RBO REVISTA BRASILEIRA DE ORTOPEDIA
www.rbo.org.br

Original Article

Comparative Study of the Use of Intra-articular and Systemic Meloxicam to Control Experimentally Induced Osteoarthritis in Rabbit Knees☆,☆☆

Valéria Trombini Vidotto[a,b,c,*], *Rodrigo Tesser da Rocha*[a], *Caroline Lorraine de Paiva*[d], *João Ricardo Nardotto*[e], *Anderson Farias*[f,g,h], *Sandro Alex Stefanes*[f,i,j]

[a] *Postgraduate Program on Animal Science, União Pioneira de Integração Social, Brasília, DF, Brazil*
[b] *Discipline of Domestic Animal Anatomy, Veterinary Medicine Course, Faculdade de Jaguariúna, Jaguariúna, SP, Brazil*
[c] *Orthopedics and Neurology Service, Veterinary Hospital, Faculdade de Jaguariúna, Jaguariúna, SP, Brazil*
[d] *Veterinary Medicine Course, União Pioneira de Integração Social, Brasília, DF, Brazil*
[e] *Centro de Diagnóstico Diagnopet, Brasília, DF, Brazil*
[f] *Postgraduate Program on Veterinary Medicine, Universidade Estadual Paulista Júlio de Mesquita Filho, São Paulo, SP, Brazil*
[g] *Discipline of Anesthesiology, Veterinary Medicine Course, União Pioneira de Integração Social, Brasília, DF, Brazil*
[h] *Anesthesiology Service, Veterinary Hospital, União Pioneira de Integração Social, Brasília, DF, Brazil*
[i] *Discipline of Surgery, Veterinary Medicine Course, União Pioneira de Integração Social, Brasília, DF, Brazil*
[j] *Orthopedics and Neurology Service, Veterinary Hospital, União Pioneira de Integração Social, Brasília, DF, Brazil*

ARTICLE INFO

Article history:
Received 9 April 2013
Accepted 2 May 2013

Keywords:
Osteoarthritis
Anti-inflammatory agents
Injections, intra-articular
Knee
Rabbits

ABSTRACT

Objective: This study aimed to evaluate morphologic changes, as well as chondroprotective and intra-articular effects of meloxicam on joint repair in rabbits induced by experimental trochleoplasty, minimizing possible adverse side effects.
Methods: Thirty-five rabbits were divided into four groups: the control group, which did not undergo surgery, and operated groups, which used different ways of administering the anti-inflammatory agent: systemic, 0.2 mg/kg; intra-articular, 0.5 mg/kg; positive group control, without meloxicam. Each operated group was divided according to the periods of 7 or 30 days evaluation after surgery.
Results: Regarding macroscopic and histological evaluation of cartilage, after 30 days, most animals showed almost complete joint repair, the presence of few or no inflammatory cells; whereas part of the animals treated with meloxicam presented necrosis in the trochlear ridge and absence of inflammatory cells after 7 days. In positive control group, it was observed moderate inflammation and connective tissue proliferation. None of the animals in the operated groups showed irregularities 30 days after surgery.
Conclusion: Either intra-articular or systemic, meloxicam revealed to be favorable to be used for joint repair and control of inflammatory reaction.

☆ Please cite this article as: Vidotto VT, et al. Estudo comparativo do uso de meloxicam por via intra-articular e sistêmica no controle da osteoartrite experimentalmente induzida em joelho de coelhos. Rev Bras Ortop. 2013;48:524–531.
☆☆ Pioneering work was done in the Union of Social Integration, Brasilia, DF, Brazil.

* *Corresponding author.*
E-mail: valeria_trombini@yahoo.com.br (V.T. Vidotto).

2255-4971/$ – see front matter © 2013 Sociedade Brasileira de Ortopedia e Traumatologia. Published by Elsevier Editora Ltda. All rights reserved.
http://dx.doi.org/10.1016/j.rboe.2013.12.011

Estudo comparativo do uso de meloxicam por via intra-articular e sistêmica no controle da osteoartrite experimentalmente induzida em joelho de coelhos

Palavras chave:
Osteoartrite
Anti-inflamatórios
Injeções intra-articulares
Joelho
Coelhos

RESUMO

Objetivo: Com o enfoque no processo de reparação da cartilagem, objetivou-se analisar o uso do meloxicam, via intra-articular, para minimizar efeitos adversos causados pela aplicação sistêmica. Avaliaram-se alterações morfológicas e remodelamento do tecido cartilaginoso em modelo experimental, em joelhos.

Métodos: Usaram-se 35 coelhos, divididos em quatro grupos: grupo controle (não operado), cinco animais, e grupos tratados, 10 animais cada. A técnica usada para indução de osteartrite foi trocleoplastia por abrasão. Grupos tratados foram subdivididos de acordo com a via de administração da medicação anti-inflamatória: sistêmica (0,2 mg/kg), intra-articular (0,5 mg/kg) e controle positivo (sem anti-inflamatório). Após sete ou 30 dias de pós-operatório, a cartilagem articular foi avaliada de forma macroscópica e histológica.

Resultados: Após 30 dias ocorreu reparação da cartilagem articular em 100% dos animais que receberam a medicação sistêmica e de 90% dos animais que receberam via intra-articular, com a presença de poucas ou nenhuma célula inflamatória, enquanto que no grupo com sete dias de pós-operatório observou-se ausência de tecido cicatricial no sulco troclear e de células inflamatórias. No grupo controle operado, sem medicação, observaram-se inflamação moderada e proliferação de tecido conjuntivo fibroso, após sete dias. Em todos os grupos submetidos a 30 dias de pós-operatório observou-se discreta irregularidade na cartilagem articular, ou ausência dela, macro e microscopicamente.

Conclusão: O meloxicam via intrarticular mostrou-se favorável para uso em coelhos e obteve os mesmos resultados da administração sistêmica quanto a remodelamento cartilaginoso e controle de reação inflamatória. No entanto, sujeito a menos efeitos colaterais já descritos na via sistêmica e maior praticidade em cirurgias.

Introduction

Osteoarthrosis is the commonest aging process among mammals.[1] It is also known as degenerative joint disease (DJD) and is characterized by its non-infectious and degenerative nature. It causes destruction of joint cartilage and leads to joint deformity due to disorders of normal cell differentiation.[2–4] Although it is classified as non-inflammatory, a continuous low-grade inflammatory process is associated with DJD and this leads to osteoarthritis.[4]

The etiology of the degenerative process begins with aging, but the inflammatory or infectious diseases that destroy the cartilaginous structure, or trauma involving the cartilage, may precipitate osteoarthrosis.[2] The process is characterized by progressive erosion of the joint cartilage and leads to reduction of the joint space, subchondral sclerosis, formation of marginal osteophytes, subchondral cysts and synovial inflammation, which results in pain and reduction of functional capacity.[5]

The objectives of therapy for osteoarthritis are to diminish the pain and maintain or improve joint function. Over the last few years, many studies have investigated the potential function of anti-inflammatory and chondroprotective agents for repairing joint cartilage, controlling inflammatory reactions and decelerating the degenerative process.[3]

Non-steroidal anti-inflammatory drugs (NSAIDs) are the agents most used for alleviating pain over short and long periods of time. However, care needs to be taken in view of the possible adverse effects, such as gastrointestinal problems, hepatotoxicity and nephrotoxicity.[6–10]

With the focus on cartilage repair, the aims here were to use the technique of trochleoplasty by means of abrasion, in order to study the morphological changes and cartilaginous tissue remodeling that were induced in experimental osteoarthritis induced in rabbits, and to analyze the use of the NSAID meloxicam directly on the target, intra-articularly, which would provide an optional route for minimizing the possible adverse effects caused by systemic administration.

Material and Method

Thirty-five healthy New Zealand rabbits (*Oryctolagus cuniculus*) of both sexes, weighing between 1 and 2 kg and of age 90 days, were used. The rabbits were subjected to general clinical and orthopedic examinations and laboratory tests. The project was approved by the Ethics Committee for Animal Use of União Pioneira de Integração Social (UPIS), under protocol number 02/10.

The rabbits were randomly divided into four groups. For the surgical procedure, it was decided to standardize on the right femorotibial-patellar joint.

Control group (CG): non-operated, with five animals.

Treated groups, with 10 animals each, subdivided according to the administration route for the anti-inflammatory medication and the postoperative period (7 or 30 days):

Systemic group (SG): subcutaneous administration route for the anti-inflammatory medication, comprising five animals with a postoperative period of seven days (**SG7**) and five animals with 30 days (**SG30**).

Intra-articular group (IAG): intra-articular administration route for the anti-inflammatory medication, comprising five animals with a postoperative period of seven days (**IAG7**) and five animals with 30 days (**IAG30**).

Positive control group (CG+): without anti-inflammatory medication, comprising five animals with a postoperative period of seven days (**CG+7**) and five animals with 30 days (**CG+30**).

The rabbits received anesthetic medication consisting of ketamine (30 mg/kg, intramuscularly) and xylazine (5 mg/kg, intramuscularly), together, and also anesthesia in the epidural lumbosacral region, with application of 2% lidocaine (0.3 mL/kg).

To experimentally induce osteoarthrosis, the technique of trochleoplasty by means of abrasion was used. The surgical access comprised a lateral approach to the knee joint, as described by Fossum.[4] The patella was dislocated to enable exposure of the femoral trochlea. The knee was flexed and, with the aid of a spherical milling device of 2 mm in diameter, coupled to a high-rotation microgrinder, the trochleoplasty procedure was performed by deepening the trochlear groove down to the subchondral bone, which avoided damaging the trochlear borders and the adjacent joint cartilage.

During the surgical procedure, after closing the capsule and retinaculum, the animals in the intra-articular group (IAG) received meloxicam, in a single dose of 0.5 mg/kg, intra-articularly.

The animals in the systemic group (SG) received meloxicam at a dose of 0.2 mg/kg, subcutaneously every 24 h, for three consecutive days.

All the animals operated received prophylactic antibiotic therapy comprising an association of penicillins and dihydrostreptomycins at a dose of 50,000 UI/kg, intramuscularly every 48 h (three applications). They also received analgesic comprising tramadol hydrochloride at a dose of 4.0 mg/kg, subcutaneously every 12 h, for three consecutive days, as described by Lichtenberger.[11]

At the preestablished times of 7 and 30 days after the operation, the animals were evaluated to described the macroscopic changes to the joint and to collect samples for histological analysis. The animals were anesthetized using ketamine (30 mg/kg, intramuscularly) and xylazine (5 mg/kg, intramuscularly) and were sacrificed by applying an overdose of 2.5% sodium thiopental and 19.1% potassium chloride, in accordance with the recommended standards for use of animals in scientific research.[12]

The distal epiphyses of the femur were collected and stored in individual flasks with 10% buffered formaldehyde solution at room temperature, for histological evaluation.

In the histopathological analysis, using sections stained by means of the hematoxylin–eosin (HE) and Gomori trichrome (GT) methods, the biological response was determined as a function of the cartilage repair process and inflammatory changes in the joint. Using a blinded analysis, the results were assessed according to their histological grading, in score tables that had been modified from previous studies conducted by Oliveira[13] and Saricaoglu et al.[14]

To evaluate the nonparametric data from the histological analysis on cell morphology and joint inflammatory reaction, the Mann–Whitney Rank Sum test was used to make comparisons between the groups. All the comparisons were made at the significance level of 5% ($p \leq 0.05$). For this, the SigmaStat for Windows statistical software, version 3.0.1, was used.

For the other evaluations, on the data obtained through macroscopic and histological analyses, descriptive methods were used.

Results

The trochlear groove of the negative control group (CG−) was evaluated as a means of macroscopic comparison. No surface changes were observed (Fig. 1A).

Seven days after the operation, the following macroscopic observations could be made in the groups evaluated:

- In four animals of the group CG+7 (4/5, 80%), areas of irregularity were observed in the repair tissue and the reddened borders at the transition to the adjacent cartilage (Fig. 2A).
- This feature was also observed in three animals of the group SG7 (3/5, 60%) and in one animal of the group IAG7 (1/5, 20%).
- In three animals in the group IAG7 (3/5, 60%) and in two animals of the group SG7 (2/5, 40%), these areas of irregularity in the repair tissue presented small areas of hyperemia and whitened tissue at the extremities of the lesion (Fig. 2B).

After 30 days, the following macroscopic observations could be made in the groups evaluated:

Fewer irregularities in the repair tissue, which presented continuity with the adjacent normal cartilage in four animals of the group CG+30 (4/5, 80%), in all the animals in the group SG30 (5/5, 100%) and in four animals of the group IAG30 (4/5, 80%) (Fig. 3).

During the microscopic evaluation on the joint cartilage, it was possible to make the following observations:

- In the animals of the group CG− (5/5, 100%), the trochlear groove presented a covering of hyaline cartilaginous tissue, with absence of inflammatory cells.

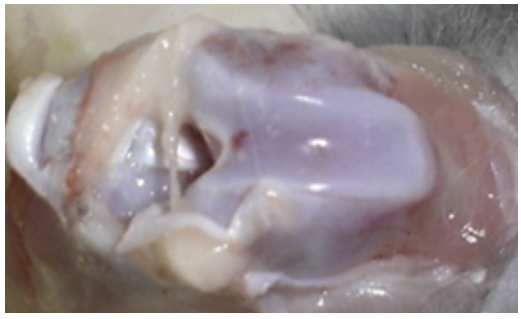

Figure 1 – Photograph of the right knee of an animal in CG−, without abnormalities, with a smooth and shiny joint surface, without changes of relief.

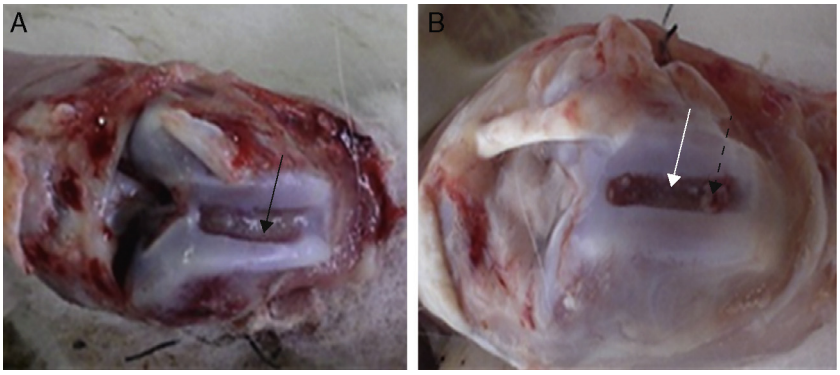

Figure 2 – (A) Photograph of the trochleoplasty region of the right knee of an animal in CG+7, with areas of irregularity in the repair tissue and reddened border at the transition to the adjacent normal cartilage (arrow). (B) Photograph of the trochleoplasty region of the right knee of a rabbit in IAG7, with areas of irregularity in the repair tissue but without areas of hyperemia (white arrow), and presenting whitened tissue at the extremities of the lesion (dashed arrow).

- Four animals of the group CG+7 (4/5, 80%) and one animal of the group SG7 (1/5, 20%) presented mild to moderate inflammatory reactions in the area of the trochlear groove, with intense deposition of fibrous connective tissue, surface irregularity, congestion and edema, along with a low neutrophil count (Fig. 4A).
- In two animals of the group SG7 (2/5, 40%) and three animals of the group IAG7 (3/5, 60%), a minimal inflammatory reaction was observed, with mild congestion and edema, areas of intense hemorrhage and absence of healing tissue in the region of the trochlear groove, where the trochleoplasty was performed (Fig. 4B).

The other animals presented mild to moderate inflammatory reactions, with the presence of neutrophils and macrophages, along with deposition of fibrocartilaginous tissue stained with hematoxylin and eosin (HE) (Fig. 4C), which was seen better on slides stained with Gomori trichrome (GT) (Fig. 5D).

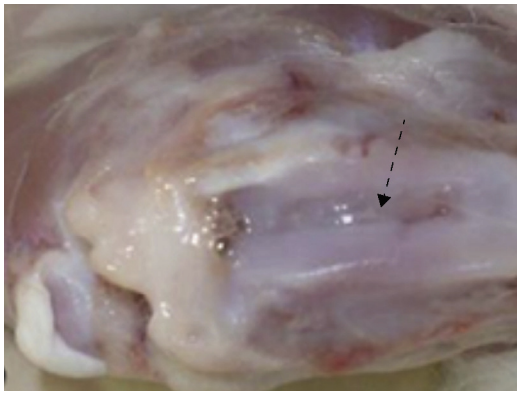

Figure 3 – Photograph of the trochleoplasty region of an animal in SG30, with regular repair tissue surface that is continuous with the adjacent normal cartilage (dotted arrow).

Also during the microscopic evaluation on the joint cartilage, in relation to the animals that were examined 30 days after the operation, it was possible to make the following observations:

- In four animals of the group CG+30 (4/5, 80%), a minimal inflammatory reaction was observed, with mild congestion and edema, presence of hyaline cartilage and little fibrocartilage (Fig. 5A).
- Four animals of the groups SG30 and IAG30 (4/5, 80%) no longer presented any inflammatory cells and only presented hyaline cartilage, which was stained using HE (Fig. 5B) and GT and showed the disorganization of the collagen (Fig. 5C).

In making statistical comparisons between the groups seven days after the operation, there were no significant differences ($p \leq 0.05$). However, in comparing the animals after 30 days, it was seen that there was a greater inflammatory reaction in the operated control group (CG+30), in relation to the group that received systemic medication (Table 1).

In addition, it was observed that there was also a change in the significant inflammatory reaction ($p \leq 0.05$), in comparing the rabbits that received systemic meloxicam and were examined seven days after the operation (SG7) with those that were examined after 30 days (SG30).

In comparing the cell morphology, there was a significant difference between the rabbits that received systemic meloxicam and were examined seven days after the operation (SG7), and those that were examined after 30 days (SG30) (Table 2).

Discussion

This study was characterized by being conducted using an intra-articular route in a rabbit model for experimental osteoarthritis. Trochleoplasty by means of abrasion was used, since this is a route with few reports in veterinary medicine.

In the histopathological evaluation of the trochlear groove, it was noted that in the group CG+7, the hyaline cartilage of the

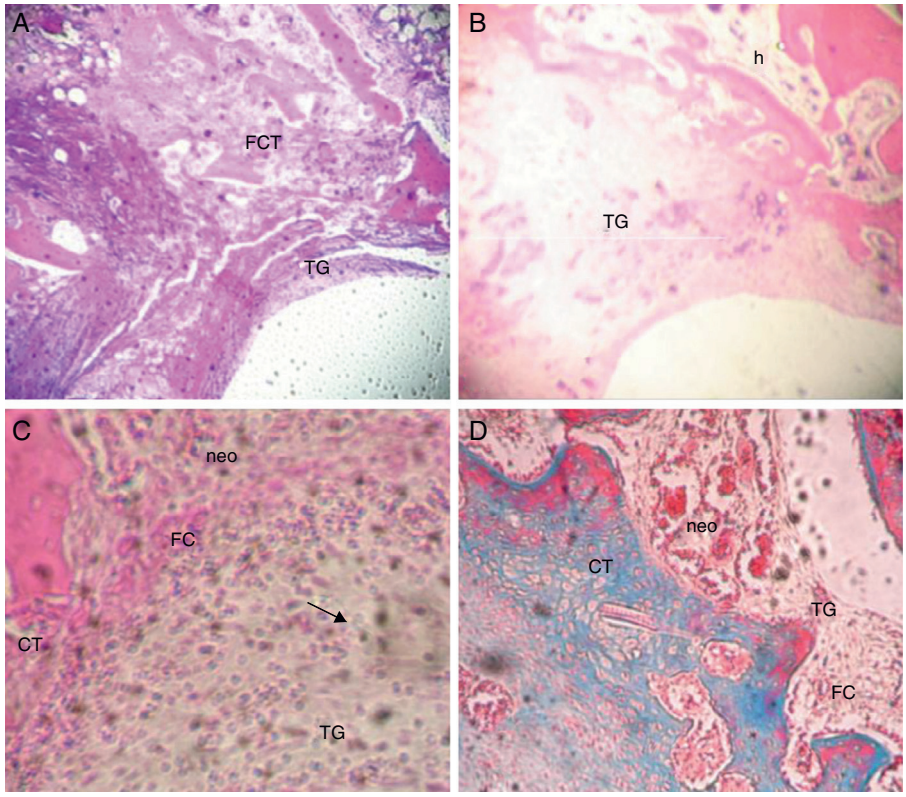

Figure 4 – Photomicrograph of the transition area between the trochlea groove (TG) lesion and the adjacent cartilaginous tissue (CT). (A) In a rabbit of the group CG+7. Note the intense formation of fibrous connective tissue (FCT) with subchondral lacunae. (B) In a rabbit of the group IAG7. Note the absence of formation of repair tissue in the area of the trochlea groove (TG) lesion, and the intense hemorrhaging (h). (C) In a rabbit of the group SG7, with formation of fibrocartilage (FC) and slight inflammatory reaction. Note the presence of mononuclear cells (arrow) and neovascularization (neo). (HE; 40×). (D) In a rabbit of the group SG7, showing irregularity, with areas filled with fibrocartilage (FC). Note area of neovascularization (neo) (GT; 40×).

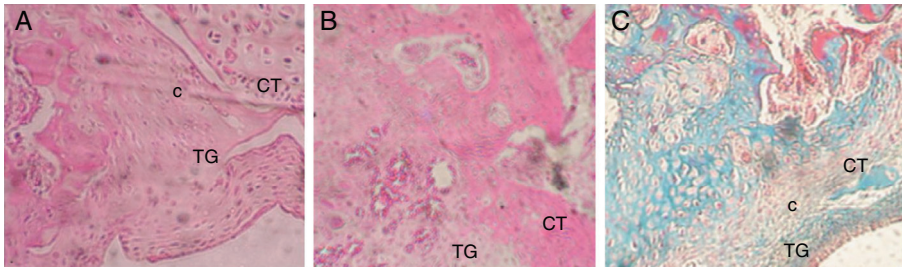

Figure 5 – Photomicrograph of the transition area between the trochlear groove (TG) lesion and the adjacent cartilaginous tissue (CT). (A) In a rabbit of the group CG+30. Note the continuity of the tissue, with intense formation of cartilaginous tissue (c). (B) In a rabbit of the group IAG30. Note continuity of the tissue (HE; 40×). (C) In a rabbit of the group SG30, with formation of cartilaginous tissue (CT). Note disorganization of the collagen (c) (GT; 40×).

joint surface was replaced by fibroblast-rich connective tissue with a delicate structure, with deposition of immature type III collagen and numerous blood vessels, and with the presence of a mild to moderate inflammatory reaction. This confirmed the observation that the joint cartilage had lost its homogenous nature and was broken and fragmented, with fibrillation. In this regard, Silva[15] also described the presence of intensely vascularized tissue, with a high cell content and dense connective tissue covering the area of the trochlear groove lesion.

Corroborating Souza et al.,[16] the macroscopic evaluated showed the presence of irregularities and reddened areas on the edges of the lesion, which confirmed that the joint tissue was avascular and the inflammatory reaction mediated by blood vessels began in the underlying tissue.

The histochemical staining of the matrix for proteoglycans was unequal, and the line of separation between the calcified cartilage and the radial zone had been invaded by capillaries.[5] For this reason, it needs to be emphasized that the subchondral bone was accessed during the trochleoplasty procedure,

Table 1 – Grading of the Cell Morphology Found in the Joint Cartilage of the Groups.

CG−	CG+7	SG7	IAG7	CG+30	SG30	IAG30
0	5	2[a]	2	1	1[#]	2
0	5	3[a]	6	1	1[#]	1
0	5	6[a]	6	1	1[#]	1
0	5	5[a]	6	1	1[#]	5
0	2	6[a]	1	5	1[#]	1

0, normal; 1, cartilage and some fibrocartilage; 2, fibrocartilage; 3, some fibrocartilage, but many non-chondrocytic cells; 4, only non-chondrocytic cells; 5, fibrous tissue; 6, absence of healing tissue. Grading adapted from Oliveira.[13]

[a] Statistical difference between subgroups ($p \leq 0.05$); grading adapted from Oliveira.[13]

Table 2 – Grading of the Inflammatory Reaction Found in the Joints of the Groups.

CG−	CG+7	SG7	IAG7	CG+30	SG30	IAG30
0	3	1[a]	3	1[b]	1[a,b]	2
0	2	1[a]	0	1[b]	0[a,b]	0
0	2	1[a]	0	1[b]	0[a,b]	0
0	3	2[a]	1	1[b]	0[a,b]	0
0	1	1[a]	1	1[b]	0[a,b]	0

0, no inflammation; 1, minimal inflammation (slight congestion and edema); 2, mild inflammation (erosion of the joint surface, congestion and edema; low neutrophil count); 3, moderate inflammation (presence of neutrophils and macrophages); 4, severe inflammation (presence of neutrophils and macrophages; fibrin exudate). Grading adapted from Saricaoglu et al.[14]

[a] Statistical difference between subgroups ($p \leq 0.05$). Grading adapted from Saricaoglu et al.[14]

[b] Statistical difference between groups ($p \leq 0.05$).

which is the primary source for developing such responses. Thus, the promoter cells had access to the lesion and enabled formation of tissue composed of fibrocartilage. This finding reflects inadequate tissue repair, given that collagens I and II are not usually expressed in cartilaginous tissue, as also observed by Velosa et al.[17] and Rossi.[18]

Fibrocartilage or fibrous cartilage is a transitional tissue and has functional and structural properties that are between those of dense connective disuse and hyaline cartilage. As cited by Ghivizzani et al.[19] and Oliveira,[13] although fibrocartilage is resistant to tension, it is characterized by the presence of collagen I. Therefore, the formation of fibrocartilage that was observed was undesired, because it altered the structural and biomechanical properties of the joint.

Although growth of this type of tissue was also found in some animals in the groups that underwent surgical intervention (SG7 and IAG7), what drew attention most was that two animals in the group SG7 (2/5, 40%) and in three animals in IAG7 (3/5, 60%), not only were there no inflammatory cells, but also, microscopically, the site only presented areas with absence of healing tissue in the area of the trochleoplasty, without signs of tissue repair. These were macroscopically observed as irregular areas and whitened tissue. This leads to the conclusion that, independent of the administration route, the presence of anti-inflammatory agents blocked the metabolization of arachidonic acid by the COX-2 route and impeded production of prostaglandins and consequently their inflammatory metabolites, in the repair tissue, as also observed in the experiment conducted by Marchionni et al.[20]

Integrins, which form one of the main families of cell surface receptors, participate in the migration of neutrophils through binding these cells to vessel walls, which enables diapedesis. However, since integrins are inhibited by the action of medications derived from oxicams, reduction of polymorphonuclear cells takes place. This was seen in the present investigation, which confirms what is said in the literature regarding meloxicam, i.e. that it is a non-steroidal anti-inflammatory agent that is preferentially selective for COX-2 and which demonstrates a capacity to inhibit inflammation during the acute phase.[20]

These cells are responsible for absorption of the fibrin of the coagulum. They synthesize growth factors that are chemotaxic and mitogenic toward the endothelial cells that are present on the periphery of the lesion, and they promote migration and formation of new vessels. For this reason, reduction of these growth factors also diminishes cell repair, given that the healing process needs to firstly go through the inflammation phase, so that the necrosed tissue can be phagocytized and fibroblasts can be recruited to start the healing cascade, and thereafter go through the phases of proliferation, differentiation and tissue maturation.[21,22]

In the same analysis, but now on the animals examined 30 days after the operation, there was no statistically significant difference between the groups operated and the positive control (CG+30), in relation to tissue repair, given that in a large proportion of the animals in the groups CG+30, SG30 and IAG30, there were large quantities of hyaline cartilage and little fibrocartilage, although they still presented disorganization of the collagen, as seen using trichrome staining. However, there was a significant difference between the medicated groups and the positive control regarding the inflammatory reaction, since the cellularity observed in the histological analysis on the medicated animals was visibly lower.

It is known that joint cartilage is a sparsely cellular tissue, and that its biochemical characteristics mainly reflect the composition of the extracellular matrix. It is formed from type II collagen and proteoglycans, which are responsible for the stiffness and elasticity of the tissue. Macroscopically, it

is a smooth and shiny tissue.[5] These observations could be made through macroscopic and microscopic evaluations on the lesion. These findings demonstrate that long-term use of anti-inflammatory agents enabled good cartilage repair, without any significant difference between the control group and the groups with systemic and intra-articular administration, but without any continuation of an inflammatory reaction.

With decreasing concentrations of inflammatory prostaglandins, the increase in vascular permeability and the tissue aggression that these mediators cause are minimized through the action of the medication. This action therefore favors fibrogenesis and makes the extracellular matrix of animals subjected to the action of meloxicam richer in cells and more organized in collagen fibers at the lesion site.[20]

Putting together the data from the four groups and the observation times, analysis on the variables relating to acute and chronic inflammation and to repair showed that meloxicam controlled the acute inflammatory reaction (seven days after the operation), independent of the administration route. Thirty days after the operation, this control over the inflammatory reaction was maintained, which enabled satisfactory repair of the cartilaginous tissue of the femorotibial-patellar joint.

It is known that many patients who undergo joint surgery may require prolonged use of anti-inflammatory agents. However, their use via a systemic route, even at a therapeutic dose, may lead to adverse reactions such as hepatotoxicity and, particularly, gastrointestinal disorders, as described by Alencar et al.[23]

A single application of meloxicam intra-articularly achieved a result similar to what was found using systemic administration. For this reason, it can be suggested that intra-articular application can be used rationally as treatment in the immediate postoperative period, for joint surgery.

Conclusion

From evaluating the results obtained from the experimental model of this study, by means of macroscopic and histopathological examinations, it can be concluded that meloxicam is effective for controlling the joint inflammatory process, both in systemic and in intra-articular applications, and it enables cartilage remodeling in an experimental model using rabbits. Thus, this study contributes toward advancing knowledge and allows several new questions to be asked, with new proposals for local anti-inflammatory treatment.

Conflicts of Interest

The authors declare no conflicts of interest.

REFERENCES

1. Pelletier JP, Yaron M, Haraoui B, Cohen P. Efficacy and safety of diacerein in orteoarthritis of the knee: a double-blind, placebo-controlled trial. The Diacerein Study Group. Arthritis Rheum. 2001;43(10):2339–48.
2. Camanho GL. Tratamento da osteoartrose do joelho. Rev Bras Ortop. 2001;36(5):135–40.
3. Caldeira FMC, Muzzi LAL, Muzzi RAL. Artrose em cães. Caderno Técnico de Veterinária e Zootecnia. 2002;37(1): 53–83.
4. Fossum TW. Cirurgia de pequenos animais. São Paulo: Roca; 2005.
5. Rezende MA, Gobbi RG. Tratamento medicamentoso da osteoartrose do joelho: drogas modificadoras da doença. Rev Bras Ortop. 2009;44(1):14–9.
6. Lees P, LandonI MF, Giraudel J, Toutain PL. Pharmacodynamics and pharmacokinetics of nonsteroidal anti-inflammatory drugs in species of veterinary interest. J Vet Pharmacol Ther. 2004;27(6):479–90.
7. Clark TP. The clinical pharmacology of cicloxigenase-2-selective and dual inhibitors. Vet Clin North Am Small Anim Pract. 2006;36:1061–85.
8. Fox DB. Current treatment strategies of canine and feline osteoarthritis. In: NAVC proceedings (North American veterinary conference) [serial on the Internet]. 2006. Available at: http://www.ivis.org/proceedings/navc/2006/SAE/319.asp?LA=1 [cited 01.10.2011]; 20:90–4 [about 4 p.].
9. Johnston SA. Ostearthrits: joint anatomy, physiology, and pathobiology. Vet Clin N Am: Small Anim Pract. 2007;27:699–719.
10. Filho MM, Rahal SC. O uso de anti-inflamatórios inibidores Cox-2 seletivos na osteoartrite canina. Veterinária e Zootecnia. 2008;15(3):407–15.
11. Lichtenberger M. Analgesia in the ferret and rabbit. In: 56° Congresso Internazionale Multisala, SCIVAC [periódico na Internet]. 2007. Available at: http://www.ivis.org [cited 03.10.2011]; [about p. 327–0].
12. CFMV. Eutanásia: resolução do CFMV institui normas e procedimentos para eutanásia em animais. Veterinária e Zootecnia em Minas Gerais CRMV/MG. 2002;17(75): 25.
13. Oliveira BJNA. Enxerto osteocondral alógeno, associado à inoculação de células mononucleares da medula óssea e proteína morfogenética óssea no reparo do sulco troclear de coelhos. [dissertação]. Uberlândia: Universidade Federal de Uberlândia Faculdade de Medicina Veterinária; 2008.
14. Saricaoglu F, Dal D, Atilla P, Ìskit AB, Tarhan O, Asan E, Aypar U. Effect of intraarticular injection of lornoxicam on the articular cartilage & synovium in rat. Indian J Med Res. 2008;127:362–5.
15. Silva AA. Avaliação clínica de *rattus norvegicus* após terapia antiinflamatória com inibidor seletivo ou não para cox-2 por extrapolação alométrica. [tese]. Santa Maria: Universidade Federal de Santa Maria Departamento de Medicina Veterinária; 2004.
16. Souza R, Raiser A, Guimarães L, Rios M, Araújo L, Leottee A, Hintze C. Precursores de glicosaminoglicanos na reparação articular após trauma iatrogênico no joelho de cães. Rev Clin Vet. 1999;23(1):33–8.
17. Velosa APP, Oliveira AM, Carrasco S, Capelozzi VL, Teodoro WR, Yoshinari NH. Meniscectomia parcial como modelo experimental de osteoartrite em coelhos e efeito protetor do difosfato de cloroquina. Rev Bras Reumatol. 2007;47(6): 401–10.
18. Rossi E. Envelhecimento do sistema osteoarticular. Einstein. 2008;6(1):S7–12.
19. Ghivizzani SC, Oligino TJ, Robbins PD, Evans CH. Cartilage injury and repair. Phys Med Rehabil Clin N Am. 2000;11(2):289–307.
20. Marchionni AMT, Pagnoncelli RM, Reis SR. A Influência do meloxicam e da dexametasona no processo inflamatório e no reparo tecidual. Rev Odonto Ciênc. 2006;21(51):22–9.

21. Lin TW, Cardenas L, Soslowsky LJ. Biomechanics of tendon injury and repair. J Biomech. 2007;37(6):865–77.
22. Iamaguti LS, Brandão CVS. Uso de membrana biossintética a base de celulose na regeneração tecidual guiada. Semina: Ciências Agrárias, Londrina. 2007;28(4):701–8.
23. Alencar MMA, Pinto MT, Oliveira DM, Pessoa AWP, Cândido IA, Virgínio CG, et al. Margem de segurança do meloxicam em cães: efeitos deletérios nas células sanguíneas e trato gastrintestinal. Ciênc Rural. 2003;33(3):525–32.