads us to hypothesize that one and two weeks after the procedure, massive tissue formation occurred in the medullary cavity and exerted a mass effect that resisted penetration by the indenter and consequently abnormally increased indentation force at 2 weeks post-procedure.

Because of its ability to effectively evaluate the presence of mineral (apatite phosphate) and organic components of bone's extracellular matrix (CH side chains and amide III), Raman spectroscopy is commonly used for structural assessment of bone healing and to provide information about the metabolic status of bone cells.[17-20] Here we found at the one- and two-week follow-ups that the band intensities of the cortical region spectra corresponded to the main collagen bands (i.e., amide III and CH side chains), while from the fourth to twelfth postoperative weeks, the band intensities of cortical region spectra corresponded to inorganic bone components (i.e., apatite phosphate); this indicated that mineralization of the newly formed tissue occurred between the second and fourth weeks after the procedure. Additionally, at 1 and 2 weeks following surgery, band intensities of medullary region spectra corresponded to apatite phosphate, while from the fourth to twelfth weeks after the procedure, the band intensities of the medullary region spectra did not correspond to apatite phosphate. These results are in accordance with biomechanical and histological findings, which showed time-dependent progressive increased indentation force and distinct healing processes observed in cortical and medullary bones, respectively, from 4 to 12 weeks post-procedure.

We also observed that the amount of collagen increased from center to the periphery of the defect. This finding was not a surprise since membranous bone ossification normally occurs from the periphery to the center of the defect. Four weeks post-procedure, the medullary canal was completely healed and exhibited a normal appearance, and the cortical bone was thicker and well formed.

In addition to chemical evaluation of bone repair, EDS of the defect site was performed. One week following surgery, the cortical region of the defect exhibited very low calcium content (3.07%) and no phosphorus; i.e., bone did not develop in that region. From the second postoperative week onward, the calcium content of the medullary canal decreased dramatically, reaching values from 5% to 8% after four weeks post-procedure. These results confirm the Raman spectroscopy findings. Our results also suggest that at the second postoperative week, a mass effect produced by isles of newly formed bone (composed mainly of hydroxyapatite) increased tissue resistance against indentation, while the cortical region of the defect was filled with immature bone (composed primarily of collagen). Subsequently, the newly formed tissue underwent progressive remodeling, so that four weeks after the procedure, the medullary canal was completely remodeled. As a result, the mass effect ceased and did not alter the hardness of the cortical bone, thereby permitting the indenter to penetrate with lower applied force.

Because the findings of this study indicate that macroindentation testing is adequate for biomechanical study of bone regeneration from four weeks post-procedure onward, two-way ANOVA and Scheffe tests were only applied to the results from this period (i.e., 4, 8, and 12 weeks post-procedure). Accordingly, macroindentation testing registered increased resistance in a time-dependent manner ($p < 0.001$).

The proposed model is more sensitive between four and eight weeks post-procedure. At eight weeks, the hardness of the defect was almost similar to the hardness of the control, but at 12 weeks, hardness of the defect was greater than that of the control. The Scheffe test showed a significant difference for the 5.0-mm diameter indenter between weeks 4 and 8 and between weeks 4 and 12. The 5.0-mm diameter indenter could detect bone maturation at 8 weeks post-procedure, but not from 8 to 12 weeks, most likely because there was complete cortical differentiation. Since the 3.2-mm diameter indenter could detect mechanical resistance in the newly developed tissue earlier than 5.0-mm diameter indenter, the 3.2-mm diameter indenter proved to be more adequate for macroindentation testing.

Bone repair from transverse monocortical defects occurs via intramembranous ossification. In contrast, bone repair from complete fractures occurs via endochondral ossification. Therefore, research on novel therapeutic methods for stimulating bone regeneration cannot be limited to the effect of intramembranous ossification. We believe that macroindentation testing should be used as a screening tool to identify therapeutic methods with the greatest potential to stimulate bone repair. Consequently, only therapeutic methods that exhibit positive results in macroindentation testing are worth testing in more complex experiment models such as osteotomy and osteosynthesis.

CONCLUSION

Macroindentation testing of rat tibia defects is suitable for quantitative assessment of bone repair through evaluating the newly developed tissue hardness from 4 to 8 weeks following surgery. Chemical and histological examination corroborated the biomechanical results.

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THE INFLUENCE OF PASSIVE TOBACCO EXPOSURE AND PHYSICAL EXERCISE ON BONE TISSUE OF YOUNG RATS

INFLUÊNCIA DO TABAGISMO PASSIVO E DO EXERCÍCIO FÍSICO NO TECIDO ÓSSEO DE RATOS JOVENS

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ABSTRACT

Objective: The objective of this study is to investigate the effect of passive smoking during pregnancy and associated with swimming on bone area growth, bone mineral density (BMD), and bone mineral content (BMC). Methods: The offspring was grouped by control matrices (G1) and passive smokers (G2). The offspring was regrouped in eight subgroups, with exposure to smoking (2x/day) and physical exercise (1 session/day), respecting the group of matrices in: sedentary control (G1CS and G2CS), swimming control (G1CN and G2CN), sedentary passive smoker (G1FS and G2FS), and passive smoker swimmer (G1FN and G2FN). The area, BMD and BMC were measured by the tibia and femur and analyzed by densitometer. The results were analyzed by One-Way ANOVA test with Tukey post-test, with a significance level of 5%. Results: In the tibia BMC study, a better rate was observed in G2CN group when compared to G1CS, G1CN and G1FN ($p \leq 0.023$). When assessing BMD in the femur, a higher density ratio was observed in G1FS group when compared to G2CS, G2CN, G2FS and G2FN ($p<0.008$). In the tibia study, the animals of the G1FS group had higher rates when compared to G2CS and G2FN groups ($p \leq 0.007$). Conclusions: The model of male offspring exposed to passive smoking during fetal development showed a strong decrease in the analyzed parameters. ***Level of Evidence I, Randomized High Quality Clinical Trial With or Without Statistically Significant Difference, But Narrow Confidence Intervals.***

Keywords: Exercise. Tobacco smoke pollution. Rats, Wistar/growth & development. Lactation. Birth weight.

RESUMO

Objetivo: O objetivo desse estudo é investigar o efeito do tabagismo passivo durante a prenhez e associado à natação no crescimento de área óssea, densidade mineral óssea (DMO) e conteúdo mineral ósseo (CMO). Métodos: Os filhotes foram gerados por matrizes controle (G1) e tabagistas (G2). Os filhotes foram reagrupados em oito subgrupos, com exposição ao tabagismo (2x/dia) e realização de exercício físico (1 sessão/dia), respeitando o grupo de matrizes em: controle sedentário (G1CS e G2CS), controle natação (G1CN e G2CN), tabagista passivo sedentário (G1FS e G2FS) e tabagista passivo natação (G1FN e G2FN). A área, a DMO e o CMO foram aferidos pela tíbia e pelo fêmur e analisados pelo densitômetro. Os resultados foram analisados pelo teste de ANOVA One-Way, com pós-teste de Tukey, com nível de significância de 5%. Resultados: No estudo do CMO da tíbia, foi observada taxa melhor no grupo G2CN quando comparada aos filhotes dos grupos G1CS, G1CN e G1FN ($p \leq 0,023$). Na averiguação da DMO no fêmur, foi observada maior taxa de densidade no grupo G1FS quando confrontado aos grupos G2CS, G2CN, G2FS e G2FN ($p \leq 0,008$). Já no estudo da tíbia, os animais do grupo G1FS apresentaram maiores taxas quando comparados aos grupos G2CS e G2FN ($p \leq 0,007$). Conclusões: O modelo de filhotes machos expostos ao tabagismo passivo durante o desenvolvimento fetal apresentou uma forte diminuição dos parâmetros analisados. ***Nível de Evidência I, Estudo Clínico Randomizado de Alta Qualidade Com ou Sem Diferença Estatisticamente Significante, Mas Com Intervalos de Confiança Estreitos.***

Descritores: *Exercício. Poluição por fumaça de tabaco. Ratos Wistar/crescimento & desenvolvimento. Lactação. Peso ao nascer.*

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INTRODUCTION

Exercise is known to have an important role in bone development.[1] There is also a known association between physical exercise and reduced bone resorption and bone formation, and exercise is consequently a strategy to reduce bone fragility and fracture risk, which are very common in childhood.[1] Notable among clinical indicators of bone health are bone mineral content (BMC) and bone mineral density (BMD).[2] Weight-bearing physical activity is

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Study conducted at the Universidade Estadual Paulista, Faculdade de Ciências e Tecnologia, Presidente Prudente, SP, Brazil.
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reported to encourage increases in BMC and BMD, but there is no consensus about non-weight-bearing exercise such as swimming.[2]
In contrast to the benefits of physical exercise, the effects of nicotine (a component of cigarettes) are indicated as a factor in bone tissue deterioration,[3] and appear to be associated with the dose-response mechanism.[4]
Finally, human and rat skeletons are known to exhibit similar responses to mechanical and hormonal influences as well as the effects of other agents.[2] This study consequently hypothesizes that passive smoking could negatively impact rat growth from gestation to adulthood, and that its influence could be minimized by physical exercise.
In this way we intend to evaluate bone formation during passive exposure to cigarette smoke during gestation and in association with physical exercise during growth by measuring BMC and BMD.

METHODS

This study used the technical experimental procedure approved by the institutional review board of the Faculdade de Ciências e Tecnologia da Universidade Estadual Paulista "Julio de Mesquita Filho", UNESP, Campus de Presidente Prudente under process 06/2011, and followed the ethical principles for animal experimentation adopted by the Sociedade Brasileira de Ciência em Animais de Laboratório (SBCAL).
Initially 15 animals were used, 11 virgin female and 4 male (72 days old) Wistar rats (*Rattus novergicus*, var. Albino, Rodentia, Mammalia). They were kept in individual cages at an average temperature of 22 ± 2°C, humidity of 50 ± 10%, 12-hour light/dark cycle (7 am-7 pm), and had free access to water and standard rat chow.
The rats were divided into two groups: G1 (control group, n=5) and G2 (group exposed to cigarette smoke, n=6). The exposure protocol began on the 72nd day of life for the breeding females and ended when lactation ended.
At the 90th day of the life, a vaginal swab was performed on the female rats to verify the phase of the estrous cycle; if estrus was observed, the female rats were placed in individual cages with a male rat, where they stayed for one night for copulation. The next morning, pregnancy was diagnosed by the presence of sperm in the vaginal smear, which characterized day zero of the pregnancy.[5]
The male rat pups were kept with the mothers until the end of lactation, on their 21st day of life, and were subsequently divided into subgroups according to their parentage.
The rats were randomly divided into groups that were subjected to a maximum of two protocols (protocols for exposure to smoking and physical exercise): G1FN (n=14) and G2FN (n=15) (exercise group exposed to cigarette smoke); G1FS (n=10) and G2FS (n=09) (sedentary group exposed to cigarette smoke); G1CN (n=11) and G2CN (n=10) (exercise group, control); and G1CS (n=08) and G2CS (n=10) (sedentary group, control).
The protocol for adaptation to water started during the pups' fifth week of life, and in the sixth week they began the protocol for physical exercise and exposure to cigarette smoke.
There were two separate study periods during which the rats were exposed to cigarette smoke. The first period occurred when the female rats reached 72 days of life, and the second on the same day as the sixth swimming session for the rat pups.
The cigarette smoke exposure protocol was divided into two stages:

- Adaptation stage: the first five days of exposure to cigarette smoke for group G1 in the smoke chamber at a temperature of 23±1°C[6] for 10 minutes, once a day, with 250 ppm (parts per million) of CO (carbon monoxide) measured using a specific gas sensor (ToxiPro device, Biosystems, Prairieville, United States); and
- Experimental stage: this stage began at the breeding females' 72nd day of life and ended at the end of lactation for the G2 group, and from the 6th session until the 21st day of lactation for the pups, with a session lasting 30 minutes, twice a day (morning and afternoon), five days per week, with 350 ppm CO per exposure.[7]

For better assimilation to the consumption of chronic smokers, the experimental dose totaled an average of two cigarettes/day/animal.[5] The animals in the G1 group inhaled compressed air with the same time and frequency characteristics as the animals which were exposed to smoke.
For this protocol two hermetically sealed chambers were used: one for the control groups, which only inhaled compressed air, and a second box for the groups exposed to cigarette smoke. The smoke inhalation chamber was divided into two compartments: one in which lit cigarettes were placed, and another which held a cage with six animals, adapted from the inhalation model described by Cendon et al.[8]
Commercially acquired cigarettes were used, containing tobacco blends, sugars, cigarette paper, plant extracts, and flavoring agents, which for each lit cigarette produced: 9.3 ± 0.93 mg/cig tar, 0.78 ± 0.078 mg/cig nicotine, and 8.0 ± 1.2 mg/cig carbon monoxide, as stated on the product packaging.
The swimming program began during the fifth week of life for the male offspring. As described by Volpato et al.,[9] we used a tank containing water at 30°C and a depth of 40 cm so that the pups could not reach the bottom of the tank with their tails, thus stimulating swimming.
The program was divided into two phases:

- adaptation to exercise: this comprised the five exercise sessions, with a progressive increase of 10 minutes' duration per day, starting with 20 minutes and lasting 60 minutes by the fifth session;
- exercise: from the sixth session, which lasted 60 minutes, to the 30th session, without additional extension of the training time.[10]

The exercise sessions took place every evening without interruption five days per week[11] for 30 sessions, and in the case of the G1FN and G2FN groups, after exposure to the smoke protocol. The sedentary animals were submitted to the same conditions as the swimming program, but in 10 cm of water for 15 minutes; this replicated the same stress resulting from exposure to water, but without the stimulus to swim.
During lactation (day 1, day 7, day 14, and day 21 of life) weight and nose-to-anus length were measured.
A digital electronic scale (Marte, model ASF11, Brazil) with a maximum capacity of 500g and minimum of 0.002g was used. Nose-to-anus length was measured using a millimeter ruler.

Bone mineral density and bone mineral content

Forty-eight hours after the 30th training session, the offspring were euthanized with xylazine (40 mg/kg, IP) and ketamine (40 mg/kg, IP). After anesthesia was confirmed, approximately 1 ml of KCl 10% was injected into the left ventricle until cardiac arrest occurred in diastole. After death resulting from cardiac arrest in diastole was confirmed, the offspring underwent a surgical procedure to extract the femur and tibia of the right hind limb.
Bone mineral density and bone mineral content were measured using a densitometer (DPX-Alpha model, Lunar Corporation, Madison, USA) equipped with software for small animals.[4]

Statistical analysis

The weight, length, BMD and BMC, and bone area of the femur and tibia were obtained from the offspring. A descriptive analysis was conducted, including means and standard deviation. Analysis of variance (one-way ANOVA) and Tukey's post-test were used to

analyze BMC, BMD, and bone area. The results followed normal distribution (according to the Shapiro-Wilk test with 5% significance) and the groups were independent. All the analyses used Statistical Analysis System software (SAS).

RESULTS

When the offspring were born, values for the parameter weight were not greater in the pups in the control group (G1) compared to the offspring of the breeding females exposed to tobacco smoke (G2) (p=0.890). This difference was not seen for the parameter body length (p=0.079). Growth occurred in an unequal manner in the two groups of pups during lactation. During the entire lactation period, the body weights for pups in the G1 group were greater than the values for the offspring of the breeding females exposed to smoke (7, 14, and 21 days - p<0.001). No statistically significant difference was seen in body length at birth, with greater values for the offspring of the breeding females in group G1 compared to the offspring in group G2 (7 days – p=0.001, 14 and 21 days - p<0.001). (Table 1)

The areas of the tibia and femur bones did not show a statistically significant difference according to ANOVA (p=0.058 and p=0.700, respectively). (Table 2)

In the bone density study, no statistically significant difference was seen (p=0.366) between the study groups for the parameter bone mineral content for the femur. However, in the study this same parameter for the tibia showed lesser values for the G2CN group compared to the offspring in the G1CS (p=0.014), G1CN (p=0.023), and G1FN groups (p=0.008). (Table 3)

When bone mineral density was analyzed, a difference was seen in the levels for the two bones which were studied. Measurement of bone mineral density in the femur showed greater density values for the G1FS group compared with the G2CS (p=0.004), G2CN (p<0.001), G2FS (p=0.008), and G2FN (p<0.001) groups. For the tibia, the animals in the G1FS group showed higher values compared to the G2CS (p=0.003) and G2FN (p=0.007) groups. (Table 4)

Table 1. Mean and standard deviation for weight and body length of offspring during lactation.

	G1	G2	P
Body weight			
Birth	6.67 ± 0.84	6.65 ± 0.67	0.890
7 days	12.50 ± 0.87	10.85 ± 1.69	<0.001
14 days	27.34 ± 4.60	21.87 ± 1.71	<0.001
21 days	34.13 ± 1.74	29.57 ± 2.55	<0.001
Body length			
Birth	5.20 ± 0.24	5.06 ± 0.35	0.079
7 days	6.46 ± 0.37	6.10 ± 0.45	<0.001
14 days	8.67 ± 0.79	7.76 ± 0.56	<0.001
21 days	10.43 ± 0.35	9.36 ± 0.71	<0.001

G1: breeding females, control group and G2: breeding females exposed to cigarette smoke.

Table 2. Mean and standard deviation of bone area.

		G1CS	G1CN	G1FS	G1FN
Area	Femur	1.34 ± 0.27	1.41 ± 0.17	1.31 ± 0.22	1.38 ± 0.22
	Tibia	1.1658 ± 0.21	1.15 ± 0.19	0.93 ± 0.16	1.13 ± 0.18
		G2CS	**G2CN**	**G2FS**	**G2FN**
Area	Femur	1.31 ± 0.14	1.43 ± 0.21	1.28 ± 0.09	1.53 ± 0.20
	Tibia	1.00 ± 0.10	0.91 ± 0.10	1.01 ± 0.13	1.00 ± 0.11

G1CS: offspring of breeding female control group, sedentary control; G1CN: offspring of breeding female control group, exercise control group; G1FS: offspring of breeding female control group, exposed to cigarette smoke and sedentary; G1FN: offspring of breeding female control group, exposed to cigarette smoke and exercise; G2CS: offspring of breeding females exposed to cigarette smoke, sedentary control group; G2CN: offspring of breeding females exposed to cigarette smoke, exercise control group; G2FS: offspring of breeding females exposed to cigarette smoke, exposed to cigarette smoke and sedentary; G2FN: offspring of breeding females exposed to cigarette smoke, exposed to cigarette smoke and exercise.

Table 3. Mean and standard deviation of bone mineral content.

		G1CS	G1CN	G1FS	G1FN
BMC	Femur	0.28 ± 0.05	0.29 ± 0.04	0.29 ± 0.05	0.29 ± 0.04
	Tibia	0.20 ± 0.03 [a]	0.19 ± 0.03 [b]	0.17 ± 0.02	0.19 ± 0.03 [c]
		G2CS	**G2CN**	**G2FS**	**G2FN**
BMC	Femur	0.26 ± 0.03	0.28 ± 0.04	0.26 ± 0.02	0.30 ± 0.04
	Tibia	0.16 ± 0.02	0.15 ± 0.02	0.16 ± 0.02	0.16 ± 0.02

G1CS: offspring of breeding female control group, sedentary control; G1CN: offspring of breeding female control group, exercise control group; G1FS: offspring of breeding female control group, exposed to cigarette smoke and sedentary; G1FN: offspring of breeding female control group, exposed to cigarette smoke and exercise; G2CS: offspring of breeding females exposed to cigarette smoke, sedentary control group; G2CN: offspring of breeding females exposed to cigarette smoke, exercise control group; G2FS: offspring of breeding females exposed to cigarette smoke, exposed to cigarette smoke and sedentary; G2FN: offspring of breeding females exposed to cigarette smoke, exposed to cigarette smoke and exercise. Letters indicate statistical difference between: a = G1CS vs. G2CN (p=0.014), b = G1CN vs. G2CN (p=0.023), c = G1CN vs. G2CN (p=0.008).

Table 4. Mean and standard deviation of bone mineral density.

		G1CS	G1CN	G1FS	G1FN
BMD	Femur	0.21 ± 0.01	0.20 ± 0.01	0.22 ± 0.02 [a, b, c, d]	0.21 ± 0.01
	Tibia	0.17 ± 0.01	0.17 ± 0.02	0.18 ± 0.02 [a, d]	0.17 ± 0.01
		G2CS	**G2CN**	**G2FS**	**G2FN**
BMD	Femur	0.20 ± 0.01	0.19 ± 0.01	0.20 ± 0.01	0.19 ± 0.01
	Tibia	0.16 ± 0.01	0.16 ± 0.01	0.16 ± 0.01	0.16 ± 0.01

G1CS: offspring of breeding female control group, sedentary control; G1CN: offspring of breeding female control group, exercise control group; G1FS: offspring of breeding female control group, exposed to cigarette smoke and sedentary; G1FN: offspring of breeding female control group, exposed to cigarette smoke and exercise; G2CS: offspring of breeding females exposed to cigarette smoke, sedentary control group; G2CN: offspring of breeding females exposed to cigarette smoke, exercise control group; G2FS: offspring of breeding females exposed to cigarette smoke, exposed to cigarette smoke and sedentary; G2FN: offspring of breeding females exposed to cigarette smoke, exposed to cigarette smoke and exercise. Letters indicate statistical difference between: a = G1FS vs. G2CS, b = G1FS vs. G2CN, b = G1FS vs. G2FS, b = G1FS vs. G2FN.

DISCUSSION

After birth, the offspring of the breeding females exposed to passive cigarette smoke remained at lower weights, and over time the difference between this group and the offspring of the breeding females in the control group widened; this phenomenon may be explained by the low levels of prolactin which have been found in women who are active smokers during pregnancy and the post-natal period.[12,13] Another study analyzed breastfeeding duration and found shorter periods of breastfeeding in children whose fathers were smokers.[13,14]

Similar to the findings of Gao et al.[15] and Ino et al.[16], in this study we also observed that the groups exposed to cigarette smoke continued to show lesser measurements in comparison with the control group.

Lower BMD and BMC values were found in the offspring of breeding females exposed to cigarette smoke in comparisons with the offspring of the control rats. Gao et al.[4] found similar results after 4 months of exposure to tobacco smoke. The literature shows that metabolic acidosis may negatively impact bone metabolism.[2] In this study, the animals were exposed to passive smoking, which produces respiratory acidosis;[6] this may suggest that the changes seen in BMD and BMC may be connected to the effects of smoke exposure.

It has already been shown that gestation and the neonatal period have a greater influence on individual growth and health,[16] and this present study confirmed that maternal exposure to passive cigarette smoke was a determining factor in reduced values for bone mineral density and content.

According to Gao et al.,[4] smoking suppresses the bone formation and increases bone reabsorption.

Exposure during growth led to significant differences in animal weight and length. The study by Gao et al.[15] found a statistically

significant difference only after 4 months of exposure; the rats which were exposed for 2 or 3 months did not exhibit differences in the bone parameters studied.[4]

With regard to the exercise variable, no alterations were seen that could be attributed to exercise; this lack of response is likely due to the protocol period (30 sessions). According to Iwamoto et al.,[17] osteopenic rats did not show a statistically significant difference in the parameter BMD in 4 or 8 weeks of exercise; a difference was only seen after 12 weeks.

Another fact that can be considered is that bone maturation only occurs after the 8th month of life in rats,[4] indicating a future possibility to investigate growth after the 8th month to assess the extent of the effect passive chronic smoking associated with swimming exercise has on a larger group of animals.

CONCLUSION

In summary, in this study the model of male rats exposed to passive smoking during fetal development exhibited a marked decrease in weight and length. Swimming exercise did not exhibit a significant impact on the parameters analyzed in this study.

In the bone tissue, maternal exposure to passive smoking was a determining factor for changes in the BMD and BMC of the offspring.

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LOCAL PERIARTICULAR ANALGESIA IN TOTAL KNEE ARTHROPLASTY

ANALGESIA LOCAL PERIARTICULAR NA ARTROPLASTIA TOTAL DE JOELHO

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ABSTRACT

Objective: To evaluate the use of infiltration of periarticular analgesic agents intraoperatively in total knee arthroplasty (TKA), with regard to benefits, reduction of pain, opioid consumption, improvement of range of motion and early ambulation. Methods: To analyze the benefits of periarticular drug infiltration, the patients submitted to TKA were evaluated, being separated into two groups. One group received the local periarticular infiltration protocol containing 0.5% bupivacaine (400mg/20ml), 1/1000 epinephrine (0.3ml), triamcinolone hexacetonide (20mg/1ml), clonidine (150mcg/1ml) and 20 ml of saline (0.9% SS) and, the other group underwent conventional intravenous analgesia. The results were compared and the variables analyzed were age, sex, BMI, comorbidities, postoperative complications, pain, functional capacity, range of motion, transfusion and rescue opioids for analgesia. Results: The mean age of the patients was 68 years and most were female and presented involvement of the left knee. Postoperatively, patients who had received periarticular infiltration showed improvement of pain as well as functional capacity. Conclusion: The analysis of data obtained demonstrated that the periarticular infiltration of analgesic agents is significantly effective for pain control and functional recovery. ***Level of Evidence II, Prospective Comparative Study.***

Keywords: Analgesia. Arthroplasty. Knee. Seepage.

RESUMO

Objetivo: Avaliar a realização da infiltração de solução de agentes analgésicos periarticulares no intraoperatório da artroplastia total do joelho (ATJ), no que tange aos seus benefícios, redução da dor, consumo de opioides, melhora do arco de movimento e deambulação precoce. Métodos: Para avaliar os benefícios da infiltração de agentes periarticulares, foram analisados pacientes submetidos à ATJ, sendo separados em dois grupos. Um grupo recebeu o protocolo de infiltração periarticular local, contendo solução de bupivacaína a 0,5% (400 mg /20 ml), epinefrina 1/1000 (0,3 ml), hexacetonido de triancinolona (20 mg/1 ml), clonidina (150 mcg/1 ml) e 20 ml de solução salina (SF a 0,9%) e outro grupo recebeu analgesia endovenosa convencional. Os resultados foram comparados e as variáveis analisadas foram idade, sexo, IMC, comorbidades, complicações pós-cirúrgicas, dor, capacidade funcional, amplitude de movimento, transfusão e resgate de opioides para analgesia. Resultados: Dos pacientes analisados a média de idade foi de 68 anos e a maioria era do sexo feminino e com acometimento do joelho esquerdo. No pós-operatório os pacientes que haviam recebido infiltração periarticular apresentaram melhora da dor, bem como da capacidade funcional. Conclusão: A análise dos dados obtidos demonstrou que a infiltração periarticular de agentes analgésicos é significativamente eficaz para o controle da dor e recuperação funcional. ***Nível de Evidência II, Estudo Prospectivo Comparativo.***

Descritores: *Analgesia. Artroplastia. Joelho. Infiltração.*

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INTRODUCTION

Many surgical procedures performed in orthopedics involve an extremely complex pain mechanism, and a number of studies have demonstrated that further study is needed on the topic of controlling perioperative pain to achieve more effective pain control.[1–4]

We know that surgical patients who receive appropriate analgesia are more adherent to postoperative rehabilitation programs. One of the main goals of postoperative analgesia is improvement in functional results and early return to routine activities, improving patient quality of life.[5]

The growing number of total knee arthroplasties and increased life expectancy reinforce the need for early rehabilitation to completely restore function in the operated joint and improve pain with the fewest complications.[6,7] In order to solve this problem, a number of studies are carried out each year to find a viable solution that will improve postoperative pain in patients.[3,4,8]

All the authors declare that there is no potential conflict of interest referring to this article.

Study performed at the Clínica Ortopédica Traumatológica (COT CEOT), Salvador, Bahia, Brazil.
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Our objective was to assess postoperative improvement after total knee arthroplasty by comparing the use of multimodal periarticular infiltration with analgesic agents with conventional analgesia. More specifically, the objective of this study was to compare the postoperative analgesia obtained through periarticular infiltration of a solution containing 0.5% bupivacaine (400mg/20ml), 1/1000 epinephrine (0.3ml), triamcinolone hexacetonide (20mg/1ml), clonidine (150mcg/1ml), and 20ml of 0.9% saline solution with the use of intravenous analgesia utilizing opiates and painkillers (tramadol 100mg and dipyrone 1g) according to the assessment of opioid analgesic consumption, function (using the WOMAC scale), and evaluation of pain (using the VAS scale).

METHODS

To evaluate the results, we conducted a prospective and comparative study from March 2008 to December 2014. We selected 59 patients with a diagnosis of primary osteoarthritis of the knee who underwent elective surgeries for TKA, and separated them into two groups using permuted block randomization.[9]

The study began after approval by the institutional review board, and was registered under process number CAAE 38426214.5.0000.5032. All patients signed an informed consent form before being included in the study.

Participants were male and female patients aged 60 to 80 years, with grade 3 or above according to the Kellgren and Lawrence classification,[10] indicated for TKA with no bone defects requiring additional grafts or implants, and did not have pronounced angular deformities. We excluded patients with psychiatric disorders, dependence on alcohol or illegal drugs, allergies to morphine, dipyrone or any local anesthetic, previous infection in the knee or other joints, systemic inflammatory diseases, congenital deformities or neurological disorders, and arthroplasty revision.

The variables evaluated were: age, sex, body mass index (BMI), post-surgical complications, pain level evaluated by the analog pain scale (VAS), ability to ambulate, time to begin walking, range of motion, and the need for transfusion and oral and intravenous rescue opioid analgesia.

The patients who underwent TKA were divided into two groups: Group 1 (29 individuals) received spinal anesthesia as well as the trans-operative analgesia protocol using infiltration of multimodal periarticular analgesic drugs. Group 2 (30 subjects) received only conventional intravenous analgesia using opiates and painkillers (tramadol 100mg and dipyrone 1g) and morphine sulfate (4mg every 2 hours) as required by the patient, which was similar in both groups. The drugs used in the spinal anesthesia were the same for all patients according to the anesthesia team protocol, namely 0.5% isobaric bupivacaine (5mg) and morphine hydrochloride (0.1mg), and were administered by the same anesthesia team. All patients who required medications outside the anesthesia team protocol for TKA were excluded from the study.

All patients received the same pre-emptive analgesia containing dipyrone (1g every 6 hours), tramadol (100mg every 8 hours), and pregabalin (75mg every 12 hours). The patients were oriented on the use of medications 24 hours prior to the surgery, and the drugs were maintained during hospitalization.

The medications used for intraoperative analgesia by the individuals in Group 1 are listed in Table 1.

The drugs used for periarticular infiltration were based on the studies by Ranawat.[11]

The medications used in the postoperative period for both groups were: dipyrone (1g IV every 6 hours), tramadol (100mg orally every 8 hours) as needed, and morphine sulfate (4mg every 2 hours) as requested for persisting pain above 7 on the visual analog scale (VAS). Extra rescue doses of opioids were recorded (usage and frequency).

Table 1. Multimodal drugs used for periarticular knee infiltration.

Bupivacaine 0.5%	400 mg/20ml
Epinephrine 1/1000	1/1000 (0.3ml) 300 Mcg
Triamcinolone hexacetonide	20mg/1ml
Clonidine	150mcg/1ml
Saline solution (0.9%)	20ml

Pain intensity was evaluated in three periods: prior to surgery, 24 hours after the procedure, and 48 hours after the procedure.

A pneumatic tourniquet at 100 mmHg above systolic blood pressure was used to control bleeding during the surgical procedure in all cases. A suction drain was used for 24 hours. After cementing and placement of the implants, periarticular infiltration was conducted using the drugs listed in Table 1.

Before placement of the polyethylene component, periarticular infiltration was performed in the following order: posterior capsule, posterior-lateral and posterior-medial structures, patellar ligament and quadriceps tendon, synovia, capsule, pes anserinus, periosteum, iliotibial band, and tibial and fibular collateral ligaments at their origins. Rehabilitation began on the first day after surgery and the protocol was identical in both groups. Assessment began 6 hours after the end of the procedure.

The quantitative variables were presented as means and their standard deviations, medians, and interquartile ranges. Categorical variables were represented using frequencies and percentages. Numerical variables were compared between groups using Student's T test for variables that assumed normal distribution and the Mann-Whitney U test for variables with non-normal distribution. Proportions were compared using the chi-squared test or Fisher's test (when necessary), and ANOVA was conducted on repeated measurements considering the VAS score at three points in time (pre-procedure, 24 hours post-procedure, and 48 hours post-procedure) between the groups (with or without periarticular infiltration), analyzing the clinically significant variables and/or those which exhibited significant differences or trends in univariate analysis: preoperative WOMAC and opioid rescue dose at 48 hours. The analyses were conducted using IBM Statistical Package for the Social Sciences software version 20.0 (SPSS, Chicago, IL, USA) and the R programming language and environment (R Core Team, 2014).

RESULTS

A total of 59 patients were selected, 36 (61%) females and 23 (39%) males. Mean patient age was 68, (65.0–75.0) and mean patient BMI was 27.0 (65.0–75.0).

Table 2 presents the clinical data for the patients studied. Of the total, 30 patients (50.8%) were affected in the right knee and 29 (49%) in the left knee. Identified comorbidities are shown in Table 2.

Table 3 presents the clinical data related to the surgery. Lower scores on the Visual Analog Scale for pain were seen in patients in Group A (3.7–3.9) 24h post-procedure as well as 48h post-procedure, respectively; group B presented higher values on the pain scale (5.3 at 24h post-procedure and 4.8 at 48h post-procedure). The partial load (with aids) was evaluated by examining the standing patient supported by a walker while exercising with the assistance of the physical therapist. In this test, higher mean scores were seen at 24 and 48h (10.3 and 11.0%) in the patients in group A and at 24h and 48 hours post-procedure (10 and 12%) in the patients in group B. The WOMAC assessment of functional capacity showed no statistically significant difference between the two groups in the postoperative period of 3 month. Clinical complications are presented in Table 3.

Table 2. Clinical data for patients undergoing TKA from 2008 to 2014.

Characteristic	Total (n = 59)	Without infiltration (n = 30)	Periarticular injection (n = 29)
Side affected			
Right	30.0 (50.8)	16.0 (53.3)	14.0 (48.3)
Left	29.0 (49.0)	14.0 (46.7)	15.0 (51.7)
Comorbidities			
High blood pressure (HBP)	30.0 (50.8)	13.0 (43.3)	17.0 (58.6)
Diabetes mellitus	10.0 (16.9)	3.0 (10.0)	7.0 (24.1)
Dyslipidemia	5.0 (8.5)	2.0 (6.7)	3.0 (10.3)
Controlled Chronic Kidney Disease	2.0 (3.4)	1.0 (3.3)	1.0 (3.4)
Previous Stroke	2.0 (3.4)	2.0 (6.7)	0.0 (0.0)
Gastroesophageal Reflux Disease	1.0 (1.7)	1.0 (1.6)	0.0 (0.0)

All data are presented as n (%).

Table 3. Data relating to surgery for groups of patients undergoing TKA from 2008 to 2014.

Visual analog Pain scale	Total (n = 59)	Without infiltration (n = 30)	Periarticular injection (n = 29)	p value
(Mean ± Standard deviation)				
Preoperative	7.9 ± 0.8	7.7 ± 0.6	8.1 ± 0.9	0.065
24h Postoperative	4.5 ± 1.2	5.3 ± 0.9	3.7 ± 0.9	< 0.001
48h Postoperative	4.3 ± 1.2	4.8 ± 1.1	3.9 ± 1.2	0.004
Functional Capacity				
WOMAC **(Mean ± Standard deviation)**				
Preoperative	28.6 ± 7.1	26.0 ± 5.2	31.2 ± 7.9	0.004
Postoperative (3 months)	47.3 ± 7.0	47.1 ± 6.6	47.4 ± 7.5	0.865
Rescue opioid				
24h	150.0 (100.0 - 300.0)	200 (100.0 - 300.0)	150.0 (100.0 - 200.0)	0.123
48h	100 (50.0 - 150.0)	150 (100.0 - 200.0)	50 (0.0 - 100.0)	< 0.001
Complications				
Nausea	9.0 (15.3)	6.0 (20.0)	3.0 (10.3)	0.472
Vomiting	5.0 (8.5)	4.0 (13.3)	1.0 (3.4)	0.353
Headache	4.0 (6.8)	4.0 (13.3)	0.0 (0.0)	0.112
Incontinence	2.0 (3.4)	0.0 (0.0)	2.0 (6.9)	0.237
Range of motion				
Preoperative (medians, extension - flexion)	0 - 120	0 - 120	0 - 120	
Postoperative (medians, extension - flexion)	0 - 100	0 - 100	0 - 110	

a - Student's t test; b - Chi-squared test; c - Mann-Whitney U test; d - Fisher's exact test.

Table 4 shows the VAS pain values in the group that did not receive infiltration, measured prior to the procedure, at 24h post-procedure, and at 48h post-procedure. These values were considerably higher, especially after the surgery, when compared to the group that received periarticular injection of the painkillers. After the surgery, at 24h and 48h post-procedure the values were significantly lower in the periarticular injection group (3.7 ± 0.2; 3.7 ± 0.2).
Figure 1 contains data relating to analysis of the Visual Analog Scale for pain over time and between the groups. In both groups, a continuous decrease was seen in the postoperative periods at 24h and 48h, and was more pronounced in the group that underwent the procedure. The VAS scale demonstrates statistically significant values at the different points in time which were analyzed.

Table 4. Estimated means according to the ANCOVA model.

Visual analog pain scale	Without infiltration (n = 30)	Periarticular injection (n = 29)
(Mean ± Standard deviation)		
Preoperative	7,8 ± 0,1 (7,5 – 8,1)	8,1 ± 0,2 (7,7 – 8,4)
24h Postoperative	5,3 ± 0,2 (4,9 – 5,7)	3,7 ± 0,2 (3,3 – 4,1)
48h Postoperative	4,8 ± 0,2 (4,3 – 5,3)	3,7 ± 0,2 (3,3 – 4,3)

Notes: a - Controlling for preoperative WOMAC and rescue opioid in 48 hours; All values are presented as mean ± standard deviation (95% confidence interval). MPA = Multimodal Periarticular Analgesia.

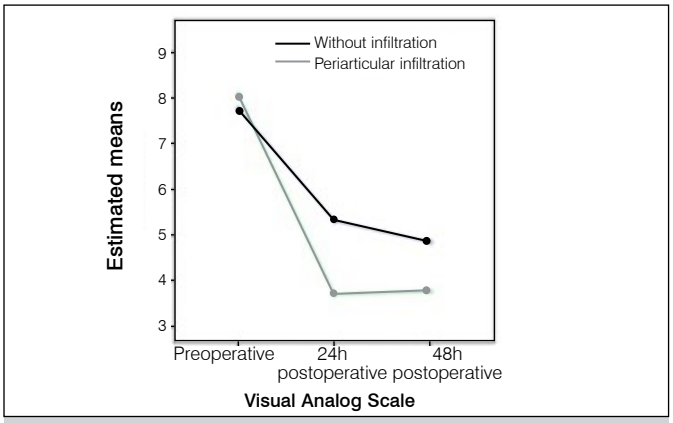

Figure 1. Mean values for VAS pre and postoperative estimated from ANCOVA of repeated measurements from patients who underwent TKA at the Clínica Ortopédica e Traumatológica in Salvador, Bahia from 2008 to 2014.

DISCUSSION

The results of this prospective randomized clinical study showed significant pain reduction as assessed by the VAS with statistically significant data, especially in the first 24 hours post-procedure, showing the benefit of periarticular anesthetic infiltration in pain reduction in the immediate postoperative period up to 48 hours post-procedure. Pain relief and functional recovery after surgery using the protocol described presented excellent security for pain control and functional recovery.
Superior pain relief provided by infiltration of analgesics for pain control over exclusively intravenous analgesia was demonstrated in a systematic review conducted by Jiang et al.[6] Twenty-one studies were included in this analysis; lack of standardization in the protocols for periarticular injection with multimodal drugs with regard to dose and application site was considered the most significant limitation of this meta-analysis.

Vendittoli et al.[12] demonstrated that the use of periarticular infiltration with multimodal drugs could result in less pain, improved functional recovery, and patient satisfaction. However, Koh et al.[13] observed that pain reduction was significant in the immediate postoperative period, with no improvement in functional results or patient satisfaction after 48 hours. Currently, multimodal management of perioperative pain has been the most common means of reducing the incidence of persistent postoperative pain. It should be noted that intra-articular analgesia has a fleeting effect and is not a substitute for other therapies after hospital discharge.[1,3,13,14].

Nevertheless, intra-articular intraoperative injection of multimodal analgesics has shown significant results in enhancing the analgesic effect without increased complications resulting from the use of oral or intravenous opioids. This control may significantly reduce the need to use opioids, and may improve patient satisfaction without apparent risks in the period following TKA surgery.[15] The greatest benefit demonstrated in this study as well as others found in the literature is reduced consumption of opioid medications such as tramadol and morphine sulfate. These drugs are frequently required in patients undergoing TKA because of the pain experienced by a large proportion of patients during this period.

Pharmaceutical synergy produces more effective analgesia by addressing pain through all its mechanisms. Epinephrine prolongs the action of local agents by decreasing absorption via vasoconstriction through its α-adrenergic effects. It can also reduce bleeding and postoperative hematoma. Morphine has central, regional, and local effects via its effect on opioid receptors. Local administration yields reduces the frequency of typical opioid side effects (for example, sedation, nausea, and respiratory depression) which occur through the opioid receptors. Clonidine works through its α2-adrenergic actions. This strengthens the action of local anesthetics and opioids through synergistic effects. By suppressing these physiological responses to surgery, pain and functional recovery are improved.[15-18.]

Limitations of this study include the sample in comparison with multi-center studies, and the focus on a specific and homogenous population. Further studies should be conducted in order to compare the analgesic drugs, defining the best protocol.

CONCLUSION

Use of periarticular infiltration in total knee arthroplasty reduces pain and improves functional capacity in the 48-hour period immediately following surgery when compared to oral and intravenous analgesia alone. We did not observe an increase in the incidence of side effects when the multimodal drug protocol was used on periarticular infiltration.

AUTHORS' CONTRIBUTIONS: Each author individually made significant contributions to the development of this manuscript. MZS (0000-0001-8097-8663)* and DS (0000-0003-3437-6180)* were the main contributors in writing the manuscript. POC (0000-0002-6697-7469)*, RJCF (0000-0001-5450-064X)*, and DS conducted the surgeries, monitored the patients, and gathered the clinical data. MZS and DS evaluated the data from the statistical analysis. DS, DPS (0000-0002-0518-0528)* and RAA (0000-0002-4667-6052)* conducted the bibliographical research, revised the manuscript, and contributed to the intellectual concept of the study. *ORCID (Open Researcher and Contributor ID).

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NEGATIVE-PRESSURE WOUND THERAPY IN THE TREATMENT OF COMPLEX INJURIES AFTER TOTAL KNEE ARTHROPLASTY

TERAPIA COM PRESSÃO NEGATIVA EM FERIDAS NO TRATAMENTO DE LESÕES GRAVES APÓS ARTROPLASTIA TOTAL DO JOELHO

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ABSTRACT

Objective: To present an experience with negative-pressure wound therapy (NPWT) in the treatment of surgical wounds in patients treated for infections after total knee arthroplasty (TKA) with or without dehiscence and prophylaxis in wounds considered at risk of healing problems. Methods: We prospectively evaluated patients with TKA infection with or without surgical wound dehiscence and patients with risk factors for infection or surgical wound complications treated with Pico® device for NPWT in addition to standard treatment of infection or dehiscence in our institution. We considered as an initial favorable outcome the resolution of the infectious process and the closure of the surgical wound dehiscences in the treated cases and the good progression of the wound without complicating events in the prophylactic cases. Results: We evaluated 10 patients who used Pico® in our service. All patients had a favorable outcome according to established criteria. No complications were identified regarding the use of the NPWT device. The mean follow-up of the patients after the use of the device was 10.5 months. Conclusion: The NPWT can be safely used in wound infections and complications following TKA with promising results. Long-term randomized prospective studies should be conducted to prove its effectiveness. ***Level of Evidence IV, Case Series.***

Keywords: Negative-pressure wound therapy. Arthroplasty, replacement, knee. Surgical wound dehiscence. Infection.

RESUMO

Objetivo: Apresentar uma experiência com a terapia com pressão negativa (TPN) no tratamento das feridas cirúrgicas de pacientes tratados por infecções em artroplastias totais do joelho (ATJ) associadas ou não à deiscência e como profilaxia nas feridas consideradas em risco de problemas de cicatrização. Métodos: Foram avaliados prospectivamente pacientes que apresentavam infecção de ATJ associada ou não à deiscência de ferida operatória e pacientes com fatores de riscos de infecção ou complicações de ferida cirúrgica tratados com dispositivo PICO® para TPN além do tratamento padrão da infecção ou deiscência em nossa instituição. Consideramos como desfecho favorável inicial a resolução do processo de infecção e o fechamento das deiscências de ferida operatória nos casos de tratamento e a boa evolução da ferida operatória, sem eventos complicadores, nos casos profiláticos. Resultados: Foram avaliados 10 pacientes que usaram PICO® em nosso serviço. Todos os pacientes apresentaram desfecho favorável de acordo com os critérios estabelecidos. Não foram identificadas quaisquer complicações com relação ao uso do dispositivo de TPN. A média de seguimento dos pacientes após o uso do dispositivo foi de 10 meses e meio. Conclusão: A TPN pode ser usada em complicações de ferida e infecção depois de ATJ de maneira segura e com resultados promissores. Estudos prospectivos randomizados prolongados devem ser realizados para comprovar sua eficácia. ***Nível de Evidência IV, Série de Casos.***

Descritores: *Tratamento de ferimentos com pressão negativa. Artroplastia do joelho. Deiscência da ferida operatória. Infecção.*

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INTRODUCTION

Total knee arthroplasty (TKA) is an increasingly common surgery. It is estimated that in 2030 nearly 3.5 million TKA procedures will be performed in the United States.[1] As the number of arthroplasties increases, the number of complications resulting from this procedure also rises, including surgical wound complications and infection.[2] Known risk factors for skin complications and infection after TKA include diabetes, obesity, poor nutrition, smoking, and especially prior surgeries.[2,3]

Among the measures recommended in the literature to reduce the risk of infection after TKA are the use of prophylactic antibiotics before the incision is made, removing hair with an electric surgical clipper and not a razor, appropriate antisepsis of the hands and forearms, strictly sterile technique, skin preparation with alcohol solution, control of comorbidities such as diabetes and malnutrition in the perioperative period, maintenance of normothermia during the procedure, and appropriate surgical technique which respects the dissection planes.[4]

Dr Camilo Partezani Helito and Dr Marco Kawamura Demange served as speaker for Smith Nephew in the last two years. All the others authors declare that there is no potential conflict of interest referring to this article.

Study conducted at Universidade de São Paulo, Faculdade de Medicina, Department of Orthopedics and Traumatology, Laboratório de Investigação Médica do Sistema Musculoesquelético, Knee Surgery Division, São Paulo, SP, Brazil.
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Once infection is diagnosed, treatment ranges from antibiotics to surgical procedures to clean the wound and remove the surgical implants.[5] Typically, treatments are long and involve losses in quality of life and function for patients as well as high costs for health services.[6,7]
One treatment modality for post-arthroplasty wounds that is becoming more widely known in the orthopedic literature is negative pressure wound therapy (NPWT).[8,9] Although its use is well established in other areas of medicine and orthopedics, particularly in cases of trauma and open fractures, its usage in the field of arthroplasty is not yet well-defined.[8-11]
The few studies on these devices in cases of primary arthroplasty do not allow definitive conclusions to be drawn about their use, and despite a theoretical benefit demonstrated by one recent review, no prospective studies clearly demonstrate their benefits.[8,9] Among the possible promising uses for NPWT in arthroplasty are applications in patients at high risk for wound complications, patients with established wound complications, patients with dehiscence or prolonged secretions, and patients with infections. Consequently, more studies are required to investigate each of these clinical situations.
The objective of this present study is to show our experience with NPWT in treating surgical wounds in patients with infections after TKA, associated with or independent of dehiscence, and also as a prophylaxis in wounds considered to be at risk for healing problems.

METHODS

Two profiles of patients treated in our service were evaluated: patients who presented TKA infection associated with or independent of surgical wound dehiscence, and patients with risk factors for infection or complications of the surgical wound. The study was approved by the institutional ethics board under process number 1247, and all patients in the study signed a consent form.
In the cases of infection, from the time of diagnosis the patients were treated according to the protocol for arthroplasty infection at our institution, which involves antibiotic therapy associated with surgical cleaning and debridement and optional removal of the implant. After the usual treatment, a NPWT device was placed on the wound as an additional measure.
In at-risk patients, the device was immediately installed after the surgical procedure while the patient was still in the surgical suite. The use of this device did not hinder patient participation in the standard rehabilitation they would have received if they did not use the device, since range of motion and gait were stimulated, except when treatment was contraindicated.
In this study we used a portable single-use PICO device (Smith & Nephew) that applies continuous negative pressure of 80 mmHg.[12] (Figure 1) After seven days (the working life of the device), we examined the wound and determined whether installation of a new device was necessary. This procedure was repeated every seven days when the device reached the end of its functional life. The total therapy time for each patient was quantified.
We considered resolution of the infection process and closure of dehiscenses in the surgical wound as favorable outcomes in the cases of treatment, and good progress of the surgical wound without complications when this therapy was used prophylactically.

RESULTS

We assessed 10 patients in our service who used the PICO device. NPWT was indicated in six of these cases for infection, in two cases for infection associated with dehiscence, and two cases in patients at risk. Patient data are summarized in Table 1. Four patients used the device for 14 days (two sessions) and six patients used it for seven days (one session). Mean patient use time was 9.8 days. No patient required NPWT for more than 14 days.

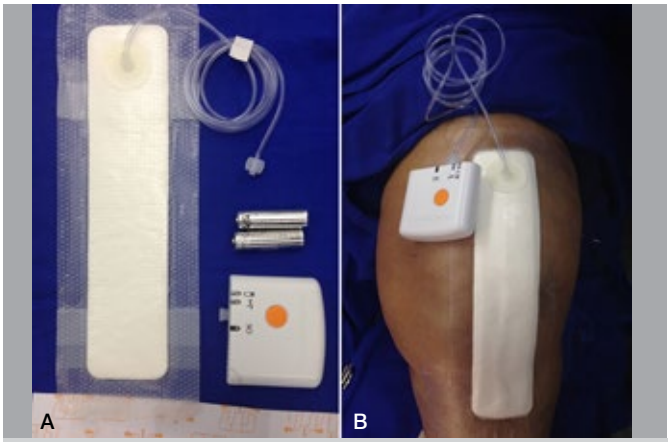

Figure 1. The PICO negative pressure dressing (A) and after application in a patient undergoing surgical cleaning of left knee after arthroplasty (B).

Table 1. Summary of assessed patient data.

Patient	Indication for NPWT	Comorbidities	Days NPWT used	Follow-up after use (months)
1	Infection	RA, HBP, DM	14	14
2	Infection	HBP	7	14
3	Prophylactic in at-risk patient	HBP, DM, Obesity	7	13
4	Infection	DM, Obesity	7	12
5	Infection	HBP, DM	7	11
6	Infection	HBP, DM	7	10
7	Infection + dehiscence	HBP, DM	14	10
8	Infection	Gout	14	9
9	Infection + dehiscence	RA	14	9
10	Prophylactic in at-risk patient	HBP, DM, Chagas	7	3 (death)

As for outcomes, all patients had favorable outcomes according to the criteria: the two patients who received NPWT as a prophylaxis demonstrated healing of the surgical wound without complications, the two cases of dehiscence associated with infection demonstrated closure of the wound and control of the infectious process without the need for surgical intervention, and the six patients who underwent surgery to treat infection showed clinical improvement in infection and good healing. (Figures 2, 3, and 4).
We did not identify any complications related to the NPWT device. Average patient follow-up time after the use of the device was 10.5 months, ranging from 3 to 14 months. The patient who received three months of follow-up died from causes unrelated to the knee surgery three months after initial treatment, and the wound situation was resolved at that time.

DISCUSSION

The main finding of this study is that NPWT can be used safely to treat post-TKA wound complications and infection without complications and without impeding patient rehabilitation, with promising initial results.
The active mechanisms of NPWT described in the literature which are potentially significant in the use of this therapy in arthroplasty include removal of fluid and reduction of edema, dead space, and soluble inflammatory molecules,[13] mechanical stabilization, reduction of tension on the wound,[14] and increased blood flow and angiogenesis.[15]

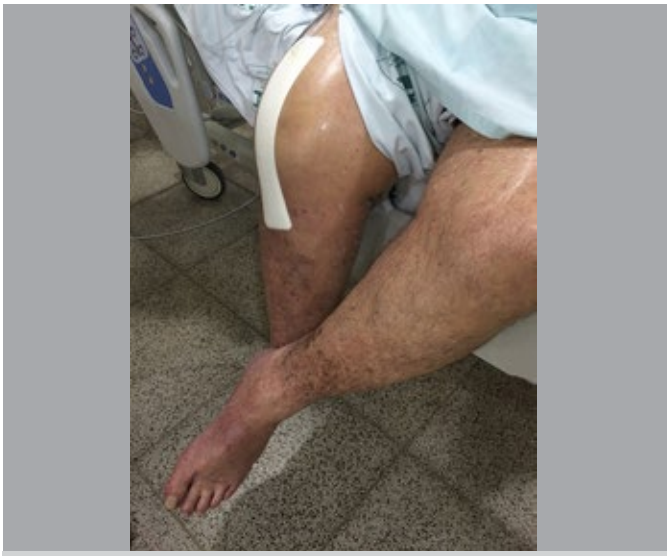

Figure 2. Patient with PICO NPWT dressing on right knee. Note that the dressing does not interfere in range of motion activities during the postoperative period.

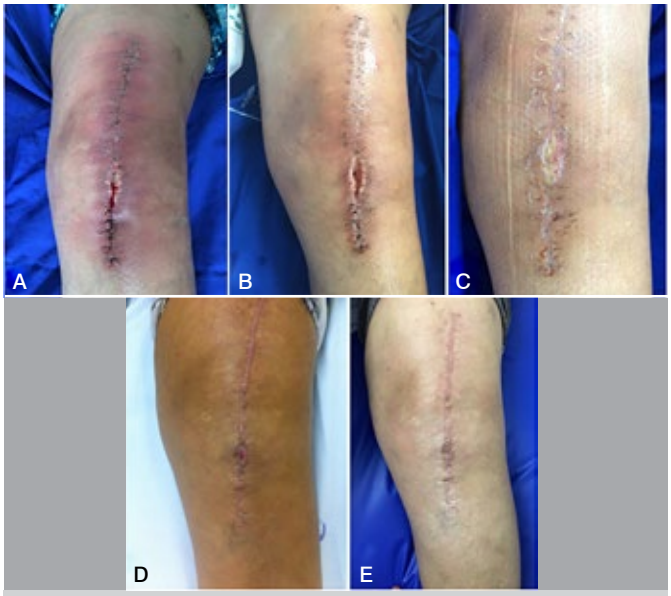

Figure 3. Clinical progress of surgical wound in patient treated with PICO NPWT dressing after dehiscence associated with infection. Photos show initial moment (A) when treatment was indicated and progress at 7 (B), 14 (C), 21 days (D), and 3 months (E). The patient used the dressing for 14 days.

The potential to control wound complications is significant since this is associated with a great increase in the risk of infection. Patel et al.[16] estimated that each day of persistent drainage represents a 42% increase in the chance of infection, and Saleh et al.[17] calculated that after the fifth day of secretion, this chance increases 12.7-fold. In a series of 109 cases of hip arthroplasty with persistent post-operatory secretion, Hansen et al.[18] found that 76% resolved without surgery after negative pressure therapy used for an average of two days (range: 1–10 days). In another series of hip arthroplasties, Pachowsky et al.[19] observed less seroma in ultrasound in patients who received NPWT. There is no direct relationship between the amount of secretion and post-operatory infection, but patients with prolonged drainage of secretions from the wound (5 or more days post-procedure) have a higher risk of infection.[17] The decrease in seroma may have been a protective factor for these patients. It is

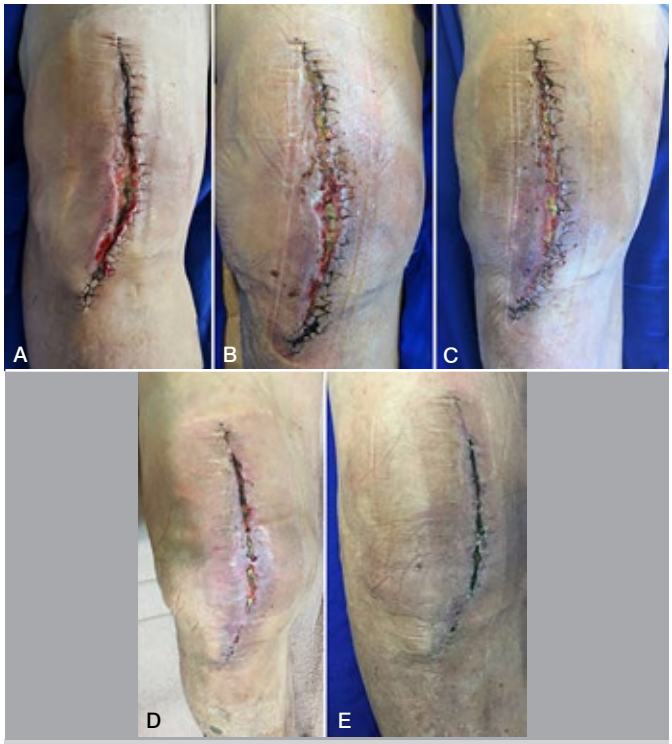

Figure 4. Clinical progress of surgical wound in patient treated with PICO NPWT dressing after dehiscence associated with infection. Photos show initial moment (A) when treatment was indicated and progress at 7 (B), 14 (C), 21 (D), and 30 days (E). The patient used the dressing for 14 days.

important to note that NPWT should not delay surgical treatment of wound complications or the surgical site in arthroplasties, since as shown by Jaberi et al.,[20] delayed surgery in the case of secreting wounds leads to an increased risk of failure for treatments involving surgical debridement and irrigation.

In a non-randomized retrospective study, Cooper et al.[21] compared the use of NPWT with the use of antibiotic dressings in revision arthroplasties of the knee and hip and found fewer wound complications (6.7% versus 26.9%) and fewer instances of infection in the surgical site (3.3% versus 18.5%) with the use of negative pressure therapy.

As for the use of NPWT as an adjunct to treatment of infections in arthroplasty, only small case series have been published,[22-24] showing encouraging results similar to those of this present study. One randomized study using NPWT in knee arthroplasty had to be halted due to the formation of blisters on the skin surrounding the wound.[25] Because of this complication, changes were made to avoid blister formation, and this technology was incorporated into the new devices. The PICO NPWT system consists of a multiple-layer silicone dressing designed to avoid the formation of blisters or maceration of the wound.[26] In our series, we did not observe any complications directly related to NPWT, similar to the other studies which used the same updated device.[26,27]

Current contraindications to the use of NPWT include exposed vessels or nerves and unexplored fistulas. Patients with an increased risk of bleeding or who are using anticoagulants should be carefully monitored if they use the device. Circumferential bandages should also be avoided.[9]

Another benefit of the type of therapy used in this study is the possibility of outpatient treatment. Once the dressing is placed, the patient does not require daily dressing changes and the unit can be easily transported. Payne et al.[28] studied the use of these devices in a wide variety of infections and skin lesions and found a potential

cost reduction since patients do not require hospitalization. Dal-Paz et al.[6] found a significant increase in the costs of treating infections after knee arthroplasty in a tertiary hospital, so that investments in patient safety can bring significant savings to the health system. Matsumoto et al.[27] concluded that prophylactic NPWT in high-risk patients was reasonable, considering the high costs of treatments resulting from wound complications in arthroplasties.

Although NPWT is widely used in other areas of medicine and is related to improved healing and limb preservation in the treatment of open fractures, it has not yet been proven for use in arthroplasty surgery.[9] A pilot study conducted by Gillespie et al.[29] in primary hip arthroplasties suggested that a randomized trial with 900 patients would be required to detect differences in the incidence of complications such as infection, due to the low absolute risk of this complication. Several prospective studies and randomized trials are currently underway to test the efficacy of this therapy.

Despite the small number of cases, the initial results presented in this study are promising. In treating infections, NPWT should be used as an additional tool for patient treatment, and in no way should substitute the gold standard treatments such as antibiotic therapy, surgical treatments, and removal of the implants if necessary.[5] Our series presented two incidents of dehiscence: one was more superficial and the patient maintained the implant, and the other was deeper since the patient had a cement spacer. Both were successfully treated without the need for a surgical approach. These patients were treated with NPWT for 14 days, since only one dressing was not sufficient. The use of an additional, new dressing should be expected in such high-complexity cases.

Considering eventual recidivism, although these patients were not followed for a long time we focused on healing and skin complications and followed the usual protocols recommended in the literature for treating prosthesis infections, but these cases continue to be monitored for a longer follow-up period in relation to relapse. Limitations of this study include the small number of patients and short follow-up time, as well as the heterogeneous sample and the absence of a control group. Nevertheless, we believe that the study is important to demonstrate the possible complications and indications of this therapy.

CONCLUSION

NPWT can be used safely to treat wound complications and infections after knee arthroplasty, with promising results. Long-term prospective randomized studies are still required to prove its effectiveness.

AUTHORS' CONTRIBUTIONS: Each author individually made significant contributions to the development of this manuscript. CPH (0000-0003-1139-2524)* was responsible for the literature review, participation in the surgical procedures, and supervision. DKB (0000-0002-7281-2054)* participated in the literature review and data analysis. PNG (0000-0002-5855-0975)* and MBB (0000-0002-4468-9693)* participated in the surgical procedures and drafted the article. JRP (0000-0003-0287-4548)* and MKD (0000-0003-1999-9478)* guided and supervised all phases of work. *ORCID (Open Researcher and Contributor ID).

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STUDY OF THE ANTEROLATERAL LIGAMENT OF THE KNEE IN FORMALIN-EMBEDDED CADAVERS

ESTUDO DO LIGAMENTO ANTEROLATERAL DO JOELHO EM CADÁVERES FORMOLIZADOS

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ABSTRACT

Objective: To verify the incidence and characterize morphologically the anterolateral ligament of the knee (ALL) in cadaveric samples of the collection of the Laboratory of Anatomy of the Department of Morphology of the Universidade Federal do Espírito Santo. Methods: Dissections and cross sections were performed for mesoscopic analysis of the anterolateral region of 15 knees preserved in 4% formalin solution in order to identify the ALL. Results: After dissection of the skin and subcutaneous tissue of the knee anterolateral region, it was possible to identify the iliotibial tract (ITT), the patellar ligament and the femoral biceps tendon. The ITT was removed from the Gerdy tubercle and the following structures were visualized: knee joint capsule, fibular collateral ligament and popliteal tendon. However, the ALL was not identified in any of the samples. Conclusions: The ALL could not be identified in any of the specimens studied, either through dissection or mesoscopic analysis. ***Level of Evidence III, Diagnosis Studies – Investigation of an Exam for Diagnosis.***

Keywords: Knee. Ligaments, articular. Joint instability. Cadaver.

RESUMO

Objetivo: Verificar a incidência e possivelmente caracterizar morfologicamente o ligamento anterolateral do joelho (LAL) em amostras cadavéricas do acervo do Laboratório de Anatomia do Departamento de Morfologia da Universidade Federal do Espírito Santo. Métodos: Foram realizadas dissecações e secções transversais para análise mesoscópica da região anterolateral de 15 joelhos conservados em solução de formalina a 4% a fim de identificar o LAL. Resultados: Após a dissecação da pele e da tela subcutânea da região anterolateral dos joelhos foi possível identificar o trato iliotibial (TIT), o ligamento patelar e o tendão do músculo bíceps femoral. Após a desinserção do TIT no tubérculo de Gerdy as seguintes estruturas foram visualizadas: cápsula articular do joelho, o ligamento colateral fibular e o tendão do músculo poplíteo. Entretanto, o LAL não foi identificado em nenhuma das amostras. Conclusões: O LAL não pôde ser identificado em nenhum dos espécimes estudados, seja através da dissecação ou da análise mesoscópica. ***Nível de Evidência III, Estudos Diagnósticos - Investigação de um Exame para Diagnóstico.***

Descritores: *Joelho. Ligamentos articulares. Instabilidade articular. Cadáver.*

Citation: Fardin PBA, Lizardo JHF, Baptista JS. Study of the anterolateral ligament of the knee in formalin-embedded cadavers. Acta Ortop Bras. [online]. 2017;25(2):89-92. Available from URL: http://www.scielo.br/aob.

INTRODUCTION

In 1879, Segond[1] described an avulsion fracture of the proximal anterolateral tibial region and mentioned the existence of a fibrous and resistant band that becomes taut by medial rotation. The term "Segond fracture" consequently describes an avulsion fracture of this region. After this description was made, some studies demonstrated the presence of a ligamentous structure between the lateral condyle of the femur and the anterolateral tibial region.[2-11] In 2007, Vieira et al.[8] introduced the term anterolateral ligament (ALL) of the knee to describe the ligament that originates in the lateral condyle of the femur anterior to the fibular collateral ligament (FCL) which has an oblique path in the anteroinferior direction with insertion in the proximal tibia between Gerdy's tubercle and the head of the fibula.

As a result of injury to the anterior cruciate ligament (ACL), many patients present anterolateral knee instability even after ligament reconstruction surgery.[12] Considering that the ALL is not normally approched in reconstruction surgeries, it may be involved in destabilization of the knee after injury.[1,13] This led to a broad scientific search to confirm and characterize the ALL.

Consequently, proper anatomical description of the ALL are extremely important in the clinical approach to knee ligament injuries, since the ALL seems to be involved in anterolateral stabilization and in limiting rotational movements of the knee.

Therefore, the objective of this study was to verify the incidence of the ALL in formalin-embedded cadavers, and after identification describe its characteristics and anatomical relationships.

All the authors declare that there is no potential conflict of interest referring to this article.

Work carried out at Laboratory of Applied Morphology (LEMA) at UFES, Vitória, ES, Brazil.
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MATERIALS AND METHODS

This research was submitted to Plataforma Brasil and approved (Opinion 1,316,575). We studied 15 knees (8 right and 7 left) routinely fixed in 4% formalin solution to the human anatomy collection at the Department of Morphology at the Centro de Ciências em Saúde (CCS) at the Universidade Federal do Espírito Santo (UFES). With regard to the morphological characteristics of this collection, the average age in this sample was 50 years and the specimens were taken from male individuals. Only knees containing all cutaneous and fascial strata were included in the study; in other words, only those that had skin, subcutaneous tissues, and deep fasciae intact were selected. Specimens which had undergone any type of previous dissection, had malformations, scarring, or any sign of injury were not included in the sample.

Dissection was performed carefully from the anatomical position and followed the methodology of Claes et al.[10] First, skin and subcutaneous tissue were dissected from the medial to the lateral region of the knee in order to identify the iliotibial tract (ITT), the patellar ligament, and the tendon of the biceps femoris muscle (Figures 1A and B). The ITT was sectioned 5 cm from the lateral epicondyle of the femur and detached from Gerdy's tubercle in order to permit identification of the joint capsule, the FCL, and the popliteus muscle tendon. (Figure 1C) At this point of the dissection we expected to be able to identify the ALL, but this structure was not seen in the first 3 samples, contrary to the results found in the literature.[10,14]

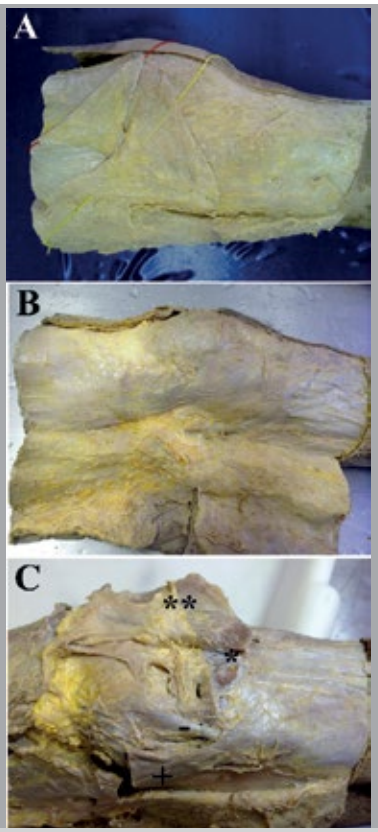

Figure 1. Photographs of the anterolateral region of the knees, right antimere. (A) Note the strata in the anterolateral region of the knee: skin folded back to the side, subcutaneous tissue folded back and marked by the yellow line, the iliotibial/fascia lata tract, partially folded back and marked by the red line. (B) Note that the skin and the subcutaneous tissue were folded back to demonstrate the iliotibial/fascia lata tract, patella, patellar ligament, and lateral retinaculum and crural fascia; (C) dissection of the iliotibial tract and the knee joint capsule: (*) detached Gerdy's tubercle; (**) iliotibial tract and articular capsule of the knee, folded back; (-) fibular collateral ligament; (+) tendon of the biceps femoris muscle.

With this in mind, the remain specimens (n=12) were dissected to expose the ITT, the patellar ligament, and the tendon of the biceps femoris muscle (Figures 2A and B). Next, an anatomical block of the anterolateral region of the knee was extracted via cross sections of approximately 7 cm at the level of Gerdy's tubercle and the lateral epicondyle of the femur, and sagittal sections of approximately 7 cm at the level of the lateral edge of the patella and the posterior edge of the femoral condyle and the fibula head (Figure 2C). This block was carefully removed and underwent micro-dissection and analysis in a stereomicroscope (Stemi2000C and AxioVision image analysis software, Zeiss, Germany - Laboratory of Applied Morpology - LEMA). A cross section was performed along the articular line of the knee to permit micro-dissection, identification, and isolation of the anterolateral structures such as the synovial membrane, the joint capsule, and the fibrous bands which form the ligaments in the region in order to identify the ALL.

RESULTS

This methodology allowed easy identification of the skin, subcutaneous tissue, ITT, patellar ligament, tendon of the biceps femoris muscle, FCL and its relation to the tendon of the popliteus muscle, the joint capsule, and the lateral meniscus (Figures 3A-D); however, in none of the samples we were able to isolate the ALL as a distinct fibrous band.

DISCUSSION

Although the first description of the ALL of the knee was made by Segond[1] in 1879, recent studies have given to this structure international prominence in the field of anatomy and surgery. In this context, it is important to highlight that all these investigations used

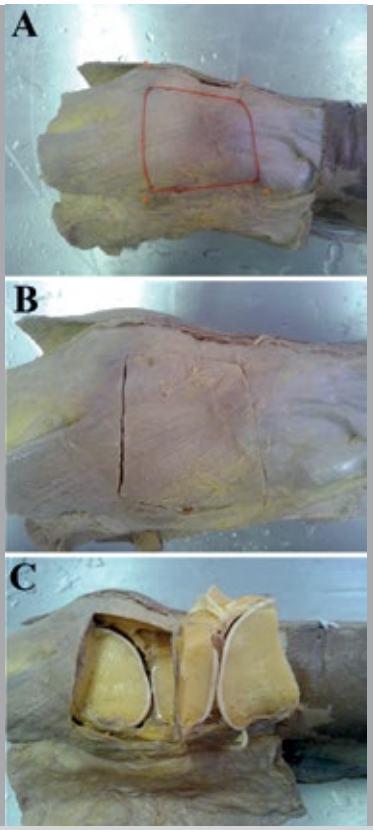

Figure 2. Photographs of the anterolateral region of the knees, right antimere. (A) Demarcation of the area of the block to be removed; (B) Sectioning of the block; (C) Careful removal of the block for mesoscopic study.

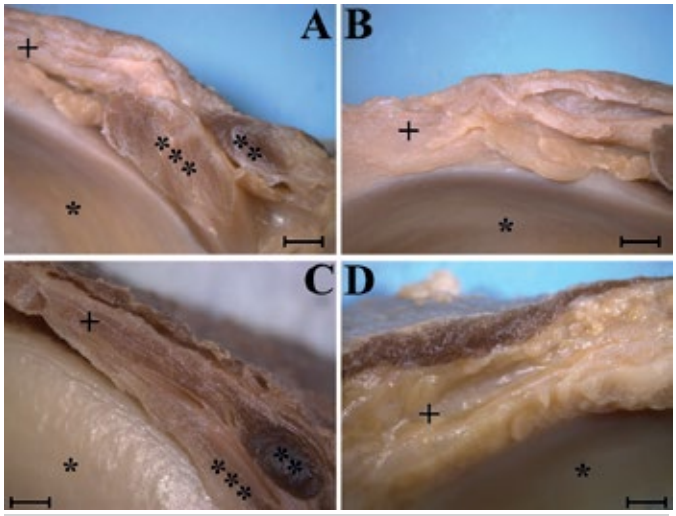

Figure 3. Mesoscopic-level photographs of the anterolateral region of 4 knees, right antimere (A-D). Scale bar 2mm. (*) Lateral meniscus, (**) fibular collateral ligament, (***) popliteus muscle tendon. (+) Indicates the presumed region of the anterolateral ligament of the knee, namely the region between the joint capsule and the lateral retinaculum. Note that there is no structure compatible with a ligament, although this region comparatively presents a denser constitution in A and C, and is more lax in B and D. Medial to the region indicated by the (+) is the synovial membrane, and laterally the iliotibial tract.

(in whole or in part) samples from fresh cadavers[10,14-16] or studied living individuals through images such as magnetic resonance.[15,17,18] However, there is no consensus among the results of these studies on the anatomical characteristics of the ALL:[10,16,19,20] while some studies verified the presence of the ALL in most of the samples,[10,15,16] others did not identify this ligament in even half of the specimens,[21,22] and one study show no ALL in their samples.[19] Furthermore, contradictory results exist within the same investigation: Vincent et al.[9] identified the ALL of the knee as a capsular structure in individuals during arthroscopic knee surgery, while in its cadaver sample this ligament was found to be intracapsular. Moreover, there is no consensus about the precise location, form, and fixation of the ALL, unlike other ligaments in this region.

We were motivated by these contradictory results, and initially we adopted the dissection method which was used in other studies.[10,23] Even though the same method of Claes et al.[10] and Daggett et al.[23] was adopted, we were not able to identify the ALL in any of our specimens, in contrast with the findings by these authors. In the latter study, the authors dissected and carefully folded back the ITT in order to avoid interference with the attachment of the ALL, since this ligament is presumably adhered to the ITT. Next, Daggett et al.[23] were able to identify the ALL as originating in the lateral epicondyle of the femur and inserting between Gerdy's tubercle and the fibular head. However, these authors obtained better visualization of this anatomy after sectioning the knee capsule, where it was seen that the ligament originates posterior to the lateral epicondyle and also inserts into the lateral meniscus, in addition to the insertions which have already been described. Again, although we used the same careful dissection technique, it was not possible to verify the ALL. It should be noted, however, that when analyzing the images obtained by Claes et al.[10] and Daggett et al.[23] using similar dissection techniques, the structures referred to as the ALL of the knee are not identical: while Claes et al.[10] showed a chordoid and cylindrical structure, Daggett et al.[23] showed the ALL flat or laminar with less precise form. This may suggest an artifact of the dissection with consequent bilamination of the ITT, since the authors themselves stated that the ITT should be carefully dissected considering that the ALL is closely inserted into its deep surface.[23]

The study conducted by Shea et al.[20] also featured contradictions between the results and the discussion; these authors identified the ALL in only 1 of the 8 specimens studied (specimen age: 3 and 4 months, 1, 2, 3, 8, and 10 years), even though they used the same dissection process which was applied in this study and by the other authors.[10,23] As an argument, Shea et al.[20] stated that this result arises from the possibility that the ALL is a ligament which develops during growth and therefore would only be present in older specimens, which would explain the absence of the ligament in the samples studied. However, their data show that the one specimen in which it was possible to identify the ALL was only 1 year of age. The hypothesis that the ALL might actually be a thickening of the joint capsule and not necessarily a ligament[24] would explain the discrepant results derived from studies involving this ligament. In fact, the data obtained so far are not sufficient to morphologically characterize the ALL as a ligament. Corroborating this idea as well as our results, Capo et al.[19] was unable to identify the ALL in any of the cadaver samples they studied using ultrasound. What these authors observed was a structure located in the anterolateral region of the knee that was suggested as a thickening of the ITT or even a fascia, and although the specimens were subsequently dissected, the absence of the ALL was confirmed.

Considering that dissection did not allow us to identify the ALL in the present study, we used mesoscopy, a methodology which has not yet been explored in the literature. It is important to highlight that micro-dissection using mesoscopy, after creating a transverse section along the joint, presented the intact strata of the anterolateral region of the knee, completely eliminating the bias of bilaminating the fascial strata or the ITT at the time of dissection. Again, according to the results obtained by the dissection the ALL was not identified. One limitation of our study may be the use of a restricted sample compared with previous studies,[10,15,16] although several current studies have used fewer specimens.[11,19,20,23]

The methodology applied in this present study allowed us to assert that it was not possible to identify the ALL of the knee as an isolated structure with specific anatomical features (like other ligaments in the region), as has been indicated in research in this area.[10,14,15] Therefore, the results we obtained along with the methodology we employed characterize the original nature of our research.

In conclusion, we reaffirm that the primary and possible explanation for our conflicting results are the artifact of dissection with consequent bilamination of the structures of the anterolateral region: namely the ITT, the lateral retinaculum of the knee, or the knee joint capsule. Consequently, the structure known as the ALL would not necessarily be an individualized ligament but rather part of another structure of the knee which in the cross section does not resemble the anatomical characteristics of the other ligaments of the region.

CONCLUSION

It was no possible to indentify the ALL of the knee as an individualized ligament in formalin-embedded cadavers. This result does not conclude the discussion, but suggests the need for future research using larger samples that effectively represent a population.

AUTHORS' CONTRIBUTIONS: Each author contributed individually and made significant contributions to the development of this manuscript. JHFL (0000-0001-7768-3098)* and JSB (0000-0003-0514-8170)* were the main contributors in the drafting of this manuscript. JHFL, JSB, and PBAF (0000-0003-3623-2674)* conducted the dissection and mesoscopic analysis, evaluated the data from the statistical analysis, conducted the bibliographical research, revised the manuscript, and contributed to the intellectual concept of the study. *ORCID (Open Researcher and Contributor ID).

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SPORTS INJURIES AMONG AMATEUR ATHLETES AT A BRAZILIAN UNIVERSITY

LESÕES ESPORTIVAS EM ATLETAS AMADORES DE UMA UNIVERSIDADE BRASILEIRA

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ABSTRACT

Objective: To obtain information on the incidence and nature of sports injuries at a Brazilian university. Method: Data from 396 student amateur athletes (61% male) playing 15 different sports during the 2013 season were retrospectively evaluated. Subjects completed the National Collegiate Athletic Association Injury Surveillance System questionnaire at the conclusion of the 2013 sports season. Injuries that resulted in at least one day of time lost were included. Exposure was defined as one student amateur athlete participating in one practice or game and is expressed as an athlete-exposure (A-E). Results: Injury rates were significantly greater in games (13.13 injuries per 1000 A-Es, 95% CI = 10.3–15) than in practices (4.47 injuries per 1000 A-Es, 95% CI = 3.9–5.1). The mechanisms that accounted for the most injuries in games and practices were player contact (52.9%) and non-contact (54.5%), respectively. Ankle ligament sprains were the most common injury (18.2% of all reported injuries). A relatively high incidence of anterior cruciate ligament injury was also observed (0.16 injuries per 1000 A-Es). Conclusion: Brazilian student amateur athletes are at great risk of sustaining non-contact injuries such as ankle sprains and anterior cruciate ligament injuries. ***Level III of Evidence, Study of non consecutive patients; without consistently applied reference "gold" standard.***

Keywords: Athletic injuries. Epidemiology. Ankle. Anterior cruciate ligament.

RESUMO

Objetivo: Obter a incidência e as características das lesões esportivas em atletas de uma universidade do Brasil. Métodos: Os dados de 396 atletas amadores universitários (61% homens) de 15 modalidades, referentes ao ano de 2013, foram avaliados retrospectivamente. Os atletas responderam o questionário ISS (Injury Surveillance System) adotado pela NCAA (National Collegiate Athletic Association) no final da temporada esportiva de 2013. Foram incluídas as lesões que resultaram em pelo menos um dia de afastamento. A exposição foi definida como um atleta amador universitário participando de um treino ou jogo e foi expressa como uma exposição-atleta (E-A). Resultados: As taxas de lesões em jogos (13,13 lesões por 1000 E-A, 95% IC = 10,3 - 15) foram significantemente maiores do que em treinos (4,47 lesões por 1000 E-A, 95% IC = 3,9 - 5,1). Os mecanismos envolvidos na maioria das lesões em jogos e em treinos foram contato com outro jogador (52,9%) e sem contato (54,5%), respectivamente. A torção de tornozelo foi a lesão mais comum (18,2% entre todas as lesões). Observou-se alta incidência de lesões do ligamento cruzado anterior do joelho (0,16 lesões por 1000 E-A). Conclusão: Os atletas amadores universitários brasileiros têm maior risco de sofrer lesões sem contato, como torção de tornozelo e lesão do ligamento cruzado anterior. ***Nível de Evidência III, Estudo de pacientes não consecutivos; sem padrão de referência "ouro" aplicado uniformemente.***

Descritores: *Traumatismos em atletas. Epidemiologia. Tornozelo. Ligamento cruzado anterior.*

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INTRODUCTION

Since 1982, The American National Collegiate Athletic Association (NCAA) has supported an Injury Surveillance System (ISS), which collects injury and exposure data from 16 sports.[1] Over time, the data collected from ISS turned to be one of the most important source of knowledge in the sports medicine field.

One of the most serious sports injuries, anterior cruciate ligament (ACL) tear, had its mechanism and gender distribution elucidated by ISS by a 5 year study with basketball and soccer players from NCAA as subjects.[2] In addition to orthopedics and sports medical areas, other ones were supported by data from ISS. The prevalence of sudden cardiac death[3] and the effects of sports related concussions in collegiate athletes,[4] both topics of increasing interest in the literature, were addressed by ISS and published in journals of great impact.

Data regarding sports injuries have resulted in numerous successful injury prevention initiatives, including new models of football helmets to protect players from concussions[5] and equilibrium exercises to prevent ankle sprains in volleyball and basketball players.[6] This is in agreement with the 4 step injury prevention model proposed by van

All the authors declare that there is no potential conflict of interest referring to this article.

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Mechelen et al.,[7] in which we: (1) identify the problem, (2) establish etiology and mechanisms, (3) develop, evaluate, and implement interventions, and (4) reevaluate the effect via continued surveillance. Sports injuries preventive measures have improved across the years. The "American Academy of Orthopaedic Surgeons" (AAOS) and the "American College of Sports Medicine" (ACSM) currently support neuromuscular training in girls who play soccer to help reduce the rate of ACL injury.[8] Besides, recently, evidence of the efficacy of such programs in male soccer players have also been found.[9] The purpose of this study is to get information on the incidence and on the nature of injuries student athletes get in sports practicing at a Brazilian University. In the future, this study may allow adoption of injury prevention strategies similar to those implemented by the NCAA's ISS.[1]

METHODS

The study participants were 427 student amateur athletes who were official graduating students from either the Medical School or from The Physical Education School of the same Brazilian university who were practicing at least one of the 15 sport modalities offered by these schools in 2013. Athletes who were not official graduating students were excluded (e.g., athletes who had already graduated). An appropriate institutional review board approved the project (CAPPesq 513.548 – 22/01/2014) and each participant provided written informed consent prior to participation. The study is in accordance with the Helsinki Declaration of 1975, which was revised in 1983. Data composed of exposures and injuries regarding the 2013 season were collected retrospectively by the adoption of NCAA's ISS questionnaire.[1] The athletes answered the questionnaire after the last practice or game of the 2013 season. (Appendix 1)

A reportable injury had to meet the following criteria: (1) injury occurred as a result of participation in a university practice or game in 2013 and (2) injury resulted in restriction of the student-athlete´s participation or performance for one or more days beyond the day of injury.[1] An exposure was defined as one athlete participating in one practice or one game (athlete-exposure, A-E).[1]

Quantitative data concerning exposure in games was obtained by summing up the number of athletes who took part in each game in 2013. The quantitative data concerning exposure in practicing was obtained by multiplying the total number of student athletes by the number of practicing sessions in 2013, and afterwards, subtracting the number of absences from the result of the multiplication. Both game and practicing exposure data were calculated, separately, for each type of sport. The calculations were based on the ISS exposure report.[1] All the information necessary to obtain the exposure data was provided by the athletes by answering a questionnaire.

A retrospective analysis was carried out after injury and exposure data compilation. Outcomes included game and practice injury rates (both overall and by sport), injury mechanism (non-contact, other contact, player contact and unknown), the distribution of injuries by body part (head and neck, upper extremity, trunk and back, lower extremity and other system), and the rates of select injuries (ankle ligament sprains and anterior cruciate ligament) by sport.

Injury rates were expressed as the number of injuries per 1000 A-Es,[10] with a confidence interval of 95%. Data regarding injury mechanism and the distribution of injuries by body part were determined by percentages.

RESULTS

Sample characteristics

Among the 427 student athletes included in the study, 396 (92.8%) answer the questionnaire and so participated as subjects. Among those subjects, 241 (60.9%) were men and 155 (39.1%) were women, with an overall mean age of 24.15 (±5.63) years old. Table 1 shows the distribution of athletes across 15 sports modalities. Most sports, including indoor soccer, handball, volleyball, basketball, athletics, swimming, table tennis, karate and tennis have both men´s and women´s teams. Rugby, judo and water polo include only men´s teams, while softball is composed of only a women´s team.

Injuries Rates

Among the 396 subjects who answered the questionnaire, 228 (57.6%) suffered at least one injury. Among those who suffered at least one injury, 68% (156) suffered just one injury, 23% (52) suffered two injuries, 8% (17) suffered three injuries and 1% (3) suffered four injuries. Altogether, in 2013, 59,491 exposures and 323 injuries were totaled.

Across all sports, the game injury rate (13.13 per 1000 A-Es, 95% CI = 10.3 – 15) was 2.93 times higher than the practice injury rate (4.47 per 1000 A-Es, 95% CI = 3.9 - 5). These rates equate to one injury every four games and one injury every 10 practices for a team of 20 participants.

Overall practice and game injury mechanisms are shown in Figure 1. The mechanism that accounted for the majority of injuries in games was player contact (52.9%) and in practice was non-contact (54.5%).

Table 1. Number and percentage of athletes by sport.

Sports	Number and percentage of athletes
Indoor Soccer	73 (18.4%)
Handball	69 (17.4%)
Volleyball	59 (14.8%)
Basketball	56 (14.1%)
Soccer	45 (11.3%)
Rugby	31 (7.8%)
Athletics	30 (7.5%)
Softball	23 (5.8%)
Water Polo	21 (5.3%)
Swimming	20 (5%)
Baseball	16 (4%)
Judo	13 (3.2%)
Table Tennis	10 (2.5%)
Karate	10 (2.5%)
Tennis	6 (1.5%)

Note: The sum of percentages is more than 100% due to the fact that 22.7% of student-athletes played two modalities.

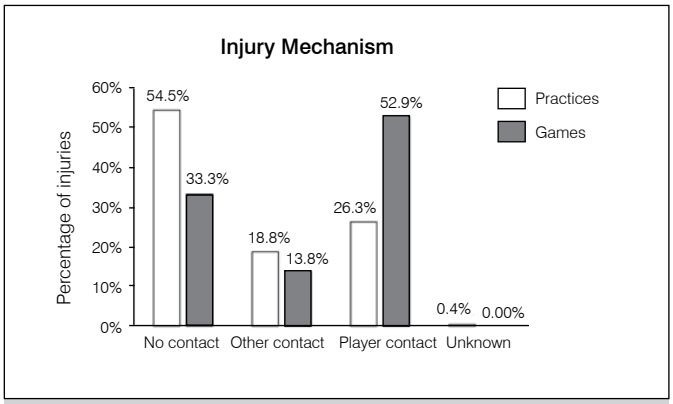

Figure 1. Distribution (percentages) of injuries by injury mechanism for practice and games for 15 sports in 2013. Player contact = contact with another competitor; Other contact = contact with playing surface, apparatus, ball or with other in environment (e. g., wall, fence, spectators); No contact = no apparent contact (rotation about planted foot) or no apparent contact (other).

The overall distribution of injuries by body part is shown in Figure 2. In both practices and games, more than 50% of all reported injuries were in the lower extremity. The ankle (18.2%) and knee (11.2%) accounted for the most injuries.

Game and practice injury rates by sport are shown in Figure 3A-B. For games, rugby had the highest rate of injury (42.42 per 1000 A-Es) and athletics had the lowest (3.97 per 1000 A-Es). For practice, judo had the highest rate of injury (13.47 per 1000 A-Es) and swimming had the lowest (0.81 per 1000 A-Es). Swimming, tennis and karate presented injuries only in practice, while table tennis did not present any practice or game injuries.

Rates of Select Injuries (Ankle Ligament Sprains and Anterior Cruciate Ligament Injuries) by Sport

Table 2 and 3 show the frequency, distribution and rates of select injuries (ankle ligament sprains and ACL injuries, respectively). Ankle ligament sprains were reported 59 times. These injuries accounted for approximately one quarter of all injuries in soccer, volleyball and indoor soccer. Soccer (2.33 per 1000 A-Es) and volleyball (2.11 per 1000 A-Es) had the highest rates of ankle ligament sprains. Regarding ACL injuries, 10 injuries were reported. Basketball (0.45 per 1000 A-Es) and handball (0.38 per 1000 A-Es) had the highest rates. (Table 3)

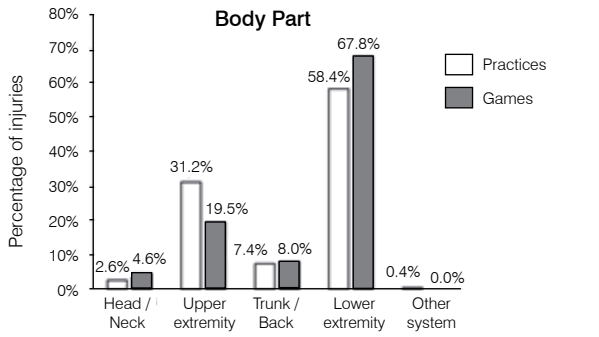

Figure 2. Distribution (percentages) of injuries by body part for games and practices for 15 sports in 2013.

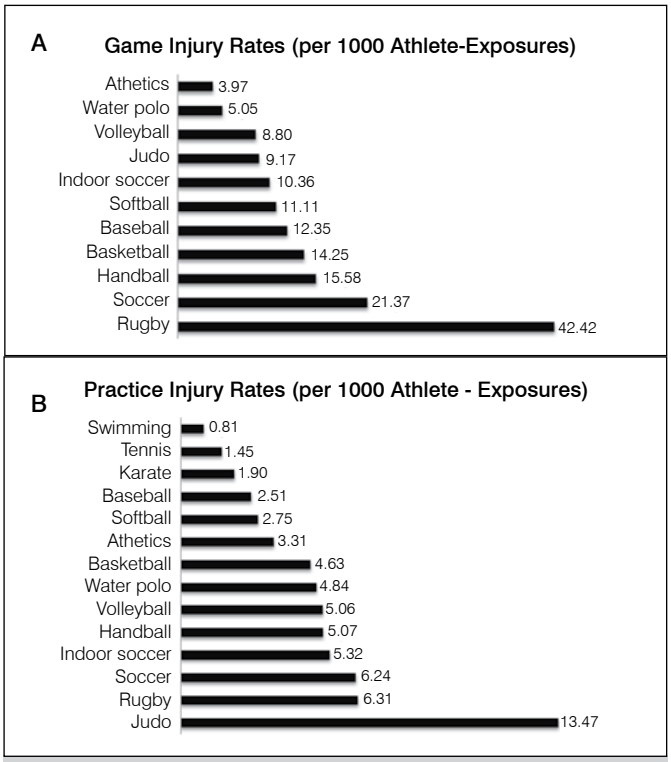

Figure 3. Overall (A) game and (B) practice injury rates by sport in 2013.

Table 2. Frequency, distribution, and rates of ankle sprains in games and practice combined in 2013.

Ankle ligament sprains	Frequency	Percentage of all injuries	Injury rate per 1000 athlete-exposures	95% Confidence interval
Soccer	11	26.8	2.33	0.9 - 3.7
Volleyball	9	25.0	2.11	0.7 - 3.5
Rugby	6	19.3	1.98	0.4 - 3.6
Judo	2	14.2	1.86	-0.8 - 4.5
Indoor Soccer	11	22.9	1.37	0.5 - 2.2
Basketball	9	21.9	1.35	0.5 - 2.3
Handball	9	16.9	1.14	0.4 - 1.9
Softball	1	9.0	0.26	-0.3 - 0.8
Athletics	1	5.0	0.16	-0.2 - 0.5
Total ankle ligament injuries	59	18.2*	0.99*	0.99 - 1.0*

These data include all sports, not just sports that presented ankle ligament sprains.

Table 3. Frequency, distribution, and rates of anterior cruciate ligament injuries in games and practice combined in 2013.

Anterior cruciate ligament injuries	Frequency	Percentage of all injuries	Injury rate per 1000 athlete-exposures	95% Confidence interval
Basketball	3	7.3	0.45	-0.007 - 0.97
Handball	3	5.6	0.38	-0.06 - 0.82
Indoor Soccer	2	4.1	0.24	-0.1 - 0.6
Soccer	1	2.4	0.21	- 0.21 - 0.64
Athletics	1	5.0	0.16	-0.17 - 0.51
Total anterior cruciate ligament injuries	10	3.1*	0.16*	0.16 - 0.17*

* These data include all sports, not just sports that presented anterior cruciate ligament injuries.

DISCUSSION

Currently, university sports in Brazil are nonprofessional. In contrast to the United States of America collegiate model, few universities provide players with scholarships, and most students have never previously been engaged in any competitive sport. Despite the amateur nature of Brazilian university sports, the game injury rate (13.13 injuries per 1000 A-Es, 95% IC = 10.3 – 15 or one injury every four games for a team of 20 participants) and the practice injury rate (4.47 injuries per 1000 A-Es, 95% IC = 3.9 - 5.1 or one injury every 10 practices for a team of 20 participants) of this population were very similar to the NCAA´s game injury rate (13.8 injuries per 1000 A-Es, 95% CI = 13.7 - 13.9) and practice injury rate (4.0 injuries per 1000 A-Es, 95% CI = 3.9 - 4.0) (10), respectively. In addition, this study found the game injury rate to be three times higher than the practice injury rate. Again, this trend is very similar to the NCAA, which found 3.5 times more injuries in games than in practice [10]

Given the physicality, especially in games, of some NCAA sports that do not exist in Brazil, such as football and hockey, and the intense level of competition throughout the NCAA, we excepted to see a lower game per practice injury rate in Brazilian than in NCAA collegiate athletics. This is what was observed when comparing National Basketball Association (NBA) players with others from the Spanish Professional Basketball League, a less competitive basketball league. Factors such as longer games, less time of ball possession, and the dominance of man to man marking may be responsible for game injury rates in the NBA being twice as high as practice injury rates, compared to the Spanish Professional Basketball League in which the game injury rate is about one third of the practice injury rate.[11]

Data from the NCAA[10] and the present study also support higher game injury rates compared to practice injury rates when examining just the sports played in both the USA and Brazil, such as soccer, volleyball, basketball, baseball and softball.

Although overall game, practice, and game per practice injury rates in this study were similar to those of the NCAA, the injury mechanism distribution was different between populations. While player contact is the major mechanism involved in game injuries in both this study (53%) and the NCAA (58%),[10] most practice injuries in this study were non-contact (54%). This is in contrast to NCAA, where player contact is also the major mechanism of practice injuries (42%). In addition, non-contact injuries account for almost double the number of game injuries in this study (33%) compared to the NCAA (17%).[10]

One reason for the difference in injury mechanism distribution between this study and NCAA is the higher intensity and physicality of NCAA sports, games and practices. Furthermore, this study included individual sports such as swimming, athletics, tennis and table tennis, where an injury caused by player contact is rare. However, other aspects must be involved in the injury mechanism difference because many athletes in this study (83%) played contact sports, such as rugby, soccer and basketball. (Table 1)

Another important aspect behind the observed injury mechanism differences may be that student athletes from Brazil´s universities are generally much less physically trained than NCAA athletes. This may make them more prone to non-contact injuries, similar to the non-contact anterior cruciate ligament sprain predisposition of athletes who have worse neuromuscular control.[12]

Given most injuries among NCAA athletes occur from player contact, preventative measures from ISS have largely focused on rules and policies that promote more secure contact between players, such as the no spearing and no clipping rules instituted in football.[10] In order for effective injury prevention strategies to be implemented at Brazil´s universities, one must consider that our needs are different from the NCAA, as advocated by van Mechelen et al.[7]

In this study, almost all sports had higher rates of injury in games than in practice. Rugby, the sport with the most contact between players, had the greatest difference: 6.72 times more injury in games (42.42 injuries per 1000 A-Es) than in practice (6.31 injuries per 1000 A-Es). Water polo had the lower difference: 1.05 times more injury in games (5.05 injuries per 1000 A-Es) than in practice (4.84 injuries per 1000 A-Es), followed by athletics, which had 1.19 times more injury in games (3.97 injuries per 1000 A-Es) than in practice (3.31 injuries per 1000 A-Es).

Judo was the only sport in which the opposite trend was observed: 1.46 times more injury in practice (13.47 injuries per 1000 A-Es) than in games (9.17 injuries per 1000 A-Es). Although higher game per practice injury rates in water polo and judo may be expected due to the large amounts of player contact, this was not observed. In water polo, the intense contact between players happens inside the water, which may lessen the injury risk. In judo, the higher incidence of injury in practice compared to games may be due to the time duration of each event. One practice session, which typically lasts around two hours, and one fight in a competition, which typically lasts around seven minutes, were both considered 1 A-E.

Similar to the NCAA, our study found the lower limbs to be the most prevalent location for injury, accounting for 68% of injuries in games and 58.4% of injuries in practice (versus 54% in both practice and games in the NCAA).[10] The lower limbs have also been found to be the most affected body part in various sports, such as rugby,[13,14] football,[15] soccer,[16,17] basketball[11] and volleyball,[18] as well as in overuse injuries.[19] This study found ankle ligament sprains and knee injuries to be most prominent, accounting for 18% and 11% of injuries, respectively. In the NCAA, ankle sprain is also the most common injury (15% of all injuries).[10] In addition, other studies have found ankle sprain to be the most common injury in volleyball[20] and basketball.[11]

A much smaller percentage of head and neck injuries were found in this study compared with the NCAA. These injuries account for 12.8% of game injuries and 9.8% of practice injuries in the NCAA[10] but only accounted for 2.6% and 4.6% of injuries in this study, respectively. This is most likely due the NCAA's inclusion of football and hockey athletes, which have relatively high concussion rates. These sports were not played among our study population, and are not common in Brazil.

In this study, the ACL injury rate (0.16 injuries per 1000 A-Es, 95% CI = 0.16 - 0.17) and the ankle ligament sprain rate (0.99 injuries per 1000 A-Es, 95% CI = 0.99 - 1.0) were both statistically higher than in the NCAA (ACL injury rate of 0.15 injuries per 1000 A-Es, 95% CI = 0.14 - 0.15 and ankle ligament sprains rate of 0.83 per 1000 A-Es, 95% CI = 0.82 - 0.84).[10] As non-contact injuries were most common in this study, and given the high incidence of non-contact ACL[21] and ankle sprain[18] injuries, it is easy to understand their increased occurrence. The School of Medicine and the School of Physical Education and Sports in this study also had a higher ACL injury rate (2.5% per person per year) than amateur athletes (0.03 - 1.62% per person per year) and a similar rate to professional athletes (0.15% - 3.67% per person per year),[22] reinforcing a recent retrospective study that indicated ACL injury as one of the most common injuries in the same School of Medicine evaluated by the present study in the last 20 years.[23]

There are several examples of successful lower limbs injury prevention programs. A prospective controlled trial with more than 1100 women volleyball athletes showed a lower incidence of ankle sprain injuries in the intervention group, who performed proprioceptive exercises, compared with the control group (risk difference of 0.4 / playing 1000 hours, 95% CI = 0.1 - 0.7).[20] In Santa Monica, California, more than 2900 female soccer players between the ages of 14 and 18 years substituted proprioceptive and neuromuscular exercises, focused on correct jumping and landing technique, in the place of a traditional warm up. An 88% decreasing ACL injuries was observed.[24] These findings motivated American Academy of Orthopaedic Surgeons (AAOS) and the American College of Sports Medicine (ACSM) to support neuromuscular training programs in female soccer players to help prevent ACL injuries.[8]

Summarizing, Brazilian university athletes are at great risk of sustaining non-contact injuries, such as ankle sprain and ACL injuries. Future injury prevention programs should focus on these types of injuries in order to be effective.

Study limitation

Considering that this is a retrospective study, it may be susceptible to memory bias, which means that a subject may have listed just the injuries that he was able to remember. In contrast to the NCAA, the questionnaire was answered by the participants on their own,

not by a team certified athletic trainer or physician. Finally, although the time of an athlete-exposure across most of sports (mainly collective sports) was almost the same (around two hours), it was not uniform among all athletes, especially considering competitions in individual sports like swimming or athletics.

CONCLUSION

Brazilian university athletes are at great risk of sustaining non-contact injuries, such as ankle sprain and ACL injuries. Future injury prevention programs should focus on these types of injuries in order to be effective.

AUTHORS' CONTRIBUTIONS: Each author contributed individually and significantly to the development of the manuscript. AMA (0000-0002-5230-3711)* and TLF (0000-0002-6665-3608)* were the main contributors in the drafting of the manuscript. AMA and IMM (0000-0001-6629-9277)* performed data acquisition and interpretation for the work. IMM and AP (0000-0002-8499-7493)* evaluated the data from the statistical analysis. AMA, IMM, TLF, AP and AJH (0000-0001-8645-3956)* conducted a critical review of the study's intellectual content. AJH and AP conducted the final review and approval of the manuscript version. *ORCID (Open Researcher and Contributor ID).

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Appendix I: 2013 Individual INJURY and EXPOSURE Questionnaire.

INJURY DEFINITION: A reportable injury is defined as one that:
1. Occurs as a result of participation in an organized university practice or contest; and
2. Results in any restriction of the athlete´s participation or performance for one or more days beyond the day of injury.

1. Name:.....
2. Phone number:.....
3a. Course: (1) ( ) FMUSP (2) ( ) EEFE
4. Year:.....
5. Gender: (1) male (2) female
6. Height: .....
7. Weight:.....
8. Sport:
(1) soccer (2) rugby (3) baseball (4) softball (5) athletics
(6) swimming (7) water polo (8) tennis (9) table tennis (10) judo
(11)karate (12)volleyball (13)handball (14)indoor soccer (15)basketball
9. Exposure data:
9a. Number of practices per week in 2013:.....
9b. Number of games per month in 2013:.....
9c. 2013 season start date:.....
9d.2013 season end date:.....
9e. Vacation days in the middle of 2013 season:.....
9f. Missed practices in 2013:.....
10. Playing position:.....
11. Dominant body side: (1) right (2) left
12. How many injuries did you suffer in 2013:.....

INJURY N°1

1. Sport of injury n°1:.....
2. Month of injury n°1:
(1)jan (2)feb (3)mar (4)apr (5)may (6)jun
(7)jul (8)aug (9)sep (10)oct (11)nov (12)dez
3. Injury n°1 occurred during:
(1) Preseason (before first regular-season match)
(2) Regular season
(3) Postseason (after final regular-season match)
(99) other:
4. Injury n°1 occurred in:
(1) Practice
(2) Game
5. Injury n°1 occurred during:
(1) game or practice first half
2) game or practice second half
6. This injury n°1 is a:
(1) New injury
(2) Recurrence of injury from this season
(3) Recurrence of injury from previous season (this sport)
(4) Complication of previous injury (this sport)
(5) Recurrence of other-sport injury
(6) Recurrence of nonsport injury
(7) Complication of other-sport injury
7. Principal body part injured in injury n°1:

(1) head	(10) shoulder	(19) thumb	(28) toe (s)
(2) face	(11) clavicle	(20) pelvis or hips	(29) stomach
(3) teeth	(12) scapula	(21) groin	(30) spleen
(4) neck	(13) upper arm	(22) buttocks	(31) kidney
(5) upper back	(14) forearm	(23) upper leg	(32) external genitália
(6) ribs	(15) elbow	(24) knee	(33) coccyx
(7) sternum	(16) wrist	(25) lower leg	(34) breast
(8) lower back	(17) hand	(26) ankle	(99) other:
(9) abdomem	(18) finger(s)	(27) foot	

8. Body side injured: (1) right (2) left
9. KNEE INJURY (answer only if response in question 7 was 24):
(1) collateral ligament
(2) anterior cruciate ligament
(3) posterior cruciate ligament
(4) torn cartilage (meniscus)
(5) patella and or patella tendon
(6) other tendon
(99) other:
10. This injury involved:
(1) contact with another competitor
(2) no apparent contact (other)
(3) contact with apparatus/ball
(4) contact with other in environment (e.g.,wall, fence, spectators)
(5) no apparent contact (rotation about planted foot)
(6) contact with playing surface
(99) other:
11. Primary type of injury n°1 (circle one):

(1) contusion	(16) concussion
(2) laceration	(17) heatstroke
(3) bursitis	(18) hemorrhage
(4) tendinitis	(19) infection
(5) ligament sprain (incomplete tear)	(20) avulsion (tooth)
(6) ligament sprain (complete tear)	(21) nerve injury
(7) muscle-tendon strain (incomplete tear)	(22) blisters
(8) muscle-tendon strain (complete tear)	(23) hernia
(9) osseous edema	(24) foreign object in body orifice
(10) torn cartilage	(25) internal injury (nonhemorrhage)
(11) AC separation	(26) infection
(12) dislocation (partial)	(27) periostitis
(13) dislocation (complete)	(28) inguinal hernia
(14) fracture	(99) other:
(15) stress fracture	

12. Did this injury require surgery?
(1) Yes, in-season
(2) Yes, postseason
(3) No
13. Describe the joint surgery?
(1) Arthrotomy
(2) Diagnostic arthroscopy
(3) Operative arthroscopy
(4) no joint surgery:
(99) other:
14. Injury assessment (best assessment procedure):
(1) clinical exam by athletic trainer
(2) clinical exam by physician
(3) X-ray
(4) MRI
(5) other image technique
(6) surgery
(7) blood work lab test
(99) other:
15. Type of surface?
(1) wood
(2) natural grass
(3) synthetic grass
(4) cement
(5)rubber
(7) water
(99) other:
16. How many days did this injury keep student-athlete from participating in the sport:.....

Additional comments (optional):.....

This questionnaire is a version of Injury Surveillance System from NCAA (Dick, R., Agel, J., and Marshall, S.W. (2007). National collegiate athletic association injury surveillance system commentaries: Introduction and methods. Journal of Athletic Training 42, 173-182.). With permission of Brian Hainline, MD. NCAA Chief Medical Officer.

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BONE FRAGILITY, FRACTURE RISK AND TRAUMA: A COMPLICATED TRIANGLE IN CHILDREN

FRAGILIDADE ÓSSEA, RISCO DE FRATURA E TRAUMA: UM TRIÂNGULO COMPLICADO EM CRIANÇAS

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ABSTRACT

Objective: To analyze whether association between bone fragility and risk of fracture depends on the trauma level. Method: All participants along with their mothers underwent DXA scan and body measurements. The subjects answered a self-report questionnaire about their physical activities and the precipitating causes. The questionnaire results were associated with DXA performed at the baseline visit. Results: A total 374 children with available DXA scan and complete follow-up of 5 years were included in the final analysis. Of the 374 children, 53 (14.2%) had one fracture, and 11 (20.7%) had more than one fracture. Based on the modified Landin classification, the trauma level was determined. Of the 53 (14.2%) children who had one fracture, 39 (73.6%) were classified, namely 19 (48.7%) with mild trauma, 16 (41%) with moderate trauma and four (10.2%) with severe trauma. Trauma level could not be assigned to 14 (26.4%) children due to limited information. Children without fractures had significantly higher values in all bone parameters compared to those with fractures caused by mild trauma. Conclusion: Subjects with mild trauma fractures had an inversely proportional ratio between bone fragility parameters and fracture risk compared with subjects without fractures. ***Level of Evidence IV, Case Series.***

Keywords: Fractures, bone/epidemiology. Bone density/physiology. Child. Risk factors.

RESUMO

Objetivo: Analisar se a associação entre fragilidade óssea e risco de fratura depende do nível de trauma. Método: Todos os participantes, juntamente com suas mães, foram submetidos à DEXA e medições corporais. Os participantes responderam um questionário de autorrelato sobre atividades físicas e descrição de como o trauma ocorreu. Os resultados do questionário foram associados à DEXA realizada na primeira visita do estudo. Resultados: Um total de 374 crianças com DEXA disponível e acompanhamento completo de 5 anos foi incluído na análise final. Das 374 crianças, 53 (14,2%) tiveram uma fratura e 11 (20,7%) tiveram mais de uma fratura. Com base na classificação de Landin modificada, foi determinado o nível de trauma. Das 53 (14,2%) crianças que tiveram uma fratura, 39 (73,6%) foram classificadas, sendo 19 (48,7%) com trauma leve, 16 (41%) com trauma moderado e quatro (10,2%) com trauma grave. O nível de trauma não pôde ser atribuído a 14 (26,4%) crianças, devido a informações limitadas. As crianças sem fraturas apresentaram valores significantemente mais altos em todos os parâmetros ósseos, em comparação com os que tinham fraturas causadas por trauma leve. Conclusão: Os indivíduos com fraturas por trauma leve apresentaram relação inversamente proporcional entre os parâmetros fragilidade óssea e o risco de fratura em comparação com indivíduos sem fratura. ***Nível de Evidência IV, Série de Casos.***

Descritores: *Fraturas ósseas/epidemiologia. Densidade óssea/fisiologia. Criança. Fatores de risco.*

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INTRODUCTION

A bone fracture is defined as damage in the continuity of bone. Analysis of data from many studies has shown that fractures comprise 10-25% of childhood trauma.[1] Despite this high prevalence, healthcare professionals and public health programs tend to focus on the adult population. Epidemiological studies have shown that the incidence of fractures during childhood is somewhat similar to the incidence of fractures in the elderly population.[2,3]

It is a well-established fact that low bone mineral density and a previous history of fracture are the strongest risk factors for future fractures.[4,5] However, it is assumed the relationship between the history of fracture and risk of future fracture is strongest for fractures that occur as a consequence of low trauma, such as falls from an upright position.[6] During evaluation of risk factors for osteoporosis and other bone diseases, history of childhood fractures is generally ignored on the assumption that childhood fractures are primarily caused by high trauma.[7-9] Bone fragility that might cause both high and low trauma fractures is itself not considered a risk for future fractures.[10] However, there is emerging evidence that childhood fractures are associated with underlying skeletal fragility.[11,12]

All the authors declare that there is no potential conflict of interest referring to this article.

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A meta-analysis of case control studies by Clark et al.[13] showed an inverse relationship between bone mineral density and risk of fracture during childhood. These findings are also supported by other observational studies.[14,15] The Avon Longitudinal Study of Parents and Children (ALSPAC) observed an inverse association between volumetric bone mineral density (vBMD) and fracture risk.[14] The overall results of these studies indicated that childhood fractures are associated with underlying skeletal fragility.

Landin[16] derived a classification system defining different levels of trauma in children based on the events that preceded injuries or fractures in his study population. The three main components of his classification system were height of fall, type of activity, and any device that may have resulted in the fall; these components were used to categorize trauma into three different levels (slight, moderate, and severe trauma, respectively). Using a modified version of Landin's classification system,[10] we conducted a prospective cross-sectional study to examine whether association between bone fragility and fracture risk depends on the level of trauma preceding injury. Landin's modified trauma levels used in the current study are as follows: low trauma includes falling and landing on the ground (<0.5 m) or a resilient surface (0.5-3 m), falling from a bed/sofa/cot, injuries sustained during play on the playground or low-impact sports such as gymnastics, judo, etc. Moderate trauma injuries include falling and landing on a non-resilient surface (0.5-3m), falling from a bicycle, skateboard, swing, slide, rollerblades, or bunkbed. High/severe trauma includes falling from >3 m, traffic accidents, and being hit by a heavy moving object.

METHODS

A total of 457 healthy children (mean 10.1 years of age) visiting Shandong Jining No.1 People's Hospital were included in the current study. This study was approved by the ethics committee of Shandong Jining No.1 People's Hospital (approval number : ZK242403). The majority (64.7%) were female. Children with malnutrition, chronic diseases, or any history of bone disease or mal-absorption were excluded. We also excluded children who took medications regularly or who had been prescribed calcium and vitamin D supplements. The study was approved by the institutional review board. All participating children gave verbal consent, while the guardians signed a term of free and informed consent. All participating children were invited to come to the clinic accompanied by their mothers to undergo DXA scanning and further measurement of height, weight, body mass index (BMI, kg/m^2), and collection of other basic demographic data. Based on the recommendations from the International Society for Clinical Densitometry (ISCD), instead of full-body DXA scans we used the total body less head (TBLH) bone area (BA) and TBLH bone mineral content (BMC) in the current study.[17] In children, TBLH is recommended for its accuracy and precise results. We also opted not to use the full-body DXA scan because the head is not receptive to stimuli (such as exercise).[18] Height was measured with subject standing straight with feet flat on the ground and heels touching the back plate of the measuring instrument. Height was measured to the last millimeter (mm) while weight was measured to the nearest 50 g. Measurement of TBLH BA and TBLH BMC was taken with a Lunar Prodigy DXA device. The precision of the DXA scan was expressed in terms of coefficient of variation (CV), i.e. 0.8%. The CV value is based on 150 repeated scans. After measurement of the physical parameters, the subjects took a self-reported questionnaire inquiring about their participation in physical activities such as dancing, running, swimming, aerobics, etc. and the amount of time they engaged in such activities per week. Puberty was assessed using the Tanners and Whitehouse classification of breast development and pubic hair[19] through drawings. Parental race, educational qualification, and social status were noted by a researcher on a self-reported questionnaire.

To collect information on fracture incidence and description of events surrounding the injury, subjects were given a self-reported questionnaire at their each yearly follow-up visit for a 5-year period. These results were then linked with the subjects' DXA scan, which was performed during their first visit when the study began. Subjects who reported a fracture were then asked to fill out another questionnaire collecting information about the nature of the injury and preceding circumstances. Finally, in order to confirm fracture, the subjects' parents were asked to provide the X-ray report, if this was available. When the X-ray report was not available, "not confirmed fracture" was used as an outcome. Additional data was collected using a modified version of Landin's classification.

The demographic data were presented as mean and frequencies when appropriate. The two-tailed Student's t-test was used to find significant differences between children with and without fractures. In order to determine bone variables in children who had fractures and those without fractures, we ran a linear regression model, using both unadjusted and adjusted models (age, sex, race, economic status). All statistical analysis was done using SPSS (Statistical Package for Social Sciences) software version 20.

RESULTS

Of the 457 healthy children initially recruited for the study, 383 children completed the 5 year follow-up. Of the 383 DXA scans, 9 scans could not be interpreted, yielding a total of 374 available scans of the children with complete follow-up who were included in the study (Figure 1). The demographic and clinical profiles of the children who had fractures and did not have fractures are shown in Table 1. Of the total population of 374 followed for 5 years, 53 (14.2%) sustained at least one fracture, and of this group 11 (20.7%) experienced more than one fracture. Using the modified Landin trauma classification, we assigned a trauma level in 39 (73.6%) of the 53 children who reported a fracture: 19 cases of slight trauma (48.7 %), 16 cases of moderate trauma (41%), and 4 cases of severe trauma (10.2%). Trauma level could not be assigned in 14 cases (26.4%) due to limited information from both parents and children regarding the incidents preceding the fractures.

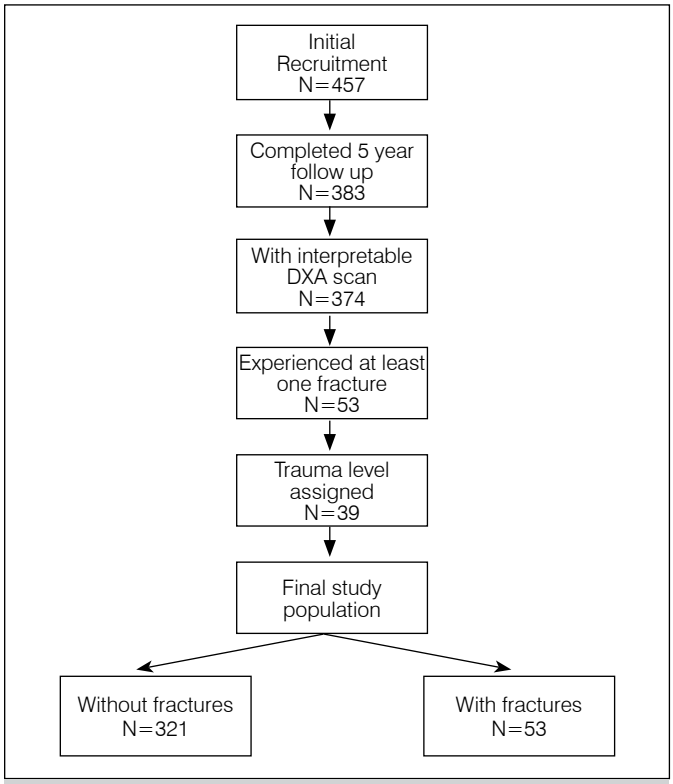

Figure 1. Methodological flowchart of study.

Of the 53 (14.2%) children who experienced a fracture, the majority of the fractures were reported to be in the forearm, with 25 cases (47%), while the least-reported fracture site was the humerus, with 1 case (2%). Other reported fracture sites were the elbow, with 9 cases (17%), the tibia and fibula with 6 cases (11.3%), the fingers with 4 cases (7.5%), the toe with 3 cases (6%), the clavicle with 3 cases (5.6%), and the thumb with 2 cases (4%) (Figure 2).

Without adjusting for variables, we compared demographic data as well as different bone parameters in children with fractures and those without fractures. (Table 1) Based on this analysis, except for BMI and weekly level of physical activity there was no significant difference in the demographic variables of the study subjects. As for bone parameter variables, subjects who did not experience fractures had a statistically significant increase in humeral volumetric density (cm^3) while no difference was seen in the other parameters (TBLH BMC, TBLH BA, TBLH BMD). To pursue more detailed analysis, we further subdivided the children with fractures according to trauma level. Because the number of cases with fracture caused by severe trauma were so low, for this analysis we combined fractures with moderate and severe levels of trauma and compared them with fractures caused by low trauma level and no fractures. (Table 2) Children without fractures had statistically significant higher values for all bone parameters compared to children who experienced fractures caused by slight trauma. However, only humeral vBMD and TBLH bone size relative to body size was lower in children with fractures caused by high levels of trauma, while statistically significant decreases were not seen in other parameters. We also performed an adjusted analysis (age, sex) and found a similar reduction in humeral vBMD in all the children who experienced fractures compared with those without fractures. Finally, subjects with low trauma fractures weighed less (approximately 7%) and subsequently had lower BMIs than their counterparts who experienced high or moderate trauma fractures. Moreover, subjects with low trauma fractures also had lower BMD, BA AND TBLH BMC values than those subjects who had high or moderate trauma fractures.

Table 1. Demographic profile of study subjects.

Variable	Subjects without fracture (N=321)	Subjects with fracture (N=53)	p-value
Age (years)	10.2 ± 0.4	10.2 ± 0.3	0.347
Male sex	158 (49.2%)	28 (52.8%)	0.251
Height (cm)	138.2 ± 6.3	138.6 ± 5.9	0.614
Weight (kg)	35.4 ± 6.4	36.0 ± 8.3	0.315
BMI (kg/m^2)	17.1 ± 2.4	17.9 ± 3.9	0.041
Socioeconomic status			
Low	109 (33.9%)	17 (32.0%)	0.06
Moderate to high	212 (66.1%)	36 (68%)	
Parental education			
School	87 (27.2%)	15 (28.3%)	0.328
College	135 (42.0%)	22 (41.5%)	
University	99 (30.8%)	16 (30.1%)	
Tanner staging			
1	161 (50.1%)	27 (50.9%)	0.158
2	146 (45.4%)	23 (43.3%)	
>3	14 (4.3%)	3 (5.6%)	
Weekly physical activity			
<3 times	167 (52%)	19 (35.9%)	0.024
>3 times	154 (48%)	34 (64.1%)	

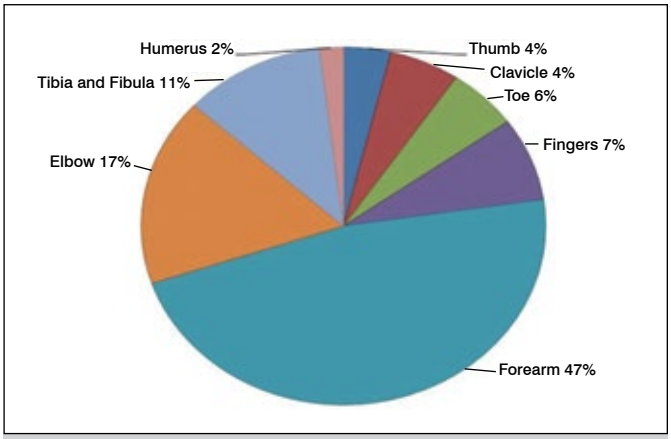

Figure 2. Types of fractures reported.

DISCUSSION

To the best of our knowledge, this is the first prospective study following Chinese children over a long follow-up period (5 years) that evaluates the relationship between future fracture risk and underlying skeletal fragility and whether this relationship is influenced by trauma level. The incidence of fracture in our study cohort was 14.2%, which is comparable to previously conducted studies. Clark et al. followed 7725 children in a community over a span of 2 years and found an overall fracture incidence rate of 8.9%.[10]

Our findings showed that overall fracture risk is greater in boys and low trauma fractures are more common in children. Increased fracture risk in boys has been reported in many previously conducted studies and is attributed to their behavior and restless nature.[20,21] Regardless of the trauma level preceding fracture, children with fracture had reduced bone parameters such as humeral vBMD, TBLH bone size relative to body size, and TBLH vBMD. These findings are consistent with other prospective and case controlled studies which showed similar results in children belonging to different age groups.[10,15,22]

Our main focus in this paper was to observe the association between skeletal fragility and fracture risk and trauma level. We found that subjects with low trauma fractures had an inverse relationship between bone fragility parameters (TBLH vBMD, humeral vBMD, TBLH bone size relative to body size) and fracture risk compared with subjects who did not have fractures. Interestingly, with the exception of TBLH vBMD, other bone fragility parameters (humeral vBMD, TBLH bone size relative to body size) were also inversely related to fracture risk in children with moderate to severe trauma before fracture. Although more skeletal fragility is observed in subjects with low trauma, we conclude that skeletal fragility in early life is related to future fracture risk even at high trauma levels.In contrast, we have observed that among subjects with fractures the bone parameters such as TBLH BMC and TBLH vBMD are reduced compared to those subjects without fractures. This discrepancy in results can be explained by the fact that majority of fractures in our study affected the upper limb. Compared to the whole body, upper limb fractures are weakly related to skeletal fragility parameters.

We unexpectedly found weight differences among subjects with low and high trauma levels. Subjects with high trauma fractures had more fat and lean mass and consequently higher BMIs than children with low trauma fractures. Contrary to the observation that obese adults are at less risk for osteoporosis,[23,24] increased weight is a risk factor for fractures in children.[11,25] It has been proposed that overweight children have low bone area for their weight, placing them at high risk for fracture.[26,27] Our results showed that subjects with high trauma fractures had higher TBLH and BMC values than subjects with low trauma fractures. On the other hand, bone size relative to body size was reduced in both high trauma and low trauma fractures, suggesting that higher values for bone parameters (TBLH BA and BMC) in overweight children cannot compensate for their increased body weight. Lastly, despite trauma level, fracture risk in childhood was associated with level of physical activity in our study cohort. Subjects with active or rigorous participation in physical

Table 2. Difference in bone parameters of subjects without fractures and subjects with fractures categorized by trauma level.

Bone parameter	Subjects without fracture N=321	Subjects with fracture N=53	p-value *	Subjects with low trauma fractures N=19	p-value #	Subjects with high trauma fractures N=20	p-value ^
TBLH BMC (g)	889 ± 187	881 ± 175	0.416	845 ± 156	0.002	901 ± 179	0.425
TBLH BA (cm^2)	1132 ± 163	1129 ± 149	0.384	1101 ± 135	0.014	1147 ± 158	0.342
TBLH BMD (g/cm^2)	0.775 ± 0.053	0.771 ± 0.051	0.058	0.759 ± 0.051	0.004	0.774 ± 0.054	0.572
Humeral vol. density	0.489 ± 0.05	0.473 ± 0.05	<0.001	0.471 ± 0.05	<0.001	0.469 ± 0.05	0.003

*p-value: for difference between children without fractures and children with fractures. #p-value: for difference between children without fractures and children with low trauma fractures. ^ p-value: for difference between children without fractures and children with high trauma fractures. All statistically significant values (p-value >0.05) are shown in bold. BMC: bone mineral content, BA: bone area, BMD: bone mineral density, TBLH: total body less head.

activities reported more fractures. These findings are consistent with previously reported studies.[28,29] MA and Jones conducted population based case control studies to evaluate the risk of upper limb fractures and physical activity and found similar results.[28]

The main limitation associated with the current study is self-categorization of trauma level and self-reported responses by the participants in different questionnaires. Since questionnaires were not given to participants immediately after the fracture occurred but rather some time later during the scheduled follow-up meeting, recall bias cannot be ignored. Moreover, trauma level was not assigned in all participants and not all reported fractures were confirmed by X-ray reports. Despite these limitations, the current study is strengthened by its prospective nature and long follow-up period. Moreover, the DXA scans were done at the beginning of the study before the fractures occurred, assuring that the scan results were not be influenced by the fracture. Lastly, the drop-out rate in our study was quite low, permitting generalized results.

CONCLUSION

The current study conclusively confirms the proposed hypothesis that regardless of trauma level preceding the injury, skeletal fragility contributes to fracture risk in children. Further longitudinal observational studies are needed to explore whether this risk is transient or remains persistent. Furthermore, future studies should observe the influence of skeletal fragility on fracture risk in both elderly men and women. Because fractures are among the most important clinical and public health concerns in both adults and children, future studies should target both populations.

AUTHORS' CONTRIBUTIONS: Each individual author contributed individually and significantly to the development of this manuscript. DH (0000-0003-3395-0427)* contributed to the intellectual concept of the study and the entire research project and reviewed the manuscript. DL (0000-0003-0245-3129)* wrote and reviewed the manuscript and performed the scans. QZ (0000-0002-1908-1897)* performed the statistical analysis and assisted during the follow-up; LZ (0000-0003-4304-3388)* analyzed the data, wrote the article, analyzed the slides, and reviewed the article. *ORCID (Open Researcher and Contributor ID).

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CUSTOMIZED GUIDE FOR FEMORAL COMPONENT POSITIONING IN HIP RESURFACING ARTHROPLASTY

GUIA PERSONALIZADA PARA POSICIONAMENTO DE COMPONENTE FEMORAL PARA *RESURFACING* EM ARTROPLASTIA DO QUADRIL

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ABSTRACT

Objective: To prove the accuracy of a customized guide developed according to our method. Methods: This customized guide was developed from a three-dimensional model of proximal femur reconstructed using computed tomography data. Based on the new technique, the position of the guide pin insertion was selected and adjusted using the reference of the anatomical femoral neck axis. The customized guide consists of a hemispheric covering designed to fit the posterior part of the femoral neck. The performance of the customized guide was tested in eight patients scheduled for total hip arthroplasty. The stability of the customized guide was assessed by orthopedic surgeons. An intraoperative image intensifier was used to assess the accuracy. Results: The customized guide was stabilized with full contact and was fixed in place in all patients. The mean angular deviations in relation to the what was planned in anteroposterior and lateral hip radiographs were $0.5^{o} \pm 1.8^{o}$ in valgus and $1.0^{o} \pm 2.4^{o}$ in retroversion, respectively. Conclusion: From this pilot test, the authors suggest that the proposed technique could be applied as a customized guide to the positioning device for hip resurfacing arthroplasty with acceptable accuracy and user-friendly interface. ***Level of Evidence IV, Cases Series.***

Keywords: Arthroplasty, replacement, hip/instrumentation. Femur neck. Imaging, three-dimensional. Surgery, computer-assisted. Prosthesis design.

RESUMO

Objetivo: Comprovar a precisão de uma guia personalizada desenvolvida a partir de nosso método. Métodos: Esta guia personalizada foi desenvolvida a partir do modelo tridimensional da parte proximal do fêmur reconstruída usando dados de tomografia computadorizada. Com base na nova técnica, a posição de inserção do pino da guia foi selecionada e ajustada usando a referência do eixo anatômico do colo do fêmur. A guia personalizada consiste em um revestimento hemisférico projetado para encaixar na parte posterior do colo do fêmur. O desempenho da guia personalizada foi testado em oito pacientes que seriam submetidos à artroplastia total do quadril. A estabilidade da guia personalizada foi avaliada por cirurgiões ortopedistas. Para avaliar a precisão, usou-se um intensificador de imagem intraoperatório. Resultados: A guia personalizada foi estabilizada com contato total e foi fixada em todos os pacientes. Os desvios angulares médios com relação ao planejado nas radiografias anteroposteriores e laterais do quadril foram de $0,5^{o} \pm 1,8^{o}$ em valgo e $1,0^{o} \pm 2,4^{o}$ em retroversão, respectivamente. Conclusão: A partir deste teste piloto, os autores sugerem que a técnica proposta poderia ser aplicada como guia personalizada para o dispositivo de posicionamento para resurfacing em artroplastia de quadril com aceitável precisão e interface amigável. ***Nível de Evidência IV, Série de Casos.***

Descritores: *Artroplastia de quadril/instrumentação. Colo do fêmur. Imagem tridimensional. Cirurgia assistida por computador. Desenho de prótese.*

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INTRODUCTION

Hip resurfacing arthroplasty (HRA) is an alternative to total hip arthroplasty (THA). The advantages of this procedure include preservation of the femoral bone stock,[1] minimized dislocation rate,[2] and improved range of motion.[3] However, HRA is a technically demanding procedure and femoral neck fracture has been documented as the most common cause of early failure.[4] This complication is related to varus malposition of the femoral component and superior notching of femoral neck.[5,6]

Accurate positioning of the femoral component has been reported in association with successful long-term outcomes.[7] Optimal alignment traditionally is achieved using manual devices, and accuracy relies largely on visual inspection and the surgeon's experience. Computer assisted navigation can increase the accuracy of femoral guide pin insertion compared to conventional instrumentation.[8,9] Nevertheless, it has distinctive disadvantages, including increased surgical time and cost.[8] Patient-specific instrumentation for HRA is a novel device fabricated using rapid prototyping technology (RP). Computed tomography (CT) scanning provides individual 3D geometric anatomy data to construct a patient-specific instrument. The instrument is used to guide the position of pin insertion to avoid malpositioning of the femoral component. The most important reference axis for

All the authors declare that there is no potential conflict of interest referring to this article.

Study conducted at Siriraj Hospital, Bangkok, Thailand
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determining guide pin direction is the femoral neck axis (FNA). In clinical practice, determining the true FNA can still be problematic. Although several patient-specific guides (PSG) have been proposed in the literature and demonstrated utility with good accuracy,[10-14] few studies state the method for defining true FNA.[11,14] To our knowledge, the best-known technique was developed by Mahaisavariya et al.,[15] who established a method for geometrical assessment of the proximal femur in three dimensions. This method uses CT images combined with reverse engineering to obtain the 3D geometry of the proximal femur. This technique can be applied to HRA in order to identify the true FNA. Consequently, the objectives of this study were to use this technique to design a PSG to assist in femoral component positioning in HRA, as well as assess the accuracy of this device.

PATIENTS AND METHODS

Between May and August 2011 we recruited eight patients scheduled for unilateral primary THA to participate in the study. Preoperative CT scans of the hip were performed with a 1-mm slice thickness. The axial cross-sectional images of the body were formatted into Digital Imaging and Communications in Medicine (DICOM) files and transferred to National Metal and Materials Technology Center (MTEC, National Science and Technology Development Agency, Pathumthani, Thailand). Medical imaging processing software (Mimics, Materialise N.V., Belgium) was used to convert the set of DICOM files to a three-dimensional image of hip. In the reconstruction process, the stack of DICOM files was sequenced in such the way that the relative proximal cross-section images were above the distal cross-sectional images. This allowed the femoral head to be oriented proximally to the femoral shaft. Each image was within the threshold range for Hounsfield unit (HU) values to capture bone density. Images of the proximal femoral region were separated from other bones using a region-by-region growing algorithm.[15] The captured boundaries of the proximal femoral region were interpolated in a 3D computer aided design (CAD) model of the proximal femur, as illustrated in Figure 1. PSG design can achieve success in HRA because it can precisely determine the true FNA. Nevertheless, if the femoral head was severely deformed, the mirror image technique from the contralateral side was used to calculate this axis. The engineers at MTEC developed a technique to derive true FNA as follows: the least square regression of ellipse and sphere was performed at the femoral neck region and femoral head, respectively. The centers of the ellipse and sphere together derived the line using the linear regression technique; this derived line was the true FNA. However, since is difficult to determine the correct cross-section plane at the femoral neck used for least square regression of the ellipse, the iteration of the aforementioned least square regression technique was performed until the FNA resulting from the current iteration was no more than $\pm 0.5^{o}$ different from the FNA resulting from the previous iteration.[15]

The guide pin was planned following the true FNA for 5 cases and plus additional overcorrection of 5 degrees valgus for 3 cases. (Figure 2) The PSG was hemispherical to cover the femoral head, and was designed to be placed on the posterior part of the femoral head and neck. (Figure 3) In addition, the PSG contained the sleeve to control drilling direction, allowing a 3.2-mm diameter guide pin to be inserted through it. The primary goal of these devices was to securely fit the femoral neck, because of concerns related to the indistinct contours of articular cartilage in the CT images. The PSG was fabricated using a RP machine developed in our facility using an acrylate resin biocompatible for bone contact. The PSG was then polished and cleaned to remove residual particles, and sterilized using gamma radiation.

Before PSG was used in surgery, trials were performed in all cases. The PSG were tested to assess contact with the physical model of the proximal femur, stability of fixture, and contact clearance, as well as evaluate the direction of the guide after drilling. These assessments were made by the orthopedic surgeons as well as the engineers.

This study was approved by the institutional review board of Siriraj Hospital. All preoperative CT scans were done within 4 weeks prior to surgery. All surgical procedures were performed by the senior author (CK). The patient was placed in a lateral decubitus position, and a posterolateral approach of the hip was performed. After dislocation of the femoral head, the PSG was wrapped around the posterior part of femoral head and neck and locked in a stable snap-fit position. (Figure 4) The contact obtained at the neck portion and the stability of fixture was graded by the surgeons (full contact/unmovable, partial contact/unmovable, and partial contact/movable). A 3.2-mm-diameter guide pin was inserted via the pinhole and passed through the femoral neck. After removing the PSG, another end of the pin was cut at the level of 2 mm above the femoral head. The femoral head containing the pin was relocated. Pin alignment was assessed using

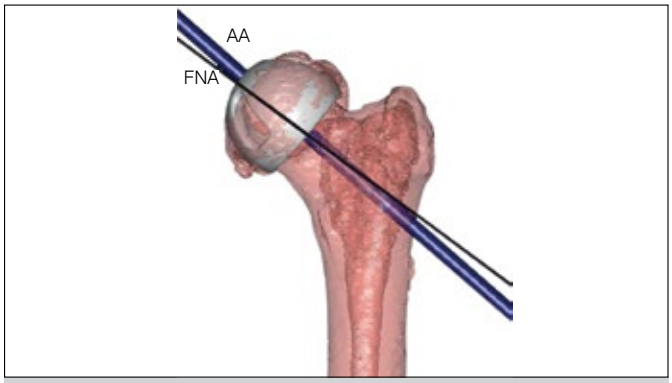

Figure 2. Adjusted axis (AA) to the direction of 5^{o} valgus from the true femoral neck axis (FNA).

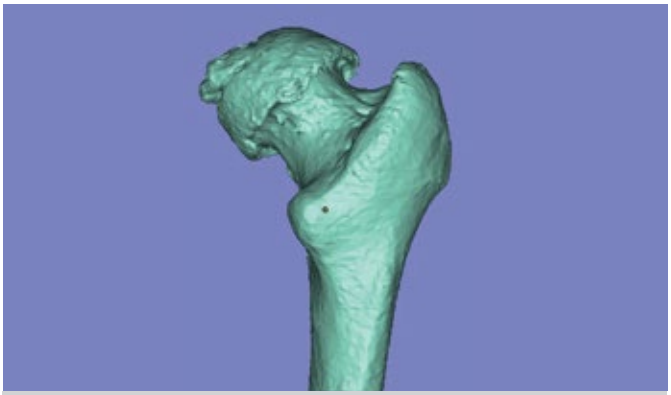

Figure 1. Three-dimensional graphic model of the proximal femur.

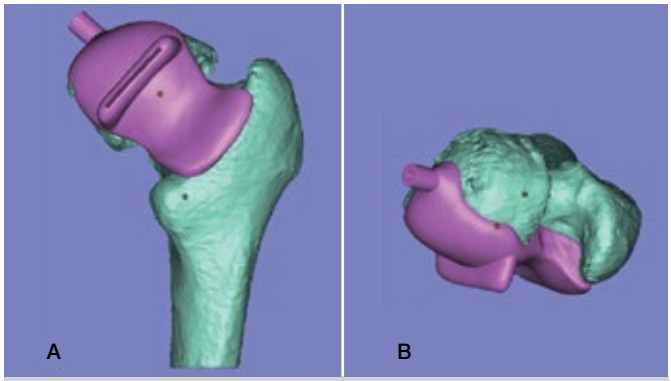

Figure 3. Design of patient-specific guide, (a) posterior and (b) superior view of proximal femur.

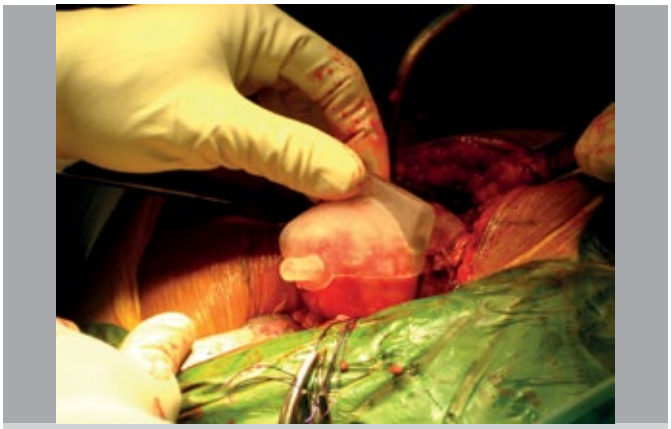

Figure 4. Intraoperative application of the patient-specific guide.

the intraoperative image intensifier. For the anteroposterior (AP) view, the image intensifier was positioned perpendicular to the hip with femoral internal rotation of 15º. Without moving the image intensifier, the lateral view was obtained with a hip position of 45º flexion, 45º abduction, and 30º external rotation. After radiologic examination, the femoral head was dislocated again and the guide pin was removed. The remainder of the THA procedure was carried out as usual. No intra- or postoperative complications occurred in this series.

Radiographic evaluation

Two blinded assessors were assigned to evaluate the radiographs. From the AP view, we modified Muller's method[16] to determine FNA as follows: the center of the femoral head was located with a circle. Reference points for the circle arc were the inferomedial and inferolateral border. The point of deepest concavity on the lateral border of femoral neck was marked. Another circle arc using the center of femoral head as the center was drawn. The points where the circle intersected the femoral neck were connected and defined as the transcervical line. Another line drawn perpendicular to the transcervical line through the center of the femoral head represented the FNA. This method was also applied in the lateral view, but used the anteroinferior and posteroinferior border to define the femoral head. (Figure 5)
The direction of the guide pin was compared to the FNA in either the AP or lateral radiographs. Deviations between these two lines were defined as angular deviations; varus, neutral or valgus angulation in the AP view and anteversion, neutral or retroversion in the lateral view.

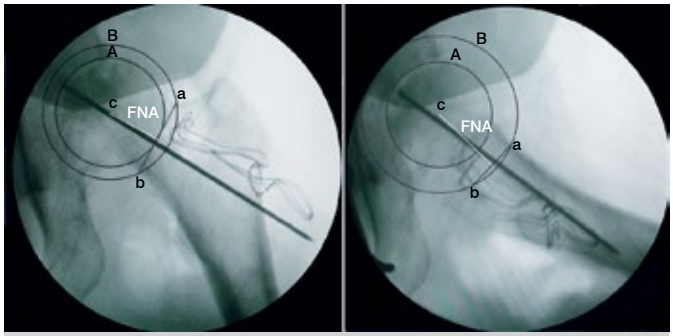

Figure 5. Radiographic assessment of guide pin position in anteroposterior (left side) and lateral (right side) radiographs of the hip; the center of the femoral head (C) is located within circle A. Another circle arc (B) was drawn using the center of the femoral head (C) as the center. Points a and b, where circle B intersects the deepest concave point of the femoral neck, are connected and defined as the transcervical line (ab line). The line drawn perpendicular to the transcervical line through the center of the femoral head (C) is represented as the femoral neck axis (FNA).

Statistical analysis

Statistical analysis in this study was performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL). Mean ± standard deviation (SD) was used to explain the descriptive statistics. Intraclass correlation coefficients (ICC) were used to assess the intra- and inter-rater reliability of radiographic measurements.

RESULTS

The characteristics of the patients and details of the assessed outcome are presented in Table 1. Mean patient age was 47.0 ± 12.1 years. The majority of the patients were diagnosed with osteonecrosis. The PSG was stabilized with full contact and was unmovable in all patients. The mean angular deviations from planning in the AP and lateral radiographs were 0.5º valgus ± 1.8º and 1.0º retroversion ± 2.4º directions, respectively. The ICC for inter-rater reliability was 0.83 and 0.91, while ICC for intra-rater reliability was 0.91 and 0.96 for angular deviation assessment in AP and lateral radiographs, respectively.

Table 1. Patient characteristics and radiographic outcomes.

Number	Sex	Age (yrs)	Side	Diagnosis	Anteroposterior radiograph		Lateral radiograph	
					Aim	Angular deviation	Aim	Angular deviation
1	Female	26	Right	ON	0º	3º varus	0º	3º anteversion
2	Female	52	Left	ON	0º	1º valgus	0º	2º retroversion
3	Female	38	Right	PVNS	0º	neutral	0º	4º retroversion
4	Female	62	Right	OA	0º	neutral	0º	3º retroversion
5	Female	54	Left	OA	0º	3º valgus	0º	neutral
6	Female	58	Left	DDH	5º valgus	6º valgus	0º	3º retroversion
7	Female	48	Right	ON	5º valgus	7º valgus	0º	neutral
8	Male	38	Right	ON	5º valgus	5º valgus	0º	1º anteversion

ON = osteonecrosis, PVNS = pigmented villonodular synovitis. OA = osteoarthritis, DDH = developmental dysplasia of the hip.

DISCUSSION

Various computer aided design and manufacturing technologies (CAD/CAM) were employed in this study to obtain the PSG used for HRA surgery. Proper selection of HU values in image processing along with reverse engineering technologies permit an accurate geometric model of the proximal femur to be constructed based on CT images. Determination of the true FNA based on the 3D proximal femur involves geometric approximation using various least square regressions, i.e. fit ellipse, fit sphere, and fit line. Until recently, the technologies described in this paper were not available for HRA, and FNA for most procedures was determined by the surgeon's skill, with varying results. These results may vary because the anthropometry of the Thai proximal femur, especially FNA, presents a wide range of values (110º–140º).[15] Therefore, the specific instrument for HRA presented in this study was reasonable. The PSG we developed is meant to facilitate the surgical procedure by precisely determining the true FNA and reducing trial and the use of radiography.
Unlike conventional radiographic imagery, three-dimensional CAD allows the true FNA to be determined. In order to demonstrate the accuracy of FNA determined through the PSG, we assessed the position during surgery and the angles measured in the AP and lateral views. The results show that the PSG has an acceptable coronal alignment accuracy of ±5º.[17] In the sagittal alignment, although there was no evidence of acceptable alignment for anteversion, little angular deviation was shown from the study.
True FNA is important for placing the femoral component in HRA. Most studies investigating PSG do not mention how to determine

FNA;[10,12,13,17,18] only one method, the so-called translucent cylinder method, appears in the previous literature. A translucent cylinder is created and superimposed on the 3D femoral model, and the position, orientation, and size of this cylinder are adjusted to identify FNA and neck diameter.[11,14] Using the translucent cylinder method, Kunz et al.[11] reported an angular deviation of 1.14º in coronal alignment and 4.49º in sagittal alignment. Du et al.[14] assessed reports of angular deviation after using PSG with translucent cylinder method were displayed, and the results concentrated on the stem-shaft angle (SSA) difference between PSG and conventional instruments. Different PSG designs and surgical approaches have been proposed in the literature. (Table 2) Most authors used the PSG via the posterior approach to the hip. Acceptable coronal alignment was demonstrated in most studies,[10-14,18] except for Olsen et al.,[17] who reported an angular deviation of 6.4 ± 2.9º in the coronal plane. In the sagittal plane, a maximum angular deviation of 4.49º was reported using 3D CT navigation assessment.[11]

In the current study, the authors developed the PSG according to the true FNA obtained from CAD in conjunction with various regression techniques. Compared to other studies, the PSG we developed can be applied with good stability and provides acceptable accuracy in guide pin placement for HRA. (Table 2) Nevertheless, there are several limitations in this study; first, this study is preliminary and was only conducted in a small group of THA patients. Future studies should investigate the use of this device in HRA in larger groups. Second, PSG was designed only for the posterior approach. During surgery, damage to the vessels in the posterior capsule of the hip may cause avascular necrosis of the femoral neck, resulting in femoral neck fracture.[19] Finally, the authors assessed the alignment using an image intensifier. Although we try to control the position of hip and leg, some imaging error may occur. Intraoperative CT scanning is the best option in this situation, but is not available in our institute.

CONCLUSION

This study presents the use of CAD/CAM in conjunction with various least square regression techniques to determine true FNA and develop and fabricate a PSG for femoral component positioning in HRA. The initial results from eight patients using CT based PSG are encouraging. The shape of the PSG was applied to the femoral neck and a secure fit was obtained, and accurate guide pin insertion using this device was verified.

Table 2. Comparison with previous studies investing the accuracy of patient-specific guides.

Study	Published year	Subjects	Surgical approach of the hip	Outcome measurement	Angular deviation (mean SD)	
					Coronal plane	Sagittal plane
Kunz et al.[11]	2010	45 HRA	Anterolateral	CT navigation	1.14º	4.49º
Raaijmaakers et al.[12]	2010	5 THA	Anterolateral	Optical scan	Maximal 2.9º	
Zhang et al.[13]	2011	10 HRA	Posterior	Image intensifier	1.3 ± 1.0º	NA
Audenaert et al.[10]	2011	5 cadavers	Posterior	CT	4.05 ± 1.84º	
Du et al.[14]	2013	16 HRA	Posterior	Plain radiographs	NA	
Kitada et al.[18]	2013	12 synthetic femoral models	Posterior	CT	2.5 ± 2.4º	1.5 ± 2.3º
Olsen et al.[17]	2009	6 cadavers	Direct lateral Posterior	Plain radiographs	6.4 ± 2.9º	1.0 ± 0.4º
Current study		8 THA	Posterior	Image intensifier	0.5 ± 1.8º	1.0 ± 2.4º

SD = standard deviation, HRA = hip resurfacing arthroplasty, THA = total hip arthroplasty. CT = computed tomography, NA = not applicable.

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FEMORAL NECK FRACTURES GARDEN I AND II: EVALUATION OF THE DEVIATION IN LATERAL VIEW

FRATURAS DO COLO DO FÊMUR GARDEN I E II: AVALIAÇÃO DO DESVIO NA INCIDÊNCIA RADIOGRÁFICA LATERAL

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ABSTRACT

Objective: To evaluate the rate of deviation in the lateral radiographic incidence in patients with femoral neck fracture classified as non-diverted in the anteroposterior view (Garden I and II). Methods: Nineteen selected patients with femoral neck fractures classified as Garden I and II were retrospectively evaluated, estimating the degree of deviation in the lateral view. Results: Fifteen cases (79%) presented deviations in lateral view, with a mean of 18.6 degrees (±15.5). Conclusion: Most fractures of the femoral neck classified as Garden I and II present some degree of posterior deviation in the X-ray lateral view. ***Level of Evidence III, Retrospective Comparative Study.***

Keywords: Femur neck. Radiography. Classification.

RESUMO

Objetivo: Avaliar a taxa de desvio na incidência radiográfica lateral em pacientes com fratura do colo femoral classificadas como não desviadas na incidência anteroposterior (Garden I e II). Métodos: foram avaliados retrospectivamente 19 pacientes selecionados com fraturas do colo do fêmur classificadas como Garden I e II, estimando-se o grau de desvio na incidência radiográfica lateral. Resultados: Quinze casos (79%) apresentaram desvio no perfil, com média de 18,6 (± 15,5). Conclusão: A maioria das fraturas do colo femoral classificadas como Garden I e II apresenta algum grau de desvio posterior na incidência radiográfica lateral. ***Nível de Evidência III, Estudo Retrospectivo Comparativo.***

Descritores: Colo do fêmur. Radiografia. Classificação.

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INTRODUCTION

Femoral neck fractures are common in the elderly population, accounting for 50% of hip fractures.[1] Frequently used classifications include the Arbeitsgemeinschaft fur Osteosynthesefragen/ Orthopaedic Trauma Association (AO/OTA) scale, the classification by Pauwels,[2] and the Garden classification. The Garden classification[3] has significant clinical importance since it is frequently used in indicating treatment. It divides femoral neck fracture into 4 grades; types I (incomplete with impaction in valgus) and II (complete without displacement) are considered non-displaced, and types III (partial displacement) and IV (complete displacement) are considered displaced.

Although fractures are typically diagnosed with at least two radiographic views, recent studies question the need to perform profile x-ray imaging in proximal femur fracture.[4-8] These studies have suggested algorithms[8] in which lateral radiographs should only be requested when the fracture exhibits no displacement in the anteroposterior view, which occurs in 18% of femoral neck fractures, or when occult fractures are suspected.[9]

The average failure rate for displaced fractures of the hip in the elderly is 42% for internal fixation, 11% for partial arthroplasties, and 6% for total arthroplasties.[10-12] Other authors, however, indicate that surgical outcome is influenced by the dorsal angle,[13-15] with posterior deviation of 20 degrees or more indicating re-operation.[14] The objectives of this study were to assess the rate of subjects with displacement in the lateral radiograph in patients with femoral neck fracture classified as not displaced in the anteroposterior view (Garden I and II); to measure the displacement in the lateral radiograph; and to investigate the association between the presence of displacement in the profile view and the occurrence of complications.

METHODS

A retrospective survey was conducted of all femoral neck fractures operated in our department from January 2011 to January 2014. From these we selected the cases classified as Garden type I and II to evaluate the anteroposterior and lateral x-rays. The study was approved by the local ethics committee (process number: 1.051.880). Cases where the x-rays were inadequate or the

All the authors declare that there is no potential conflict of interest referring to this article.

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radiographic sequence was incomplete were excluded. Participants were not excluded because of age or multiple fractures. The flow of patients in the study is shown in Figure 1.

Radiography was performed in our institution according to the following standards:

Anteroposterior view: patient in supine position on the examination table with legs extended in neutral abduction and internal rotation of 15 degrees; anteroposterior X-ray was taken of the pelvis with the film centered on the pubic symphysis with the X-ray tube 120 cm from the table.

Profile view (lateral): patient supine, limb to be X-rayed extended and the opposite side semiflexed and abducted; hip profile was radiographed with the beam angled 45 degrees cranially.[16]

Demographic data, type of surgical intervention performed and outcome, as well as the need for reintervention were recorded. The x-rays were classified and measured by an evaluator specifically trained for this task. For the profile view, a normal cervico-diaphyseal angle of 180° was considered, and any anterior or posterior angulation was regarded as fracture displacement.

Descriptive statistics were compiled for the demographic data and clinical outcomes, and the association between the presence of displacement and the occurrence of complications was investigated using the chi-squared test. A sample was not calculated in advance, since the study's sample was defined by the number of patients who received surgery during the defined period. The statistical analysis was performed using Stata 13.0 software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

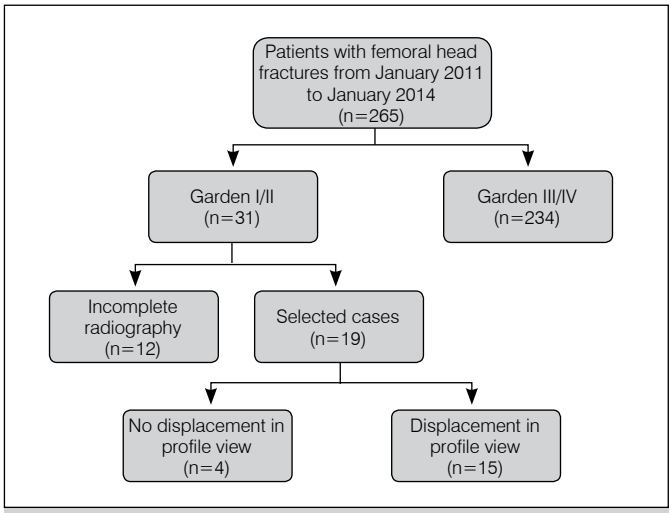

Figure 1. Flowchart showing study design.

RESULTS

Nineteen patient records were reviewed and included in the study. The demographic data for the patients included in the study are shown in Table 1. The fracture characteristics are shown in Table 2, including Pauwels classification and AO/OTA classification. Fifteen of the 19 cases slowed displacement in the profile view (79%), all in the posterior direction.

Mean time to surgery was 7.3 days (±5.9). Fixation with three cannulated screws was used in 17 patients (89%), bipolar hemiarthroplasty was used in one (5%), and a cephalomedullary rod was used in one patient (5%).

Of the patients assessed, four (21%) had complications from the procedure and required re-operation. In all of these cases, the initial treatment used fixation with cannulated screws in an inverted triangle. The mean displacement in the profile view in this sub-group was 26°, and the average age was 56.2 years. There were no cases of failure in the cases where no displacement was seen in the profile view. The association between the presence of displacement in the profile view and the occurrence of complications was not statistically significant (p = 0.240).

Table 1. Demographic data.

	N=19
Age	58.4 (± 22.3)
Sex	
Male	6 (32%)
Female	13 (68%)
Mechanism	
Hit by vehicle	2 (11%)
Motorcycle accident	2 (11%)
Automobile accident	2 (11%)
Spontaneous fracture	2 (11%)
Fall from standing height	11 (56%)

Table 2. Fracture characteristics.

	N = 19
Side	
Right	10 (53%)
Left	9 (47%)
Garden classification	
Garden I	6 (32%)
Garden II	13 (68%)
Pauwels Classification	
Pauwels A	3 (16%)
Pauwels B	10 (53%)
Pauwels C	6 (31%)
AO Classification	
31B1	9 (47%)
31B2	10 (53%)
31B3	0
Cervico-diaphyseal angle in the AP view	138.7° (± 16.7)
Displacement in the profile view	
No	4 (21%)
Yes	15 (79%)
Displacement angle in the profile view	18.6° (± 15.5)

DISCUSSION

Our study identified posterior displacement in 79% of the patients with femoral neck fracture classified as Garden grades I or II. Palm et al.[14] defined 20 degrees of posterior deviation as an independent predictive factor for re-operation in a study that followed patients for one year. These authors reported a mean angle of 13 degrees, with 23% reoperations. In our study, four patients (26%) required re-operation. In the retrospective assessment, two of these patients had displacement of more than 20 degrees (35 and 41 degrees), while two had displacement of less than 20 degrees (14 and 18 degrees), confirming the findings of Palm et al.[14]

Lapidus et al.[17] performed a study similar to Palm et al.,[14] with a higher number of cases and a five-year follow-up period, and found 12% reoperations and mean posterior angulation of 12 degrees. The authors demonstrated association between the presence of posterior displacement and the need for re-operation, but found no correlation between the degree of displacement and reoperations.

Some studies recommend not performing lateral x-rays in cases of clear displacement, thus reducing patient exposure to radiation and costs. Almazedi et al.[4] showed that adding a lateral x-ray to the anteroposterior view increases the sensitivity of diagnosis for displacement fractures from 53% to 91%, and specificity from 88% to 91% in proximal femur fractures. Riaz et al.[5] confirmed these findings in a similar study. Both concluded that profile x-rays were effective in differentiating displacement fractures that did not appear to be displaced in the anteroposterior view, but they did not alter procedure in the cases in which the anteroposterior view showed a fracture with displacement.

Considering these findings, performing a lateral x-ray in femoral neck fractures that do not show displacement in the anteroposterior plane is relevant. Khan et al.[18] demonstrated that the presence of posterior femoral neck multifragmentation in non-displaced and displaced fractures showed no association with complications, which occurred in 18% of non-displaced fractures. Parker et al.[19] observed that the results of fixation in non-displaced fractures were better than arthroplasty in displaced fractures. However, the need for reintervention was greater in non-displaced fractures that were treated with fixation (17%). In another study, Paker et al.[20] identified non-union in 30% of cases of displaced fractures treated with internal fixation, compared to 9% in fractures without displacement. Conn and Parker[13] demonstrated that advanced age, associated with posterior angle and the need for walking assistance prior to the fracture are indicative of non-union after fracture of the proximal femur.

The gender distribution of our series was similar to that of other studies,[4-8,17] but the average age was lower (58 years); this was explained by the inclusion of mostly young patients with multiple trauma. Despite the significant rate of patients with posterior displacement, fixation with cannulated was applied in most cases. Our re-operation rate of 21% demonstrates that the surgical method must consider the findings from the lateral x-ray. Computed tomography can be used in cases where the x-rays are inconclusive. It is important to emphasize the lack of a statistically significant association between posterior displacement and the re-operation rate, which may represent a false negative result due to the limited size of our sample.

This study has a number of limitations. The limited case series decreases the power to search for associations between the presence of displacement and complications. The retrospective design predisposes the study to selection bias and limited the registration of information, mainly related to patient follow-up.

CONCLUSION

Most of the femoral neck fractures classified as Garden grades I and II exhibit some degree of posterior displacement in the lateral x-ray. This finding, coupled with the significant rate of synthesis material failure in these patients, should be considered in choosing the treatment method.

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to the development of this manuscript. KEK (0000-0002-3700-2718)* and JSS (0000-0001-9753-3644)* were responsible for developing the concept of the project. NZL (0000-0001-8614-4678)* and FBAS (0000-0002-0359-9704)* designed the study and analyzed the data. LPM (0000-0002-1965-2100)* and DGN (0000-0002-8933-7472)* collected the data and drafted the manuscript. FBAS (0000-0002-3493-7235)* conducted the statistical analysis and review. *ORCID (Open Researcher and Contributor ID).

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CIÊNCIA E NATUREZA
CONTRA DORES MUSCULARES E INFLAMAÇÃO

Referências Bibliográficas: 1) Bula do produto ACHEFLAN: creme. Farmacêutico Responsável: Dr. Wilson R. Farias. Aché Laboratórios Farmacêuticos S.A. 2) BRANDÃO, D.C. et al. Estudo fase III, duplo-cego, aleatório, comparativo para avaliar eficácia e tolerabilidade da Cordia verbenacea e do diclofenaco dietilamônio, em pacientes portadores de contusões, entorses, traumas e lesões musculares, com início inferior a 24 horas. Revista Brasileira de Medicina, v.63, n.8, p.408-415, 2006. 3) REFSIO, C. et al. Avaliação clínica da eficácia e segurança do uso de extrato padronizado da Cordia verbenacea em pacientes portadores de tendinite e dor miofascial. RBM Revista Brasileira de Medicina, v.62, n.1/2, 40-46, 2005. 4) OLIVEIRA JÚNIOR, E.M. et al. Estudo piloto de avaliação da influência do ultrasom na estabilidade do alfa-humuleno e trans-cariofileno presentes no fitomedicamento antiinflamatório, creme de Cordia verbenacea 5 mg/g. Med Reabil, v.25, n.2, p.50-54, 2006. 5) Kairos Web Brasil. Disponível em: http://brasil.kairosweb.com.Acesso em: Dez/2016. 6) Invenções com Depósitos de Patentes junto ao INPI: Acheflan - PI8805094, PI0419105. 6) Disponível em:<http://www.redetec.org.br/inventabrasil/acheflan.htm>. Acesso em: Julho. 2014.

CONTRAINDICAÇÕES: INDIVÍDUOS SENSÍVEIS A CORDIA VERBENACEA DC. OU A QUALQUER COMPONENTE DA FÓRMULA. INTERAÇÕES MEDICAMENTOSAS: NÃO HOUVE RELATO DE INTERAÇÃO MEDICAMENTOSA NOS ESTUDOS CONDUZIDOS PARA AVALIAÇÃO DO ACHEFLAN.

ACHEFLAN. Cordia verbenacea DC - MS - 1.0573.0341. **Indicações: ACHEFLAN** é indicado nas seguintes situações: tendinites, afecções músculo-esqueléticas associadas à dor e inflamação, como dor miofascial (como dorsalgia e lombalgia), em quadros inflamatórios dolorosos associados a traumas de membros, entorses e contusões. **Contra-indicações: ACHEFLAN é contra-indicado nas seguintes situações: Indivíduos sensíveis a *Cordia verbenacea DC.* ou a qualquer componente da fórmula. Ocorrência de soluções de continuidade (feridas, queimaduras, lesões infeccionadas, etc). Advertências: ACHEFLAN** É PARA USO EXTERNO E NÃO DEVE SER INGERIDO. NÃO DEVE SER UTILIZADO ASSOCIADO A OUTROS PRODUTOS DE USO TÓPICO. RARAMENTE PODE CAUSAR AUMENTO DA SENSIBILIDADE LOCAL. TESTES REALIZADOS EM ANIMAIS INDICAM QUE **ACHEFLAN** NÃO APRESENTA ATIVIDADE IRRITANTE NA MUCOSA OCULAR. ENTRETANTO, RECOMENDA-SE LAVAR ABUNDANTEMENTE O LOCAL COM ÁGUA EM CASO DE CONTATO COM OS OLHOS. **Uso em idosos, crianças e outros grupos de risco:** não existe experiência clínica sobre o uso de **ACHEFLAN** em idosos, crianças abaixo de 12 anos, gestantes e lactantes. **Gravidez e lactação:** categoria de risco na gravidez C: Não foram realizados estudos em animais prenhes e nem em mulheres grávidas. "ESTE MEDICAMENTO NÃO DEVE SER UTILIZADO DURANTE A GESTAÇÃO OU AMAMENTAÇÃO SEM ORIENTAÇÃO MÉDICA". **Interações medicamentosas:** não houve relato de interação medicamentosa nos estudos conduzidos para avaliação do **ACHEFLAN**. Entretanto sua associação a outros fármacos deverá ser avaliada pelo médico. **Reações adversas:** O USO DE **ACHEFLAN** NÃO ESTÁ ASSOCIADO A RELATO DE REAÇÕES ADVERSAS. RARAMENTE PODE CAUSAR AUMENTO DA SENSIBILIDADE LOCAL. "ATENÇÃO: ESTE É UM MEDICAMENTO NOVO E, EMBORA AS PESQUISAS TENHAM INDICADO EFICÁCIA E SEGURANÇA ACEITÁVEIS PARA COMERCIALIZAÇÃO, EFEITOS INDESEJÁVEIS E NÃO CONHECIDOS PODEM OCORRER. NESTE CASO, INFORME SEU MÉDICO." **Posologia:** aplicação tópica, sobre a pele íntegra, de 8 em 8 horas. A duração do tratamento varia conforme a afecção que se pretende tratar. Nos ensaios clínicos a duração do tratamento variou entre 1 a 2 semanas podendo ser prolongado até 4 semanas. Farmacêutica Responsável: Gabriela Mallmann - CRF-SP nº 30.138. **VENDA SOB PRESCRIÇÃO MÉDICA.** MB03 SAP 4052805 e SAP 4053004

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TANDRILAX®

carisoprodol, cafeína
diclofenaco sódico, paracetamol

Uma relação de confiança se constrói com o tempo!

Referências Bibliográficas:1. Kairos Web Brasil. Disponível em: <http://brasil.kairosweb.com/index.html>.Acesso em: Dez/2016. **2.** Internal Report – CLOSE UP Dez/2016.

Contraindicação: Hipersensibilidade a qualquer dos componentes da fórmula. Interação Medicamentosa: A administração concomitante de glicocorticóides e outros agentes anti-inflamatórios não-esteróides pode levar ao agravamento de reações adversas gastrintestinais.

TANDRILAX é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas.

TANDRILAX (cafeína 30 mg / carisoprodol 125 mg / diclofenaco sódico 50 mg / paracetamol 300 mg) Comprimidos. USO ORAL. USO ADULTO. Indicações: Tratamento de reumatismo nas suas formas inflamatório-degenerativas agudas e crônicas; crises agudas de gota, estados inflamatórios agudos, pós-traumáticos e pós-cirúrgicos. Exacerbações agudas de artrite reumatóide e osteo-artrose e estados agudos de reumatismo nos tecidos extra-articulares e como coadjuvante em processos inflamatórios graves decorrentes de quadros infecciosos. **Contraindicações: Nos casos de úlcera péptica em atividade; hipersensibilidade a quaisquer dos componentes de sua fórmula; discrasias sanguíneas; diáteses hemorrágicas (trombocitopenia, distúrbios da coagulação), porfiria; insuficiência cardíaca, hepática ou renal grave; hipertensão grave. É contra-indicado em pacientes asmáticos nos quais são precipitados acessos de asma, urticária ou rinite aguda pelo ácido acetilsalicílico e demais inibidores da via da cicloxigenase da síntese de prostaglandinas. Precauções e Advertências: O uso em pacientes idosos, geralmente mais sensíveis aos medicamentos, deve ser cuidadosamente observado. Desaconselha-se o uso do TANDRILAX durante a gravidez e lactação. A possibilidade de reativação de úlceras pépticas requer anamnese cuidadosa quando houver história pregressa de dispepsia, hemorragia gastrintestinal ou úlcera péptica. Nas indicações do TANDRILAX por períodos superiores a dez dias, deverá ser realizado hemograma e provas de função hepática antes do início do tratamento e, periodicamente, a seguir. A diminuição da contagem de leucócitos e/ou plaquetas, ou do hematócrito requer a suspensão da medicação. Em pacientes portadores de doenças cardiovasculares, a possibilidade de ocorrer retenção de sódio e edema deverá ser considerada. Observando-se reações alérgicas pruriginosas ou eritematosas, febre, icterícia, cianose ou sangue nas fezes, a medicação deverá ser imediatamente suspensa. Não use outro produto que contenha paracetamol. Não é indicado para crianças abaixo de 14 anos, com exceção de casos de artrite juvenil crônica. Interações medicamentosas:** O diclofenaco sódico, constituinte do TANDRILAX, pode elevar a concentração plasmática de lítio ou digoxina, quando administrado concomitantemente com estas preparações. Alguns agentes antiinflamatórios não-esteróides são responsáveis pela inibição da ação de diuréticos da classe da furosemida e pela potenciação de diuréticos poupadores de potássio, sendo necessário o controle periódico dos níveis séricos de potássio. A administração concomitante de glicocorticóides e outros agentes antiinflamatórios não-esteróides pode levar ao agravamento de reações adversas gastrintestinais. A biodisponibilidade do TANDRILAX é alterada pelo ácido acetilsalicílico quando este composto é administrado conjuntamente. Recomenda-se a realização de exames laboratoriais periódicos quando anticoagulantes forem administrados juntamente com TANDRILAX, para aferir se o efeito anticoagulante desejado está sendo mantido. Pacientes em tratamento com metotrexato devem abster-se do uso do TANDRILAX nas 24 horas que antecedem ou que sucedem sua ingestão, uma vez que a concentração sérica pode elevar-se, aumentando a toxicidade deste quimioterápico. **Reações adversas: Distúrbios gastrintestinais como dispepsia, dor epigástrica, recorrência de úlcera péptica, náuseas, vômitos e diarréia. ocasionalmente, podem ocorrer cefaléia, sonolência, confusão mental, tonturas, distúrbios da visão, edema por retenção de eletrólitos, hepatite, pancreatite, nefrite intersticial. Foram relatadas raras reações anafilactóides urticariformes ou asmatiformes bem como síndrome de stevens-johnson e síndrome de lyell, além de leucopenia, trombocitopenia, pancitopenia, agranulocitose e anemia aplástica. o uso prolongado pode provocar necrose papilar renal. TANDRILAX é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas. Posologia:** A dose mínima diária recomendada é de um comprimido a cada 12 horas e a duração do tratamento deve ser a critério médico e não deverá ultrapassar 10 dias. Tratamentos mais prolongados requerem observações especiais (vide "Precauções"). Os comprimidos do TANDRILAX deverão ser ingeridos inteiros (sem mastigar), às refeições, com auxílio de líquido. "SE PERSISTIREM OS SINTOMAS O MÉDICO DEVERÁ SER CONSULTADO." VENDA SOB PRESCRIÇÃO MÉDICA - MS - 1.0573.0055 - MB 08 - SAP 4104203

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ALÍVIO COM[1,2]

dorene pregabalina

Rápido, eficaz e seguro no tratamento da fibromialgia.[3]

Redução da dor
a partir da primeira semana de tratamento na fibromialgia[4]

A pregabalina é eficaz
em reduzir a dor dos pacientes com fibromialgia[5]

Melhora da disfunção do sono
relacionada à fibromialgia.[6]
Grande parte desse benefício foi devido:[6]

- Efeito da pregabalina na insônia[6]
- Atividade analgésica do medicamento[6]

Referências Bibliográficas: 1) TOLLE, T. et al. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: a randomized, double-blind study. European Journal of Pain, v. 12, n. 2, p. 203-213, 2008. 2) OHTA, H. et al. A randomized, double-blind, multicenter, placebo-controlled phase III trial to evaluate the efficacy and safety of pregabalin in Japanese patients with fibromyalgia. Arthritis Research & Therapy, v. 14, N. 217, 2012. 3) BOOMERSHINE, C. S. Pregabalin for the management of fibromyalgia syndrome. Journal of Pain Research, v. 3, p. 81-88, 2010. 4) PAUER, L. et al. An international, randomized, double-blind, placebo-controlled, phase III trial of pregabalin monotherapy in treatment of patients with fibromyalgia. J Rheumatol, v. 38, n. 12, p. 2643-2652, 2011. 5) HEYMANN, R.E. et al. Consenso Brasileiro do tratamento da fibromialgia. Rev Bras Reumatol, v. 50, n.1, p.56-66, 2010. - A pregabalina é eficaz em reduzir a dor dos pacientes com fibromialgia (grau de recomendação A, nível de evidência 1b. Página 60, coluna 1, 5º parágrafo. - Consenso brasileiro do tratamento da fibromialgia, que inclui a pregabalina no tratamento da fibromialgia com grau de recomendação A e nível de evidência 1B. 6) RUSSELL, I.J. et al. The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. Sleep Med., v. 10, n. 6, p. 604-610, 2009.

DORENE (pregabalina) 75 mg e 150 mg. Cápsula. USO ORAL. USO ADULTO E PEDIÁTRICO ACIMA DE 12 ANOS (vide Indicações). Indicações: Dor Neuropática; Epilepsia; Transtorno de Ansiedade Generalizada (TAG); Fibromialgia. Contraindicações: Dorene é contraindicado a pacientes com hipersensibilidade conhecida à pregabalina ou a qualquer componente da fórmula. Precauções e advertências: **Pacientes com problemas hereditários raros de intolerância a galactose, deficiência de lactase ou má- absorção de glicose-galactose não devem utilizar pregabalina cápsulas. Alguns pacientes diabéticos sob tratamento com pregabalina que obtiverem ganho de peso podem necessitar de ajuste da medicação hipoglicêmica. Houve relatos de reações de hipersensibilidade, incluindo casos de angioedema. Pregabalina deve ser descontinuado imediatamente se ocorrerem sintomas de angioedema, tais como edema facial, perioral ou da via aérea superior. O tratamento com pregabalina está associado com tontura e sonolência, que pode aumentar a ocorrência de acidentes (queda) na população idosa. Pacientes devem ser alertados para ter cautela até que os efeitos potenciais de pregabalina sejam familiares. Visão borrada transitória e outras alterações na acuidade visual foram reportadas por pacientes tratados com pregabalina. A descontinuação da pregabalina pode resultar na resolução ou melhora desses sintomas visuais. Foram observados sintomas de retirada em alguns pacientes após a descontinuação do tratamento prolongado e de curto prazo com pregabalina. Os seguintes eventos foram mencionados: insônia, dor de cabeça, náusea, ansiedade, hiperidrose e diarreia (vide item Reações Adversas). Como é o caso com qualquer droga ativa do SNC, deve-se avaliar cuidadosamente o histórico de pacientes quanto ao abuso de drogas e observá-los quanto a sinais de abuso da pregabalina. Foi relatada melhora da função renal após a descontinuação ou redução da dose de pregabalina. Houve relatos pós-comercialização de insuficiência cardíaca congestiva em alguns pacientes recebendo pregabalina. Devido aos dados limitados de pacientes com insuficiência cardíaca congestiva grave, Dorene deve ser administrado com cautela nesses pacientes (vide item 9. Reações Adversas).** Efeitos sobre a Habilidade de Dirigir e Operar Máquinas: Dorene pode produzir tontura e sonolência que, portanto, podem prejudicar a habilidade de dirigir e operar máquinas. Os pacientes devem ser aconselhados a não dirigir, operar máquinas complexas, ou se engajar em outras atividades potencialmente perigosas até que se saiba se este medicamento afeta a sua capacidade de executar tais atividades. Uso em Idosos, Crianças e Outros Grupos de Risco: Vide item Posologia. Gravidez e lactação: Uso durante a Gravidez: Não há dados adequados sobre o uso de pregabalina em mulheres grávidas. Estudos em animais mostraram toxicidade reprodutiva. O risco potencial a humanos é desconhecido. Portanto, Dorene não deve ser utilizado durante a gravidez. Métodos contraceptivos eficazes devem ser utilizados por mulheres com potencial de engravidar. **A pregabalina é um medicamento classificado na categoria C de risco de gravidez. Portanto, este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista.** Uso durante a Lactação: Não se sabe se a pregabalina é excretada no leite materno de humanos. Entretanto, está presente no leite de ratas. Portanto, a amamentação não é recomendada durante o tratamento com Dorene. Interações medicamentosas: A pregabalina provavelmente não inibe o metabolismo de fármacos ***in vitro*** e nem se liga a proteínas plasmáticas. A pregabalina pode potencializar os efeitos do etanol e lorazepan. A pregabalina parece ser aditiva no prejuízo da função cognitiva e coordenação motora grosseira causado pela oxicodona. Em experiência pós-comercialização, houve relatos de insuficiência respiratória e coma em pacientes sob tratamento de pregabalina e outros medicamentos antidepressivos do SNC. Há relatos pós-comercialização de eventos relacionados à redução da função do trato gastrintestinal inferior (por ex, obstrução intestinal, íleo paralítico, constipação) quando a pregabalina foi coadministrada com medicamentos que têm o potencial para produzir constipação, tais como analgésicos opioides. Não foram conduzidos estudos de interação farmacodinâmica específica em voluntários idosos. Reações adversas: **As reações adversas mais comuns foram tontura e sonolência, em geral, de intensidade leve a moderada. As reações adversas comuns foram: Aumento de apetite, Confusão, desorientação, irritabilidade, humor eufórico, diminuição da libido, insônia, Ataxia, coordenação anormal, transtorno de equilíbrio, amnésia, distúrbios de atenção, dificuldade de memória, tremores, disartria, parestesia, sedação, letargia, Visão turva, diplopia, Vertigem, Vômitos, distensão abdominal, constipação, boca seca, flatulência, disfunção erétil, edema periférico, edema, marcha anormal, sensação de embriaguez, sensação anormal, fadiga e aumento de peso. As seguintes reações adversas foram relatadas durante a pós-comercialização: Sistema imune: angioedema, reação alérgica, hipersensibilidade. Sistema nervoso: dor de cabeça, perda de consciência, prejuízo mental.** Oftalmológicos: ceratite. Cardíacos: insuficiência cardíaca congestiva. Respiratório e torácico: edema pulmonar. Gastrintestinais: edema de língua, diarreia, náusea. Pele e tecido subcutâneo: inchaço da face, prurido. Renais e urinários: retenção urinária. Reprodutor e mamas: ginecomastia. Geral: mal-estar. Idosos (acima de 65 anos de idade). Num total de 998 pacientes idosos, não foram observadas diferenças quanto a segurança geral, em comparação aos pacientes com menos de 65 anos de idade. Posologia: Dorene deve ser utilizado por via oral, com ou sem alimentos. Cada cápsula de Dorene contêm 75 mg ou 150 mg de pregabalina. Dor Neuropática: A dose inicial recomendada de Dorene é de 75 mg duas vezes ao dia (150 mg/dia), com ou sem alimentos. Para a maioria dos pacientes, 150 mg duas vezes ao dia é a dose ideal. Com base na resposta individual e na tolerabilidade do paciente, a dose poderá ser aumentada para 150 mg duas vezes ao dia após um intervalo de 3 a 7 dias e, se necessário, até uma dose máxima de 300 mg duas vezes ao dia após mais uma semana. Epilepsia: A dose inicial recomendada de Dorene é de 75 mg duas vezes ao dia (150 mg/dia), com ou sem alimentos. Com base na resposta e tolerabilidade individuais do paciente, a dose poderá ser aumentada para 150 mg duas vezes ao dia após 1 semana. A dose máxima de 300 mg duas vezes ao dia pode ser atingida após mais 1 semana. Transtorno de Ansiedade Generalizada (TAG): A dose varia de 150 a 600 mg/dia, divididas em duas ou três doses. A necessidade para o tratamento deve ser reavaliada regularmente. Fibromialgia: A dose recomendada de Dorene é de 300 a 450 mg/dia. A dose deve ser iniciada com 75 mg duas vezes ao dia (150 mg/dia), com ou sem alimentos, e a dose pode ser aumentada para 150 mg duas vezes ao dia (300 mg/dia) em uma semana baseado na eficácia e tolerabilidade individuais. Descontinuação do Tratamento: Se Dorene for descontinuado, recomenda-se que isto seja feito gradualmente durante no mínimo 1 semana. Uso em Pacientes com Insuficiência Renal: A redução da dosagem em pacientes com a função renal comprometida deve ser individualizada de acordo com o clearance de creatinina. Para pacientes submetidos à hemodiálise, a dose diária de Dorene deve ser ajustada com base na função renal. Além da dose diária, uma dose suplementar deve ser administrada imediatamente após cada tratamento de 4 horas de hemodiálise. Uso em Pacientes com Insuficiência Hepática: Nenhum ajuste de dose é necessário para pacientes com insuficiência hepática. Uso em Crianças: A segurança e a eficácia de pregabalina em pacientes pediátricos abaixo de 12 anos de idade ainda não foram estabelecidas. O uso em crianças não é recomendado. Uso em Adolescentes (12 a 17 anos de idade): Pacientes adolescentes com epilepsia podem receber a dose como adultos. A segurança e a eficácia de pregabalina em pacientes abaixo de 18 anos de idade com dor neuropática não foram estabelecidas. Uso em Pacientes Idosos (acima de 65 anos de idade): Pacientes idosos podem necessitar de redução da dose de Dorene devido à diminuição da função renal. Dose Omitida: Caso o paciente esqueça de tomar Dorene no horário estabelecido, deve tomá-lo assim que lembrar. Entretanto, se já estiver perto do horário de tomar a próxima dose, deve desconsiderar a dose esquecida e tomar a próxima. **Este medicamento não pode ser partido, aberto ou mastigado.** SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. **VENDA SOB PRESCRIÇÃO MÉDICA. SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA.** MS - 1.0573.0457. MB 02_VP SAP 4475900.

Contraindicações: Dorene não deve ser utilizado se você tem hipersensibilidade (alergia) conhecida à pregabalina ou a qualquer componente da fórmula.
Interações medicamentosas: A pregabalina pode potencializar o efeito da oxicodona (analgésico), bebidas alcoólicas e de lorazepam (tranquilizante).

DORENE é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas.

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Referências Bibliográficas: 1. Internal Report. Dados de auditoria IMS-PMB. Junho/2016. **2.** Bula do produto ARTROLIVE: cápsulas. Farmacêutica Responsável: Gabriela Mallmann. Guarulhos, SP. Aché Laboratórios Farmacêuticos S.A. **3.** Bula do produto ARTROLIVE: granulado em sachê. Farmacêutica Responsável: Gabriela Mallmann. Guarulhos, SP. Aché Laboratórios Farmacêuticos S.A. **4.** MARTEL-PELLETIER, J. et al. First line analysis of the effects of treatment on progression of structural changes in knee osteoarthritis over 24 months: data from the osteoarthritis initiative progression cohort. Ann Rheum Dis, v. 74, n. 3, p. 547-556, 2015.

Contraindicação: Pacientes que apresentem hipersensibilidade a quaisquer dos componentes de sua fórmula. Interação medicamentosa: É recomendável que pacientes diabéticos monitorem seus níveis sanguíneos de glicose mais frequentemente durante o tratamento com Artrolive.

ARTROLIVE CAPS. sulfato de glicosamina + sulfato de condroitina. MS – 1.0573.0286. **INDICAÇÕES: ARTROLIVE** é indicado para osteoartrite, osteoartrose ou artrose em todas as suas manifestações. **CONTRAINDICAÇÕES: ARTROLIVE** É CONTRAINDICADO EM PACIENTES QUE APRESENTEM HIPERSENSIBILIDADE A QUAISQUER DOS COMPONENTES DE SUA FÓRMULA, GRAVIDEZ E LACTAÇÃO. **PRECAUÇÕES E ADVERTÊNCIAS:** SÃO NECESSÁRIOS O DIAGNÓSTICO PRECISO E O ACOMPANHAMENTO CUIDADOSO DE PACIENTES COM SINTOMAS INDICATIVOS DE AFECÇÃO GASTRINTESTINAL, HISTÓRIA PREGRESSA DE ÚLCERA GÁSTRICA OU INTESTINAL, DIABETES MELLITUS OU A CONSTATAÇÃO DE DISTÚRBIOS DO SISTEMA HEMATOPOIÉTICO OU DA COAGULAÇÃO SANGUÍNEA ASSIM COMO PORTADORES DE INSUFICIÊNCIA DAS FUNÇÕES RENAL, HEPÁTICA OU CARDÍACA. SE OCORRER EVENTUALMENTE ULCERAÇÃO PÉPTICA OU SANGRAMENTO GASTRINTESTINAL EM PACIENTES SOB TRATAMENTO, A MEDICAÇÃO DEVERÁ SER SUSPENSA IMEDIATAMENTE. DEVIDO À INEXISTÊNCIA DE INFORMAÇÕES TOXICOLÓGICAS DURANTE O PERÍODO GESTACIONAL, **ARTROLIVE** NÃO ESTÁ INDICADO PARA SER UTILIZADO DURANTE A GRAVIDEZ. NÃO EXISTEM INFORMAÇÕES SOBRE A PASSAGEM DO MEDICAMENTO PARA O LEITE MATERNO SENDO DESACONSELHADO SEU USO NESSAS CONDIÇÕES E AS LACTANTES SOB TRATAMENTO NÃO DEVEM AMAMENTAR. PODE OCORRER FOTOSSENSIBILIZAÇÃO EM PACIENTES SUSCETÍVEIS, PORTANTO PACIENTES COM HISTÓRICO DE FOTOSSENSIBILIDADE A OUTROS MEDICAMENTOS DEVEM EVITAR SE EXPOR À LUZ SOLAR. FORAM DESCRITOS NA LITERATURA, ALGUNS CASOS DE HIPERTENSÃO SISTÓLICA REVERSÍVEL EM PACIENTES NÃO PREVIAMENTE HIPERTENSOS. NA VIGÊNCIA DO TRATAMENTO COM GLICOSAMINA E CONDROITINA, PORTANTO, A PRESSÃO ARTERIAL DEVE SER VERIFICADA PERIODICAMENTE DURANTE O TRATAMENTO COM **ARTROLIVE**. FORAM RELATADOS POUCOS CASOS DE PROTEINÚRIA LEVE E AUMENTO DA CREATINO-FOSFOQUINASE (CPK) DURANTE TRATAMENTO COM GLICOSAMINA E CONDROITINA, QUE VOLTARAM AOS NÍVEIS NORMAIS APÓS INTERRUPÇÃO DO TRATAMENTO. **INTERAÇÕES MEDICAMENTOSAS:** O tratamento concomitante com antiinflamatórios não-esteroidais pode incorrer no agravamento de reações adversas do sistema gastrintestinal, sendo recomendado um acompanhamento médico mais rigoroso nesses casos. Alguns autores da literatura médica descrevem que o uso de glicosamina e condroitina pode incorrer em um aumento da resistência à insulina, porém, esses estudos foram realizados com doses muito superiores às indicadas na terapêutica clínica normal e sua validade ainda é discutida por vários outros autores. Estudos recentes demonstraram que a associação condroitina e glicosamina, quando empregada em pacientes portadores de diabetes mellitus tipo II, não levou a alterações no metabolismo da glicose. Os resultados destes estudos não podem ser extrapolados para pacientes com diabetes mellitus descompensado ou não-controlado. É recomendável que pacientes diabéticos monitorem seus níveis sanguíneos de glicose mais frequentemente durante o tratamento com **ARTROLIVE**. O uso concomitante de **ARTROLIVE** com os inibidores da topoisomerase II (etoposídeo, teniposídeo e doxorrubicina) deve ser evitado, uma vez que a glicosamina induziu resistência in vitro a estes medicamentos em células humanas cancerosas de cólon e de ovário. O tratamento concomitante de **ARTROLIVE** com anticoagulantes como o acenocoumarol, dicumarol, heparina e varfarina, pode levar ao aumento das chances de sangramento, devido a alterações nos valores de INR (International Normalized Ratio). Há relato de um caso na literatura de potencialização do efeito da varfarina, com consequente aumento dos valores sanguíneos de INR. Portanto, o uso concomitante de **ARTROLIVE** com anticoagulantes orais deve levar em conta avaliações rigorosas do INR. **Reações adversas: SISTEMA CARDIOVASCULAR:** EDEMA PERIFÉRICO E TAQUICARDIA. JÁ FORAM RELATADOS COM O USO DA GLICOSAMINA, PORÉM NÃO FOI ESTABELECIDA UMA RELAÇÃO CAUSAL. FORAM DESCRITOS NA LITERATURA, ALGUNS CASOS DE HIPERTENSÃO SISTÓLICA REVERSÍVEL EM PACIENTES NÃO PREVIAMENTE HIPERTENSOS. NA VIGÊNCIA DO TRATAMENTO COM GLICOSAMINA E CONDROITINA, PORTANTO, A PRESSÃO ARTERIAL DEVE SER VERIFICADA PERIODICAMENTE DURANTE O TRATAMENTO COM **ARTROLIVE**. **SISTEMA NERVOSO CENTRAL:** MENOS DE 1% DOS PACIENTES EM ESTUDOS CLÍNICOS APRESENTARAM CEFALEIA, INSÔNIA E SONOLÊNCIA NA VIGÊNCIA DO TRATAMENTO COM A GLICOSAMINA. **ENDOCRINO-METABÓLICO:** ESTUDOS RECENTES DEMONSTRARAM QUE A ASSOCIAÇÃO CONDROITINA E GLICOSAMINA, QUANDO EMPREGADA EM PACIENTES PORTADORES DE *DIABETES MELLITUS* TIPO II, NÃO LEVOU A ALTERAÇÕES NO METABOLISMO DA GLICOSE. OS RESULTADOS DESTES ESTUDOS NÃO PODEM SER EXTRAPOLADOS PARA PACIENTES COM *DIABETES MELLITUS* DESCOMPENSADO OU NÃO-CONTROLADO. É RECOMENDÁVEL QUE PACIENTES DIABÉTICOS MONITOREM SEUS NÍVEIS SANGUÍNEOS DE GLICOSE MAIS FREQUENTEMENTE DURANTE O TRATAMENTO COM **ARTROLIVE**. **GASTRINTESTINAL:** NÁUSEA, DISPEPSIA, VÔMITO, DOR ABDOMINAL OU EPIGÁSTRICA, CONSTIPAÇÃO, DIARREIA, QUEIMAÇÃO E ANOREXIA TÊM SIDO RARAMENTE DESCRITOS NA LITERATURA NA VIGÊNCIA DE TRATAMENTO COM GLICOSAMINA E CONDROITINA. **PELE:** ERITEMA, PRURIDO, ERUPÇÕES CUTÂNEAS E OUTRAS MANIFESTAÇÕES ALÉRGICAS DE PELE FORAM REPORTADAS EM ENSAIOS CLÍNICOS COM GLICOSAMINA. PODE OCORRER FOTOSSENSIBILIZAÇÃO EM PACIENTES SUSCETÍVEIS, PORTANTO PACIENTES COM HISTÓRICO DE FOTOSSENSIBILIDADE A OUTROS MEDICAMENTOS DEVEM EVITAR SE EXPOR À LUZ SOLAR. **POSOLOGIA: Adultos:** Recomenda-se iniciar a terapêutica com a prescrição de 1 cápsula via oral 3 vezes ao dia. Como os efeitos do medicamento se iniciam em média após a terceira semana de tratamento deve-se ter em mente que a continuidade e a não-interrupção do tratamento são fundamentais para se alcançar os benefícios analgésicos e de mobilidade articular. **SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. VENDA SOB PRESCRIÇÃO MÉDICA.** M803a SAP447070. **ARTROLIVE** 1,5 g sulfato de glicosamina + 1,2 g sulfato de condroitina. MS – 1.0573.0286. **INDICAÇÕES: ARTROLIVE** é indicado para osteoartrite, osteoartrose ou artrose em todas as suas manifestações. **CONTRAINDICAÇÕES: ARTROLIVE** É CONTRAINDICADO EM PACIENTES QUE APRESENTEM HIPERSENSIBILIDADE A QUAISQUER DOS COMPONENTES DE SUA FÓRMULA, GRAVIDEZ E LACTAÇÃO. **PRECAUÇÕES E ADVERTÊNCIAS:** SÃO NECESSÁRIOS O DIAGNÓSTICO PRECISO E O ACOMPANHAMENTO CUIDADOSO DE PACIENTES COM SINTOMAS INDICATIVOS DE AFECÇÃO GASTRINTESTINAL, HISTÓRIA PREGRESSA DE ÚLCERA GÁSTRICA OU INTESTINAL, DIABETES MELLITUS OU A CONSTATAÇÃO DE DISTÚRBIOS DO SISTEMA HEMATOPOIÉTICO OU DA COAGULAÇÃO SANGUÍNEA ASSIM COMO PORTADORES DE INSUFICIÊNCIA DAS FUNÇÕES RENAL, HEPÁTICA OU CARDÍACA. SE OCORRER EVENTUALMENTE ULCERAÇÃO PÉPTICA OU SANGRAMENTO GASTRINTESTINAL EM PACIENTES SOB TRATAMENTO, A MEDICAÇÃO DEVERÁ SER SUSPENSA IMEDIATAMENTE. DEVIDO À INEXISTÊNCIA DE INFORMAÇÕES TOXICOLÓGICAS DURANTE O PERÍODO GESTACIONAL, **ARTROLIVE** NÃO ESTÁ INDICADO PARA SER UTILIZADO DURANTE A GRAVIDEZ. NÃO EXISTEM INFORMAÇÕES SOBRE A PASSAGEM DO MEDICAMENTO PARA O LEITE MATERNO SENDO DESACONSELHADO SEU USO NESSAS CONDIÇÕES E AS LACTANTES SOB TRATAMENTO NÃO DEVEM AMAMENTAR. PODE OCORRER FOTOSSENSIBILIZAÇÃO EM PACIENTES SUSCETÍVEIS, PORTANTO PACIENTES COM HISTÓRICO DE FOTOSSENSIBILIDADE A OUTROS MEDICAMENTOS DEVEM EVITAR SE EXPOR À LUZ SOLAR. FORAM DESCRITOS NA LITERATURA, ALGUNS CASOS DE HIPERTENSÃO SISTÓLICA REVERSÍVEL EM PACIENTES NÃO PREVIAMENTE HIPERTENSOS. NA VIGÊNCIA DO TRATAMENTO COM GLICOSAMINA E CONDROITINA, PORTANTO, A PRESSÃO ARTERIAL DEVE SER VERIFICADA PERIODICAMENTE DURANTE O TRATAMENTO COM **ARTROLIVE**. FORAM RELATADOS POUCOS CASOS DE PROTEINÚRIA LEVE E AUMENTO DA CREATINO-FOSFOQUINASE (CPK) DURANTE TRATAMENTO COM GLICOSAMINA E CONDROITINA, QUE VOLTARAM AOS NÍVEIS NORMAIS APÓS INTERRUPÇÃO DO TRATAMENTO. **INTERAÇÕES MEDICAMENTOSAS:** O tratamento concomitante com antiinflamatórios não-esteroidais pode incorrer no agravamento de reações adversas do sistema gastrintestinal, sendo recomendado um acompanhamento médico mais rigoroso nesses casos. Alguns autores da literatura médica descrevem que o uso de glicosamina e condroitina pode incorrer em um aumento da resistência à insulina, porém, esses estudos foram realizados com doses muito superiores às indicadas na terapêutica clínica normal e sua validade ainda é discutida por vários outros autores. Estudos recentes demonstraram que a associação condroitina e glicosamina, quando empregada em pacientes portadores de diabetes mellitus tipo II, não levou a alterações no metabolismo da glicose. Os resultados destes estudos não podem ser extrapolados para pacientes com diabetes mellitus descompensado ou não-controlado. É recomendável que pacientes diabéticos monitorem seus níveis sanguíneos de glicose mais frequentemente durante o tratamento com **ARTROLIVE**. O uso concomitante de **ARTROLIVE** com os inibidores da topoisomerase II (etoposídeo, teniposídeo e doxorrubicina) deve ser evitado, uma vez que a glicosamina induziu resistência in vitro a estes medicamentos em células humanas cancerosas de cólon e de ovário. O tratamento concomitante de **ARTROLIVE** com anticoagulantes como o acenocoumarol, dicumarol, heparina e varfarina, pode levar ao aumento das chances de sangramento, devido a alterações nos valores de INR (International Normalized Ratio). Há relato de um caso na literatura de potencialização do efeito da varfarina, com consequente aumento dos valores sanguíneos de INR. Portanto, o uso concomitante de **ARTROLIVE** com anticoagulantes orais deve levar em conta avaliações rigorosas do INR. **Reações adversas: SISTEMA CARDIOVASCULAR:** EDEMA PERIFÉRICO E TAQUICARDIA. JÁ FORAM RELATADOS COM O USO DA GLICOSAMINA, PORÉM NÃO FOI ESTABELECIDA UMA RELAÇÃO CAUSAL. FORAM DESCRITOS NA LITERATURA, ALGUNS CASOS DE HIPERTENSÃO SISTÓLICA REVERSÍVEL EM PACIENTES NÃO PREVIAMENTE HIPERTENSOS. NA VIGÊNCIA DO TRATAMENTO COM GLICOSAMINA E CONDROITINA, PORTANTO, A PRESSÃO ARTERIAL DEVE SER VERIFICADA PERIODICAMENTE DURANTE O TRATAMENTO COM **ARTROLIVE**. **SISTEMA NERVOSO CENTRAL:** MENOS DE 1% DOS PACIENTES EM ESTUDOS CLÍNICOS APRESENTARAM CEFALEIA, INSÔNIA E SONOLÊNCIA NA VIGÊNCIA DO TRATAMENTO COM A GLICOSAMINA. **ENDOCRINO-METABÓLICO:** ESTUDOS RECENTES DEMONSTRARAM QUE A ASSOCIAÇÃO CONDROITINA E GLICOSAMINA, QUANDO EMPREGADA EM PACIENTES PORTADORES DE *DIABETES MELLITUS* TIPO II, NÃO LEVOU A ALTERAÇÕES NO METABOLISMO DA GLICOSE. OS RESULTADOS DESTES ESTUDOS NÃO PODEM SER EXTRAPOLADOS PARA PACIENTES COM *DIABETES MELLITUS* DESCOMPENSADO OU NÃO-CONTROLADO. É RECOMENDÁVEL QUE PACIENTES DIABÉTICOS MONITOREM SEUS NÍVEIS SANGUÍNEOS DE GLICOSE MAIS FREQUENTEMENTE DURANTE O TRATAMENTO COM **ARTROLIVE**. **GASTRINTESTINAL:** NÁUSEA, DISPEPSIA, VÔMITO, DOR ABDOMINAL OU EPIGÁSTRICA, CONSTIPAÇÃO, DIARREIA, QUEIMAÇÃO E ANOREXIA TÊM SIDO RARAMENTE DESCRITOS NA LITERATURA NA VIGÊNCIA DE TRATAMENTO COM GLICOSAMINA E CONDROITINA. **PELE:** ERITEMA, PRURIDO, ERUPÇÕES CUTÂNEAS E OUTRAS MANIFESTAÇÕES ALÉRGICAS DE PELE FORAM REPORTADAS EM ENSAIOS CLÍNICOS COM GLICOSAMINA. PODE OCORRER FOTOSSENSIBILIZAÇÃO EM PACIENTES SUSCETÍVEIS, PORTANTO PACIENTES COM HISTÓRICO DE FOTOSSENSIBILIDADE A OUTROS MEDICAMENTOS DEVEM EVITAR SE EXPOR À LUZ SOLAR. **POSOLOGIA: Adultos:** Recomenda-se iniciar a terapêutica com a prescrição de 1 envelope por dia, dissolvido em um copo com água. Como os efeitos do medicamento se iniciam em média após a terceira semana de tratamento deve-se ter em mente que a continuidade e a não-interrupção do tratamento são fundamentais para se alcançar os benefícios analgésicos e de mobilidade articular. **SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. VENDA SOB PRESCRIÇÃO MÉDICA.** M803a SAP406702.

Material técnico-científico de distribuição exclusiva à classe médica.

A ação eficaz[1] no tratamento da Osteoartrite.

Glicolive
sulfato de glicosamina

Qualidade Aché e preço acessível para o tratamento da OA.[2-5]

Referências Bibliográficas: 1) MATHESON, A. J; PERRY, C. M. Glucosamine: a review of its use in the management of osteoarthritis. Drugs Aging, v. 20, n. 14, p. 1041-60, 2003. **2)** Kairos Web Brasil. Disponível em: http://brasil.kairosweb.com Acesso em: Agosto/16. **3)** Programa Cuidados pela Vida (" O Programa Cuidados pela Vida pode alterar ou interromper esta campanha sem aviso prévio". Desconto calculado sobre o Preço Máximo ao Consumidor)". **4)** Bula do produto GLICOLIVE: pó para solução oral. Farmacêutica Responsável: Gabriela Mallmann, Guarulhos, SP. Aché Laboratórios Farmacêuticos S.A. **5)** BRASIL. ANVISA. Agência Nacional de Vigilância Sanitária. Resolução - RE nº 1.101, de 9 de abril de 2015. Concede Certificação de Boas Práticas de Fabricação ao Aché. Diário Oficial da União, Brasília DF, p. 133, 9 abr 2015. **6)** Internal Report.

Contraindicações: hipersensibilidade a glicosamina ou a qualquer outro componente da fórmula. Interações medicamentosas: o sulfato de glicosamina pode favorecer a absorção gastrintestinal de tetraciclinas e reduzir a de penicilina e cloranfenicol.

GLICOLIVE é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas.

GLICOLIVE (sulfato de glicosamina) 1500 mg pó para solução oral. USO ORAL. USO ADULTO. **Indicações:** GLICOLIVE é indicado no tratamento deartrose ou osteoartrite primária e secundária e suas manifestações. Contraindicações: **GLICOLIVE é contra-indicado em pacientes com hipersensibilidade a glicosamina ou a qualquer outro componente da fórmula. Não deve ser utilizado durante a gravidez, lactação ou em fenilcetonúricos. Cuidados e advertências: informar ao médico caso esteja utilizando outros medicamentos. Recomenda-se cautela em pacientes com sintomas indicativos de distúrbios gastrintestinais, história de úlcera gástrica ou intestinal, diabetes mellitus, portadores de insuficiência renal, hepática ou cardíaca. Caso ocorra ulceração péptica ou sangramento gastrintestinal a medicação deverá ser suspensa imediatamente. Recomenda-se evitar a ingestão de bebidas alcoólicas, durante o tratamento.** Gravidez e lactação: não há dados com relação ao uso de GLICOLIVE na gravidez e lactação humana, portanto, seu uso não é recomendado nestes casos. Interações medicamentosas: o sulfato de glicosamina pode favorecer a absorção gastrintestinal de tetraciclinas e reduzir a de penicilina e cloranfenicol. Não existe limitação para administração simultânea de analgésicos ou anti-inflamatórios esteroides e não esteroides. **Reações adversas: os efeitos colaterais mais comuns são de origem gastrintestinal, de intensidade leve a moderada, consistindo em desconforto gástrico, diarreia, náusea, prurido e cefaléia. Reações hematológicas: não foram observadas alterações clínicas significativas.Testes laboratoriais: não se observaram diferenças significativas nos valores médios nem nos dados individuais das provas laboratoriais e constantes vitais. Glicolive é um medicamento. "Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas."** Posologia: GLICOLIVE apresenta-se na forma de pó branco a levemente amarelado, com odor e sabor de abacaxi. Dispensar o conteúdo do envelope em um copo com água. Aguardar entre 2 a 5 minutos, mexer a solução com o auxílio de uma colher e consumir. Consumir 1 envelope por dia antes das refeições ou segundo indicação médica. A duração do tratamento fica a critério do médico. Para informações completas, consultar a bula na íntegra através da Central de Atendimento ao Cliente.VENDA SOB PRESCRIÇÃO MÉDICA. MS - 1.0573. 0403. MB05 SAP 4423401. "Material técnico científico de distribuição exclusiva à classe médica." SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.

Artrosil
lisinato de cetoprofeno

SMR
SMART MODULATED RELEASE[3]

O ÚNICO lisinato de cetoprofeno[1]
com **TECNOLOGIA SMR[2,3]**

SEGURANÇA[2]
- Tolerabilidade gástrica 3 a 4 vezes maior comparado ao cetoprofeno comum.[2]

RÁPIDO INÍCIO DE AÇÃO[2]

EFICÁCIA[2]
- **Potência** anti-inflamatória, analgésica e antipirética superior ao cetoprofeno.[2]
- **Liberação prolongada:** Níveis plasmáticos mantidos por até 24h.[2,4]

Apresentações[4]
Cápsulas de liberação prolongada
de 160 e 320 mg com 10 e 20 cápsulas

Referências Bibliográficas: 1) ANVISA. Consulta de produtos. Disponível em: <http://www7.anvisa.gov.br/datavisa/Consulta_Produto/consulta_medicamento.asp>. Acesso em: Abr/2016. **2)** PELOGGIA, C.C.N.; BRITO NETO, A.J.; CUNHA, J. Avaliação da eficácia terapêuta e da tolerância do antiinflamatório lisinato de cetoprofeno, na forma cápsulas. Estudo multicêntrico aberto e não comparativo. Revista Brasileira de Medicina, v.57, n.6, p.617-624, 2000. **3)** Internal Report. **4)** Bula Do Produto ARTROSIL: Cápsulas. Farmacêutica Responsável: Gabriela Mallmann. Guarulhos, SP. Aché Laboratórios Farmacêuticos S.A.

Contraindicações: Úlcera péptica na fase ativa. Interações medicamentosas: Devido à elevada ligação de cetoprofeno com proteínas plasmáticas, é necessário reduzir a dosagem de anticoagulantes, fenitoínas ou sulfamidas quando administrados concomitantemente.

ARTROSIL (lisinato de cetoprofeno) - 160 mg e 320 mg - Cápsulas de liberação prolongada - Uso oral - Uso Adulto - Indicações: Artrose, coxartrose, espondiloartrose, artrite reumatóide, bursite, flebite e tromboflebite superficial, contusão, entorse, luxação, distensão muscular. **Contraindicações: Úlcera péptica na fase ativa, anamnese positiva de úlcera péptica recorrente, dispepsia crônica, gastrite, insuficiência renal grave, leucopenia e plaquetopenia, grave distúrbio de hemocoagulação.** Hipersensibilidade a quaisquer componentes de sua fórmula. Existe a possibilidade de hipersensibilidade cruzada com ácido acetilsalicílico ou outros fármacos anti-inflamatórios não-esteroidais. Portanto, o cetoprofeno não deve ser administrado a pacientes nos quais o ácido acetilsalicílico ou outros fármacos antiinflamatórios não-esteroidais tenham provocado sintomas de asma, rinite, urticária. O uso de lisinato de cetoprofeno é contra-indicado durante o primeiro e o último trimestre de gestação, pois pode causar hipertensão pulmonar e toxicidade renal no feto, característica comum aos inibidores da síntese de prostaglandinas. Pode também levar ao aumento do tempo de sangramento das gestantes e fetos e conseqüentemente eventuais manifestações hemorrágicas no recém-nascido. Há risco de retardar o trabalho de parto. **Precauções e advertências: O uso de cetoprofeno em pacientes com asma brônquica ou com diáteses alérgicas pode provocar uma crise asmática. Em pacientes com função renal comprometida, a administração de cetoprofeno deve ser efetuada com particular cautela levando-se em consideração a eliminação essencialmente renal do fármaco.** Embora não tenha sido observada experimentalmente toxicidade embriofetal com cetoprofeno nas doses previstas para uso clínico, a administração em mulheres grávidas, durante a amamentação ou na infância não é recomendada. **Interações medicamentosas: Devido à elevada ligação de cetoprofeno com proteínas plasmáticas, é necessário reduzir a dosagem de anticoagulantes, fenitoínas ou sulfamidas quando administrados concomitantemente.** O uso com ácido acetilsalicílico reduz o nível sérico de cetoprofeno e aumenta o risco de distúrbios gastrintestinais. No caso da administração com lítio há aumento de seu nível sérico podendo levar à intoxicação. Foi observado aumento da toxicidade do metotrexato em decorrência da diminuição de seu "clearance" renal. A probenecida reduz as perdas de cetoprofeno e aumenta seu nível sérico. A metoclopramida reduz a biodisponibilidade do cetoprofeno e pode ocorrer uma pequena redução de sua absorção no uso simultâneo com hidróxidos de magnésio ou alumínio. **Reações adversas: Assim como com outros antiinflamatórios não-esteroidais, podem ocorrer distúrbios transitórios, no trato gastrintestinal, tais como gastralgia, náusea, vômito, diarréia e flatulência.** Excepcionalmente foram observadas hemorragia gastrintestinal, discinésia transitória, astenia, cefaléia, sensação de vertigem e exantema cutâneo. O produto pode ser tomado às refeições ou com leite, a fim de evitar possíveis distúrbios gastrintestinais. **Posologia:** ARTROSIL 160 mg: Uma cápsula duas vezes ao dia durante ou após às refeições. A duração do tratamento deve ser a critério médico. ARTROSIL 320 mg: Uma cápsula ao dia durante ou após às refeições. A duração do tratamento deve ser a critério médico. SE PERSISTIREM OS SINTOMAS O MÉDICO DEVERÁ SER CONSULTADO. VENDA SOB PRESCRIÇÃO MÉDICA. MS – 1.0573.0128. MB_08 SAP 4057006.

Material técnico-científico de distribuição exclusiva a profissionais de saúde habilitados à prescrição e/ou dispensação de medicamentos.

CAC
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cac@ache.com.br
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Campanha RESPEITO PELA PRESCRIÇÃO E PELA ADESÃO AO TRATAMENTO
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osteo muscular

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mais vida para você

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cloridrato de tramadol + paracetamol

A escolha certa no combate à dor

Vários estudos **confirmam** que a associação de **Revange®** (cloridrato de tramadol + paracetamol) é **superior** ao **tratamento isolado**, oferecendo[1,2,3]:

Efeito sinérgico[1]
Redução em torno de 30% a 40% na requisição de opioides

Menos efeitos adversos[2]

17 MINUTOS[3]
Rápido início de ação*[3]

Maior tempo de ação*[3]

PREÇO $ ACESSÍVEL[4]

*** Trata-se de estudo realizado em modelo de dor de dente.**

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Contraindicações: hipersensibilidade ao tramadol, paracetamol ou a qualquer componente da fórmula ou aos opioides; intoxicações agudas pelo álcool, hipnóticos, analgésicos de ação central, opioides ou psicotrópicos; pacientes em tratamento com inibidores da monoaminoxidase (MAO) ou tratados com estes agentes nos últimos 14 dias. Interações medicamentosas: REVANGE® comprimido revestido não é recomendado como medicação pré-operatória obstétrica ou na analgesia pós-parto em lactantes, pois a segurança em lactentes e recém-nascidos não foi estudada.

REVANGE® é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas.

REVANGE®, cloridrato de tramadol e paracetamol. 37,5 MG + 325 MG comprimidos revestidos. USO ORAL. USO ADULTO. Indicações: dores moderadas a severas de caráter agudo, subagudo e crônico. **Contraindicações: hipersensibilidade ao tramadol, paracetamol ou a qualquer componente da fórmula ou aos opioides; intoxicações agudas pelo álcool, hipnóticos, analgésicos de ação central, opioides ou psicotrópicos; pacientes em tratamento com inibidores da monoaminoxidase (MAO) ou tratados com estes agentes nos últimos 14 dias. Cuidados e advertências:** convulsões foram relatadas em pacientes recebendo tramadol na dose recomendada. Relatos espontâneos pós-comercialização indicam que o risco de convulsões está aumentado com doses de tramadol acima das recomendadas. A administração de tramadol pode aumentar o risco de convulsão em pacientes tomando inibidores da MAO, neurolépticos ou outros fármacos que reduzem o limiar convulsivo. REVANGE® comprimido revestido não deve ser administrado à pacientes dependentes de opioides. O tramadol reinicia a dependência física em alguns pacientes previamente dependentes de outros opioides. REVANGE® comprimido revestido deve ser usado com cautela e em dose reduzida em pacientes recebendo depressores do SNC como álcool, opioides, agentes anestésicos, fenotiazinas, tranquilizantes ou sedativos hipnóticos. REVANGE® comprimido revestido deve ser usado com bastante cautela em pacientes sob tratamento com inibidores da monoaminoxidase pois os estudos em animais mostraram aumento da incidência de óbito com a administração combinada de inibidores da MAO e tramadol. Precauções e advertências: REVANGE® comprimido revestido não deve ser administrado em conjunto com outros produtos à base de tramadol ou paracetamol. REVANGE® comprimido revestido deve ser administrado com cautela em pacientes sob risco de depressão respiratória. REVANGE® comprimido revestido deve ser usado com cautela em pacientes com pressão intracraniana aumentada ou traumatismo craniano. Alterações da pupila (miose) provocadas pelo tramadol podem mascarar a existência, extensão ou curso da patologia intracraniana. Gravidez e lactação: uso na gravidez e lactação: REVANGE® comprimido revestido somente deverá ser utilizado durante a gravidez se o potencial benefício justificar o potencial risco para o feto. Interações medicamentosas: REVANGE® comprimido revestido não é recomendado como medicação pré-operatória obstétrica ou na analgesia pós-parto em lactantes, pois a segurança em lactentes e recém-nascidos não foi estudada. Reações adversas: efeitos sobre a capacidade de dirigir e operar máquinas: mesmo quando usado de acordo com as instruções, REVANGE® comprimido revestido pode afetar a habilidade mental ou física necessária para a realização de tarefas potencialmente perigosas como dirigir ou operar máquinas, especialmente ao início do tratamento, na mudança de outro produto para REVANGE® comprimido revestido e na administração concomitante de outras drogas de ação central e, em particular, do álcool. **REVANGE® é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas.** Os eventos adversos relatados com maior freqüência ocorreram no sistema nervoso central e gastrintestinal, sendo que os relatos mais comuns foram vertigem, náusea e sonolência. **Posologia:** a dose diária máxima de REVANGE® comprimido revestido é 1 a 2 comprimidos a cada 4 a 6 horas de acordo com a necessidade para alívio da dor, até o máximo de 8 comprimidos ao dia. A administração dos comprimidos pode ser feita independentemente das refeições. Nas condições dolorosas crônicas, o tratamento deve ser iniciado com 1 comprimido ao dia e aumentado em 1 comprimido a cada 3 dias, conforme a tolerância do paciente, até atingir a dose de 4 comprimidos ao dia. Depois disso, REVANGE® comprimido revestido pode ser administrado na dose de 1-2 comprimidos a cada 4-6 horas, até o máximo de 8 comprimidos ao dia. Nas condições dolorosas agudas, o tratamento pode ser iniciado com a dose terapêutica completa (1-2 comprimidos a cada 4-6 horas), até o máximo de 8 comprimidos ao dia. Pacientes com disfunção renal: em pacientes com "clearance" de creatinina inferior a 30 mL/min, recomenda-se aumentar o intervalo entre as administrações de REVANGE® comprimido revestido de forma a não exceder 2 comprimidos a cada 12 horas. VENDA SOB PRESCRIÇÃO MÉDICA. SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA. Farmacêutica Responsável: Gabriela Mallmann CRF-SP 30.138. MS - 1.0573.0440. MB02 SAP 4389200.

CAC Central de Atendimento ao Cliente
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cac@ache.com.br
8:00 h às 17:00 h (seg. a sex.)

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Oxotron
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A NOVA OPÇÃO NO TRATAMENTO ANTI-INFLAMATÓRIO.[1,2]

RÁPIDO INÍCIO DE AÇÃO

Início de ação em aproximadamente 15 minutos[2]

- **Atividade preferencial sobre a COX-2[3,4]**
- **Fármaco seguro[3,5]**
- **Boa tolerabilidade[3]**
- **Tão eficaz quanto celecoxibe, ibuprofeno e naproxeno na redução da dor e inflamação em pacientes com dor pós-operatória, osteoartrite e ombro congelado[6]**

Referências Bibliográficas: 1) BRASIL. ANVISA. Agência Nacional de Vigilância Sanitária. Consulta de produtos. Disponível em: <http://www7.anvisa.gov.br/datavisa/Consulta_Produto/consulta_produto_detalhe.asp>. Acesso em: Out. 2016. 2) Bula do produto OXOTRON: comprimidos. Farmacêutica Responsável: Gabriela Mallmann. Guarulhos, SP. Aché Laboratórios Farmacêuticos S.A. 3) DUTRA, F.G.; ENGELKE, F. O uso do loxoprofeno sódico* nos processos inflamatórios comuns em reumatologia e ortopedia: Estudo colaborativo. RBM, v. 58, n., 1/2, p. 39-48, 2001. 4) MARONE, S.; ENGELKE, F. Loxoprofeno sódico no tratamento complementar das infecções agudas das vias aéreas superiores. Estudo colaborativo. RBM, v. 58, n. 3, p. 171-178, 2001. 5) LEDERMAN, R.; GUIMARÃES, S.; VERZTMAN, J.F. Eficácia clínica e segurança do loxoprofeno sódico (Loxonin®) no tratamento da gonartrose. RMB, v. 58, v. 4, p. 269-271, 2001. 6) GREIG, S.L.; GARNOCK-JONES, K.P. Loxoprofen: A review in pain and inflammation. Clin Drug Investig, v. 36, n. 9, p. 771-81, 2016.

Oxotron é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas

Oxotron está contraindicado em: Crianças e jovens menores de 18 anos de idade, gestantes no último trimestre da gravidez e durante o período de lactação; pessoas que apresentaram reações de hipersensibilidade ao loxoprofeno ou a qualquer um dos componentes da fórmula; portadores de úlcera péptica, graves distúrbios hematológicos, hepáticos ou renais.INTERAÇÕES MEDICAMENTOSAS: Coadministração cautelosa: Anticoagulantes cumarínicos, hipoglicemiantes sulfonilureicos, antibacteriano fluoroquinolona, metotrexate, sais de lítio, diuréticos benzotiazídicos, anti-hipertensivos.

Oxotron. Loxoprofeno sódico. MEDICAMENTO SIMILAR EQUIVALENTE AO MEDICAMENTO DE REFERÊNCIA. 60 mg. Comprimido. USO ORAL. USO ADULTO. Oxotron. Loxoprofeno sódico. **APRESENTAÇÕES.** Comprimidos 60 mg: embalagens com 8, 15 ou 30 comprimidos. USO ORAL. USO ADULTO. **COMPOSIÇÃO.** Cada comprimido de Oxotron contém: Loxoprofeno sódico anidro (como loxoprofeno sódico di-hidratado) 60 mg. Excipientes: lactose monoidratada, estearato de magnésio, hipromelose de baixa substituição, óxido férrico vermelho. **INFORMAÇÕES TÉCNICAS AOS PROFISSIONAIS DE SAÚDE. INDICAÇÕES.** Oxotron está indicado como anti-inflamatório e analgésico no tratamento de artrite reumatóide, osteoartrite, periartrite escapuloumeral, processos inflamatórios osteomusculares do pescoço, ombro, braço e lombalgias; como analgésico e anti-inflamatório em pós-cirurgia, pós-traumatismo e pós-exodontia; como analgésico anti-inflamatório e antitérmico em processos inflamatórios agudos do trato respiratório superior (acompanhados ou não de bronquite aguda). **CONTRAINDICAÇÕES.** Oxotron está contraindicado em: Crianças e jovens menores de 18 anos de idade; gestantes no último trimestre da gravidez e durante o período de lactação; pessoas que apresentaram reações de hipersensibilidade ao loxoprofeno ou a qualquer um dos componentes da fórmula; portadores de úlcera péptica, graves distúrbios hematológicos, hepáticos ou renais; portadores de disfunções cardíacas graves; indivíduos com asma induzida por AINE. Este medicamento é contraindicado para menores de 18 anos. Categoria de risco na gravidez: D (terceiro trimestre): este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica. Informe imediatamente seu médico em caso de suspeita de gravidez. **ADVERTÊNCIAS E PRECAUÇÕES:** Oxotron deve ser administrado com cautela em: Pessoas com histórico de úlcera péptica; pessoas portadoras ou com histórico de distúrbios hematológicos; pessoas portadoras ou com histórico de disfunção hepática; pessoas portadoras ou com histórico de disfunção renal; pessoas com úlcera associada ao tratamento prolongado com anti-inflamatórios não esteroides, ainda que estejam em uso de misoprostol como medida profilática; pessoas com asma brônquica de qualquer causa; pessoas com disfunção cardíaca; pessoas com história de hipersensibilidade; pessoas com colite ulcerativa; pessoas com doença de Crohn; pessoas idosas. Durante tratamento prolongado com Oxotron, exames laboratoriais, tais como urina tipo I, hemograma completo e enzimas hepáticas devem ser realizados periodicamente. Se forem observadas alterações, recomenda-se redução da dose ou interrupção do tratamento. O uso de Oxotron, bem como de outros anti-inflamatórios, pode provocar alteração do controle da pressão arterial em indivíduos hipertensos sob tratamento. Alguns efeitos indesejáveis como tontura e sonolência têm sido relatados durante o uso de Oxotron. Para segurança do paciente, solicitar cuidado ao dirigir e ao operar máquinas. A segurança do uso de loxoprofeno sódico na gestação não foi estabelecida, portanto, Oxotron somente deverá ser administrado a gestantes se os benefícios terapêuticos justificarem os riscos potenciais para o feto (particularmente no terceiro trimestre) bem como durante a lactação. Categoria de risco na gravidez: B (primeiro e segundo trimestres): Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. **INTERAÇÕES MEDICAMENTOSAS:** Coadministração cautelosa: Anticoagulantes cumarínicos, hipoglicemiantes sulfonilureicos, antibacteriano fluoroquinolona, metotrexate, sais de lítio, diuréticos benzotiazídicos, anti-hipertensivos. **REAÇÕES ADVERSAS.** Oxotron pode causar os seguintes efeitos indesejados: rash cutâneo, urticária, sonolência, edema, dor abdominal, desconforto gástrico, anorexia, náuseas e vômito, diarreia e aumento das transaminases hepáticas, prurido, úlcera péptica, constipação intestinal, pirose, estomatite, urticária, dispepsia, cefaleia, anemia, leucopenia, eosinofilia, aumento da fosfatase alcalina, palpitação, fogachos, febre, sede, distensão abdominal, úlcera no intestino delgado e/ou grosso, aumento da pressão arterial, entorpecimento, tontura, trombocitopenia, hematúria, proteinúria, disúria, dor no peito e mal estar. Outras reações adversas clinicamente significantes: choque, sintomas anafilactóides, crise asmática, Stevens-Johnson, síndrome de Lyell (necrose epidérmica tóxica), agranulocitose, anemia hemolítica, leucopenia, trombocitopenia, insuficiência renal aguda, síndrome nefrótica, nefrite intersticial, insuficiência cardíaca congestiva, pneumonia intersticial, sangramento gastrintestinal, estenose e/ou obstrução do intestino delgado e/ou grosso, perfuração gastrintestinal, disfunção hepática, icterícia, meningite asséptica e rabdomiólise. Estes casos devem ser observados cuidadosamente. A terapia com Oxotron deve ser descontinuada imediatamente e adotadas medidas de tratamento apropriadas. Foi reportado que anemia aplástica pode ocorrer com o uso de drogas anti-inflamatórias não esteroides. Em caso de eventos adversos, notifique ao Sistema de Notificações em Vigilância Sanitária - NOTIVISA, disponível em www.anvisa.gov.br/hotsite/notivisa/index.htm, ou para a Vigilância Sanitária Estadual ou Municipal. **POSOLOGIA E MODO DE USAR.** Em geral recomenda-se para o adulto a posologia de um comprimido (60 mg de Loxoprofeno sódico), três vezes ao dia, por via oral. Em casos agudos poderá ser realizada uma única administração de um a dois comprimidos (60-120 mg de Loxoprofeno sódico), por via oral, ajustando-se a dose de acordo com a idade e os sintomas. Não ultrapassar a dose diária de 180 mg, bem como evitar a administração em jejum. A segurança em pacientes pediátricos não foi estabelecida. VENDA SOB PRESCRIÇÃO MÉDICA. MS - 1.0573.0495. Código EOG 321605 00 "Material técnico científico de distribuição exclusiva à classe médica".

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