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Evaluation of two therapeutic options for naturally occurring osteoarthritis in police working dogs

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Abstract

To compare the effectiveness of intra-articular (IA) methylprednisolone-acetate and triamcinolone acetonide in the management of naturally occurring hip osteoarthritis, 20 dogs were divided into two groups according to the drug injected per joint: GT (20 mg of triamcinolone acetonide) and GMPA (40 mg methylprednisolone). Animals were treated at T0 (treatment day), and further evaluations were conducted at T1 (15 days after treatment), T2, T3, T4, T5, T6, and T7 (one, two, three, four, five, and six months after treatment respectively). Response to treatment was measured using the Canine Brief Pain Inventory and Hudson Visual Analogue Scale, $p < 0.05$.

Treatment was successful in reducing the pain severity score in two animals of GT at T1 (20 %), three at T2–T3 (37.5 %), and two at T4–T7 (28.6 %). For GMPA, treatment was successful in two animals at T1 (20 %), four at T2 (40 %), three at T3 (30 %), and two at T4–T5 (20 %). When considering pain interference score, treatment was successful in two animals in both GT and GMPA from T1–T7. No significant differences were observed when comparing each moment with T0 or between groups. Intra-articular TA and MPA injection may be a treatment option for some patients, as some benefited from IA with TA and MPA.

Keywords: Osteoarthritis; Pain; Dog; Corticosteroids; Animal model.

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Study contribution

Osteoarthritis is a species transversal degenerative joint disease difficult to treat, causing pain and dramatic changes in patient activity. This study aimed to describe the use and compare the effectiveness of intra-articular methylprednisolone-acetate and triamcinolone acetonide in the management of osteoarthritis. The results show that both may be a treatment option for dogs with naturally occurring osteoarthritis, being able to reduce pain and improve return to function, with an added cost-effectiveness when compared to other therapeutic options.

Introduction

Osteoarthritis (OA) is a species of transversal degenerative joint disease. It is difficult to treat, causing pain and dramatic changes in patient activity and overall performance.[1-4] In the dog, it presents an estimated prevalence of 20 % with a trend to rise in the future.[5-8]

Different types of animal models have been used to study OA, in all modalities and stages.[9, 10] Considering the dog's tame nature, the fact that their cartilage thickness is less than half the size of humans, and the occurrence of slowly progressing OA, [10-12] it is considered a nearly ideal species for translation research of human OA and, for those reasons, the most used model for research. It has the advantages of being anatomically, biochemically, genomically, and molecularly similar to humans, with clinical progression and treatment similarities.[12-15] This species has been one of the preferred animal models for the study, in particular, the progression of naturally occurring OA and the efficacy of drugs in its treatment.[11, 12, 16]

For managing OA, intra-articular (IA) steroids (CS) have been largely used in humans and horses (despite the doubts of their beneficial or potentially deleterious effects,[17] aiming to control and decrease pain and inflammation levels present in cartilage, bone, and soft tissues surrounding the affected joint.[18, 19, 20-27, 28] There is a lack of guidelines for managing OA and the use of IA of CS in dogs. However, they exist for humans, and a similar approach may be considered for dogs. Human guidelines provide variable strengths of recommendation for the use of IA CS, ranging from weak to strong.[29-33] In the case of symptomatic knee OA, different guidelines stated inability to recommend for or against their use.[34] Among the most used CS, methylprednisolone acetate (MPA) and triamcinolone acetonide (TA) have been pointed out by the clinicians of the American College of Rheumatologists as their preference for OA IA treatment (34.6 % and 21.7 %, respectively).[35, 36] The major concern associated with these drugs is the limited duration of their effects because of their fast clearance from the synovial space.[37]

In animal models, gait and lameness analyzes are used to assess pain levels. Multiple pain scales are already validated and routinely used in dogs.[38] The Canine Brief Pain Inventory (CBPI) is one of those validated tools, developed to access owner's opinions regarding their perception of the impact and level of chronic pain assumes in their pets.[39] It is divided into two sections, a pain severity score (PSS), which evaluates the magnitude of the pain in an animal, and a pain interference score (PIS), which measures the degree to which pain affects daily activities.[40] The Hudson Visual Analogue Scale (HVAS) is repeatable and a valid tool in the as-

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sessment of mild-to-moderate pain levels in dogs, using force plate analysis as a criterion-reference standard.[41]

We hypothesize that a single IA administration of MPA and TA can reduce pain scores in police working dogs with naturally occurring hip OA. We also described and compared the use and effectiveness of intra-articular injection of TA or MPA.

Materials and methods

Ethical statement

This study is a part of a project approved by the ethical review committee of the University of Évora (Órgão Responsável pelo Bem-estar dos Animais da Universidade de Évora, approval nº GD/32055/2018/P1, September 25th, 2018). Written, informed consent was obtained from the Institution responsible for the animals (Guarda Nacional Republicana, Portuguese Gendarmerie).

Experimental design

A sample of 20 police working dogs (N = 20) was selected from the population of police working dogs. It constituted a convenience sample, with patients signaled based on trainer complaints, physical exam, and pelvic radiographic evaluation consistent with bilateral hip OA. All patients had bilateral naturally occurring mild and moderate hip OA, classified according to the Orthopedic Foundation for Animals scoring. Animals with other diseases were ruled out through physical examination, complete blood count, and basic serum chemistry profile (BUN, CREAT, ALT, AST, GLUC), and/or under any treatment, were excluded from the study. Signed informed consent was obtained for all animals participating in the study. Dogs were randomly divided into two groups using the statistical analysis software, according to the type of drug used for hip joint intra-articular administration, namely: GT (treated with 20 mg TA per hip joint – Trigon depot, Bristol-Myers Squibb®, Spain) and GMPA (treated with 40 mg of methylprednisolone acetate per hip joint — Depo-medrol, Pfizer®, Portugal).

All intra articular procedures were performed by the same researcher and conducted under light sedation using medetomidine (0.01 mg/kg) and butorphanol (0.1 mg/kg), both given intravenously. Animals were placed in lateral recumbency, with the affected joint uppermost. A small window of 4 × 4 cm area surrounding the greater trochanter was clipped and aseptically prepared, using a chlorhexidine solution 0.2 % followed by 70 % alcohol scrub, with sterile gloves and 10 × 10 cm gauze. With the limb parallel to the table surface and in a neutral position, the operator inserted a 22 gauge 75 mm length spinal needle, closely dorsal to the greater trochanter and perpendicular to the long axis of the limb.[42] Confirmation of correct needle placement was obtained through the collection of synovial fluid. After the treatment session, animals were rested for three consecutive days and resumed their normal activity over five days.

Signs of exacerbated pain, persistent stiffness of gait, and changes in posture exhibited by the dogs, were evaluated by the veterinarian on days one and three after the IA procedure. If no complaints are reported, the animal could resume normal activity.[43, 44]

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To evaluate the response to treatment and compare it with an initial clinical condition, two validated tools for dog pain assessment were used: the CBPI and the HVAS. Seven different time points were considered: T0 (before IA treatment), T1 (15 days after IA treatment), T2, T3, T4, T5, T6, and T7 (1, 2, 3, 4, 5, and 6 months after IA treatment respectively). During and after six months, all animals remained in active service.

Statistical analysis

Collected data was analyzed with IBM SPSS Statistics version 20, and a significance level of $p < 0.05$ was set. Normality was assessed with a Shapiro-Wilk test and results of both groups by time points were compared using a Mann-Whitney Test. When comparing each instant with T0 within each group, a Paired Samples T-Test was used.

Results

The sample comprised animals of both genders (5 females and 15 males), with a mean age of 6 ±2.4 years and a body weight of 33.3 ±4.14 kg, and a body condition score of 4/9. Four breeds were represented, German Shepherd Dogs (n = 15), Belgian Malinois Shepherd Dogs (n = 3), and Labrador Retriever (n = 2), all with naturally occurring bilateral hip OA. GT included animals of both genders (two females and eight males), with a mean age of 6.2 ±2.3 years old and the body weight of 32.8 ±3.8 kg, eight German Shepherd Dogs, a Belgian Malinois Shepherd Dogs, and a Labrador Retriever. They were graded with mild (n = 3) and moderate (n = 7) hip OA. GMPA also included animals of both genders (three females and seven males), with a mean age of 6.1 ±0.7 years old and a body weight of 33.8 ±3.4 kg, seven German Shepherd Dogs, two Belgian Malinois Shepherd Dogs, and a Labrador Retriever. They were graded with mild (n = 2) and moderate (n = 7) hip OA. Of all animals enrolled in the study, three from GT were excluded-two after T2 due to the development of unrelated medical conditions, and one after T3 due to inability to keep it medical follow-up. No side effects were detected in either GT or GMPA. No significant changes in body weight were recorded throughout the study.

A reduction of ≥1 in PSS and ≥2 in PIS has been defined as individual treatment success achieved, as measured by the CBPI.[45] Treatment was successful in reducing PSS in two animals treated with TA at T1 (20 %, n = 10), three at T2 and T3 (37.5 %, n = 8), and two at T4–T7 (28.6 %, n = 7). Improvements were registered in four animals at T1 (50 %, n = 10), three at T2 (30 %, n = 10), four at T3 (50 %, n = 9), and three at T4–T7. For the GMPA, results showed that treatment was successful in two animals at T1 (20 %, n = 10), four at T2 (40 %, n = 10), three at T3 (30 %, n = 10), and two at T4–T5 (20 %, n = 10). Scores improved in six animals at T1–T2 (60 %, n = 10), seven at T3 (70 %, n = 10), and four at T4–T5 (40 %, n = 10).

Considering PIS, treatment was a success in two animals in GT and two in GMPA; in GT from T1–T7 and in GMPA from T1–T5. Also, scores increased in the same proportion as PSS. When comparing the results for each time moment with T0 or

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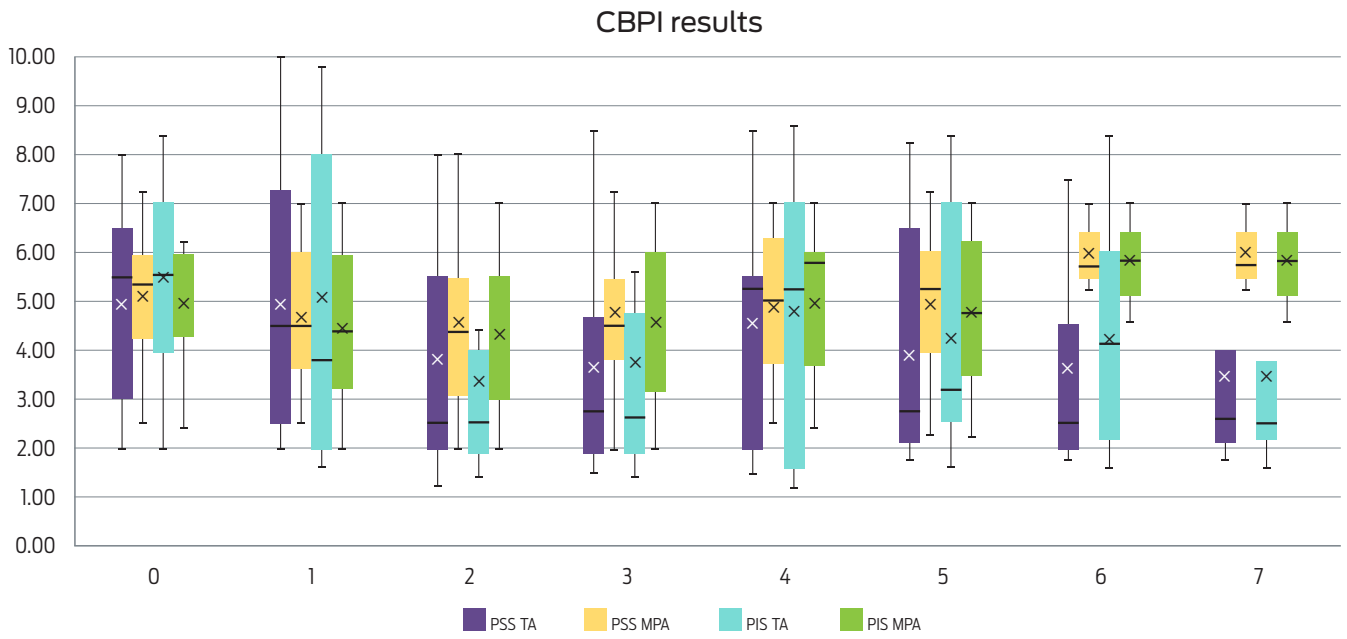

Figure 1. Overall Canine Brief Pain Inventory scores, by section and instant for methylprednisolone acetate (MPA) and triamcinolone acetonide (TA). Box plots represent median, 25th and 75th percentiles, and whiskers represent the 10th and 90th percentiles.

between the groups, no significant differences were found. The overall CBPI score evolution can be observed in Figure 1.

When comparing each moment with T0 or between groups, no significant differences were registered in the results of the HVAS. However, individual results showed an improvement in results observed in two animals of the GT at T1 (20 %), eight at T2–T3 (62.5 %), and three at T4–T7 (57.1 %). In GMPA, an improvement in scores was observed in seven animals at T1 (70 %), six at T2 (60 %), five at T3–T4 (50 %), and four at T5 (40 %).

Discussion

The focus of OA treatment is to control and decrease pain levels.[46, 47] This study results show that intra-articular CS could be an effective therapeutic option for some animals since most treated animals showed improved results, which may last for months. The recommendations for human hip and knee OA state that intra-articular CS can and should be used, especially in patients with moderate to severe pain, non-responding to oral analgesic/NSAIDs.[30, 48] These recommendations may also be adequate for dogs. There use of IA CS raises some concern since the reports of deleterious effects are available, including the production of a low quantity and high viscosity synovial fluid. These results are often based on multiple injections, particularly of methylprednisolone, while a single dose does not seem to have long-term damaging effects.[49, 50] Information on the effects of MPA and triamcinolone on canine cartilage is available from studies on a canine model of OA, showing a protective effect of MPA[51, 52] and triamcinolone.[24] A review of animal studies

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presented studies concluding that there were beneficial effects with MPA triamcinolone administration.[53]

The PSS assesses the magnitude of the pain of an animal, and the PIS, the level in which pain affects a dog's daily activities, is the body of the CBPI, used for comparisons of overall mean or median differences in pain scores between groups.[39, 40, 54] It has the advantage of quantifying the dog's activity in its environment and over a larger period using the owner's assessment. Treatment success in OA dogs has been set as a decrease in PSS ≥ 1 and in PIS ≥ 2.[45, 55] Both TA and MPA could significantly reduce the scores of some individuals, particularly PSS. In some cases of GT, beneficial results spread up to the last evaluation point, while the majority of improvements in both groups declined around T4-T5, especially in GMPA.

Triamcinolone was presented as having an extended duration of action. In some canine reports, authors recommended the use of TA over MPA.[56, 57] In horses, a study comparing the difference between TA and MPA registered no difference between the drugs used.[58] According to our results, significant individual improvements lasted longer in GT, even though more animals showed significant improvements in the GMPA. This difference may be associated with the total amount of drug administered to each joint.

Both drugs—TA and MPA, are approved for IA use and since both hip joints were to be treated in each animal, we divided the content of one vial equally between joints. Therefore, 20 mg TA and 40 mg of MPA were administered per joint in each animal sample. Further studies, involving different total doses, must determine whether different doses would provide different results.

Individual results for PIS registered less marked improvements, similar for both treatment groups. Some factors may influence this. Considering that OA pain results not only from the joint tissues and structures, but also from adjacent tissues like muscles, tendons, and ligaments, it is possible that IA therapies do not completely address all of these pain sources. Besides, the fact that animals enrolled in the study are active police working dogs, their musculoskeletal structures are under great physical stress and may require a more comprehensive multi-modal approach to OA. It may be reasonable to assume that a companion animal will need less marked and continued pain control, thus achieving better results that can also remain significant for longer periods post-treatment.

To compare different analgesic protocols, visual analog scales are usually used to address pain scores and severity. As they rely on a continuous scale, data can be modeled as a continuous variable.[59] The HVAS is very useful to assess lameness in dogs varying from mild to moderate, having force plate analysis as a criterion-referenced standard.[41] According to our results, no significant variations were observed in HVAS scores, even though individual results seemed to improve in almost all animals. This can be due to a limitation highlighted to visual analog scales, the fact that they are more sensitive in detecting and recording changes in more obvious cases of lameness. Since most animals included in the study showed only mild signs, HVAS might not be able to record subtle changes resulting from TA and MPA treatments.

The described side effects of IA CS use are mainly related to discomfort from the procedure, specifically localized pain and flushing.[59] However, no side effects were observed during the study. For that reason, both CS seem to be safe therapeutic options. Still, no follow-up radiographic evaluation was performed, and for that

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reason, we cannot comment on the evolution of radiographic signs following IA CS, but it should be addressed in future studies.

Although no significant variations were observed when comparing the results of the groups, several animals showed improvements in both GT and GMPA. Future studies should include a larger number of animals since the sample size is a limitation of this study. On the other hand, animals included had similar conformations and sizes, were kept in identical housing conditions, fed the same food, and submitted to similar workloads. As such, the information present may be of interest for treating human and canine OA.

The lack of a control group is a further limitation and, even though both the CBPI and HVAS are validated tools for pain and lameness assessment in dogs, further studies should include other evaluation methods, such as Force Plait Gait or Stance Analysis. The determination of individual characteristics of the animals that improve with this treatment may help elect the most suitable candidates for IA CS. The effect of different treatment frequencies have also to be addressed.

Conclusions

Intra-articular CS may be a treatment option for some dogs with naturally occurring OA, being particularly useful in terms of reducing pain and return to function, with an added cost-effectiveness compared to other therapeutic options. Further studies are required, aimed at determining which are the better candidates for the treatment, and to evaluate alternative drugs and drug dosages.

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Data availability

The datasets used and/or analyzed during the current study are not readily available because the data used in this study is a property of the Guarda Nacional Republicana, a governmental police force from Portugal and, by law, confidential. Access to the datasets is available from the corresponding author on reasonable request.

Funding statement

The animals were provided by the Guarda Nacional Republicana, Portuguese Gendarmerie. Experimental procedures were conducted at the Mediterranean Institute for Agriculture, Environment and Development, Instituto de Investigação e Formação Avançada, Universidade de Évora, Portugal. The medications were bought by the authors. The funder had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

The authors have no conflict of interest to declare in regard to this publication.

Author contributions

Conceptualization: JC Alves, C Lavrador, LM Carreira.
Formal analysis: JC Alves.
Investigation: JC Alves, A Santos, P. Jorge.
Methodology: JC Alves, C Lavrador, LM Carreira.
Supervision: C Lavrador, LM Carreira.
Writing – original draft: JC Alves.
Writing- review and editing: All authors.

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