A multiple-session mesotherapy protocol for the management of hip osteoarthritis in police working dogs

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OBJECTIVE
To describe the effect of a mesotherapy protocol in dogs with osteoarthritis.

ANIMALS
30 dogs.

PROCEDURES
Dogs were randomly assigned to a control (CG; n = 10) or a mesotherapy group (MG; 20). CG received meloxicam for 70 days. MG was treated with a combination of lidocaine, piroxicam, and thiocolchicoside, injected in intradermal points. Seven treatment sessions were conducted. Response to treatment was measured with different instruments: the Canine Brief Pain Inventory (divided into Pain Interference Score [PIS] and Pain Severity Score [PSS]), Liverpool Osteoarthritis in Dogs (LOAD), and Canine Orthopedic Index (COI; divided into function, gait, stiffness, and quality of life), at time 0 (T0), +15 days, +30 days, +60 days, and +90 days after T0. At each time point, the results of the 2 groups with each instrument were analyzed with the Wilcoxon signed ranks test, \( P < .05 \). Kaplan-Meier estimators were compared with the Breslow test.

RESULTS
Dogs had a mean age of 6.9 ± 2.7 years and a body weight of 31.0 ± 6.4 kg. Hip osteoarthritis was classified as mild (n = 9), moderate (17), or severe (4). No differences were found at T0. Better results were observed in MG at +15 days (\( P < .01 \) for PSS and PIS, \( P = .03 \) for function), +30 days (\( P = .01 \) for PIS and LOAD, \( P = .03 \) for PSS, and \( P = .04 \) for function, gait, and COI), +60 days (\( P < .01 \) for PSS and PIS, \( P = .01 \) for LOAD, and \( P = .02 \) for function), and +90 days (\( P = .01 \) for PSS and PIS, \( P = .03 \) for LOAD, and \( P = .04 \) for function). Kaplan-Meier estimators showed MG had longer periods with better results than CG in various scores.

CLINICAL RELEVANCE
This mesotherapy protocol reduced pain scores and other clinical metrology instrument scores lasting for longer periods.

Osteoarthritis (OA) is the most commonly diagnosed musculoskeletal disease in veterinary medicine.\(^{1}\) It is a chronic, low-inflammatory, degenerative disease characterized by pain, inflammation, decreased mobility, and function, leading to structural changes.\(^{2,3}\) In working dogs, OA affects gait, posture, activity, and overall performance.\(^{4-6}\) Disease management is challenging and often requires a multimodal approach, involving an exercise/rehabilitation program, medical and surgical interventions.\(^{7}\) Nonsteroidal anti-inflammatory drugs (NSAIDs) are often the first line of approach for OA’s medical management. Meloxicam is one of the most commonly prescribed for managing canine OA.\(^{8}\) Multiple other approaches for the management of OA have been described, such as intra-articular modalities,\(^{9-13}\) biological products,\(^{14-17}\) photobiomodulation,\(^{18}\) or oral joint supplements.\(^{4}\) Mesotherapy (also known as local intradermal therapy) is a minimally invasive technique that applies pharmaceuticals or other substances in small quantities through multipunctures of the dermis. This process creates microdeposits from where the drug(s) is slowly released to the underlying tissues.\(^{19,20}\) The joint is currently viewed as a complex organ, and the surrounding tissues, muscles, tendons, and ligaments are also a source of pain in OA.\(^{2,21}\) Since the drug(s) is administered close to the intended site of action, mesotherapy has a rapid
onset of action, a prolonged local action, and a drug-sparing effect. In humans, it has been superior to systemic therapy for musculoskeletal pain relief.22,23 However, a recent systemic review24 of mesotherapy in human medicine found that only a small percentage of studies identified had a methodology sufficiently robust to be included in the review. The authors24 also pointed out the need of comparing a standardized mesotherapy protocol with systemic treatments. In veterinary medicine, the use of mesotherapy has been described in horses and dogs.25–29

Several clinical metrology instruments (CMI) have been developed to evaluate the severity of orthopedic conditions and the response to treatment.30 The Canine Brief Pain Inventory (CBPI) is a questionnaire destined to assess owners’ perceptions of the impact of chronic pain on their own dogs.31 It is divided into a pain severity score (PSS) that evaluates the magnitude of pain and a pain interference score (PIS) that assesses the degree to which pain affects daily activities.32 Together with the Liverpool Osteoarthritis in Dogs (LOAD), they have demonstrated criterion validity compared to peak vertical force evaluation.33 The Canine Orthopaedic Impact Questionnaire (COI) is an additional CMI covering 4 domains of OA’s multiple-dimension experience in dogs: stiffness, gait, function, and quality of life. It has excellent reliability and validity and can differentiate between OA and healthy subjects.34,35 OA pain is a multidimensional experience that encompasses more than just a functional aspect. For that reason, gathering information on several CMIs may help to cover this complex experience.36–38

This study’s objective was to evaluate the effectiveness of a multiple-session mesotherapy protocol in police working dogs with hip OA, as measured with the different CMIs, and compare its results with a positive control group. We hypothesize that this protocol can reduce pain scores in dogs with hip OA-related pain similar to an NSAID, meloxicam.

Materials and Methods

This study’s protocol was approved by the Ethical Review Group of the Association of Veterinary Anaesthetists (No. 2020-010). Written, informed consent was obtained from the Institution responsible for all the animals (Guarda Nacional Republicana, Portuguese Gendarmerie). A group of 30 dogs was included in the study, constituting a convenience sample, from the population of working dogs of the Guarda Nacional Republicana (Portuguese Gendarmerie Canine Unit) presenting for hip OA treatment. Dogs were selected based on history, trainer complaints (difficulty rising, jumping, and maintaining obedience positions, stiffness, and decreased overall performance), and physical (pain during joint mobilization, stiffness, and reduced range of motion) and radiographic findings consistent with bilateral naturally occurring mild, moderate, or severe hip OA, classified according to the Orthopedic Foundation for Animals scoring (https://www.ofa.org/diseases/hip-dysplasia/grades). Additional inclusion criteria include a body weight ≥ 15 kg and age > 2 years. Other illnesses were ruled out through physical examination, complete blood count, and serum chemistry profile. Animals included in the study could not be under any other treatment.

In this prospective, randomized, double-blinded study, patients were randomly assigned using the statistical analysis software to a control group (CG; n = 10) or a mesotherapy group (MG; 20). Patients in MG were treated with a solution combining 40 mg of lidocaine (2% Anestesin; Laboratório Serológico), 20 mg of piroxicam (20 mg/mL Feldene; Pfizer), and 4 mg of tiocolchicoseide (4 mg/mL Relmus; Sanofi), based on an identical protocol previously described in dogs.26,39 A total solution volume of 4 mL was prepared, regardless of the animal’s weight. A solution volume of 0.1 mL was injected intradermally in each injection point using 4-mm, 27-gauge needles (Mesoram, Italy). Injection sites were spaced around 2 cm apart15,20 along the skin area corresponding to the location of the coxofemoral joint: laterally on a 10 X 10 cm area having the greater trochanter at its center, and medially on a similar-sized area, having the coxofemoral joint at the center. Before treatment administration, their hair and skin were thoroughly rinsed with a 0.2% chlorhexidine solution followed by 70% alcohol application around the area of interest. Depending on the dog’s size, a variable number of injection sites may be required to cover the interest area. Only mild restraint and no sedation were needed to conduct the treatment. Over 10 weeks for each animal, seven treatments sessions were performed on days 0, 7, 14, 21, 35, 49, and 63.20 Since dogs in the CG received meloxicam, patients in MG also received a 70-day course of a placebo, which was packaged in a similar fashion to meloxicam. All treatments were conducted by the same veterinarian, in a room secluded from the dog’s handlers. Patients in CG received a 70-day course of meloxicam (the approximate duration of the treatment protocol for MG), at a dose of 0.2 mg/kg, according to the manufacturer’s indications. On the same days as the treatments for MG, patients in the CG were conducted in a room secluded from their handlers. Their hair and skin were thoroughly rinsed with a skin disinfectant solution around the anatomical area of the hip joint to mimic if they had undergone a mesotherapy session.

The same assisting veterinarian, blinded to the animal’s group, examined all animals on the day after the initial procedure and three days later to evaluate for signs of increased pain and changes in posture potentially induced by the treatment. If no complaints were detected, the animal was allowed to resume regular activity. During the follow-up examination, signs of any possible adverse effects were recorded. The adverse effects of mesotherapy are presented as extremely rare and mild, including nausea, vomiting, diarrhea, mild pain, edema, pruritus, and erythema.40

Response to treatment was measured with the CBPI, LOAD, and COI before treatment (T0) and +15 (after 2 treatment sessions), +30 (after 4 treatment
Table 1—Evolution of clinical metrology instruments (median score, interquartile range, and percentual variation), by group and moment.

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<td>21.3</td>
<td>14.0</td>
<td>-33.0</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

CBPI = Canine Brief Pain Inventory. COI = Canine Orthopedic Index. LOAD = Liverpool Osteoarthritis in Dogs. QOL = Quality of life. PIS = Pain interference score. PSS = Pain severity score.

*Indicates significance when comparing groups at each follow-up moment.
sessions), +60 days (after 6 treatment sessions), and +90 days (after all 7 treatment sessions) after treatment. Blinded to the dog’s group, each dog’s trainer completed all CMIs without seeing the dog’s previous evaluation. All patients were followed up to the last evaluation moment (90 days). No additional treatment or medications were administered.

Normality was assessed with a Shapiro-Wilk test. In each evaluation moment, groups were compared using a Wilcoxon signed ranks test. Kaplan-Meier estimators were conducted to generate a time to event curves and time-to-event probability, and they were compared with the Breslow test. The outcome considered was a return to or an increase above the initial evaluation values of CMI scores. With the CBPI, a specific measure of success has been defined, set as a reduction of ≥1 in PSS and ≥2 in PIS. For these scores, the outcome considered was a drop below this improvement level. Patients with better scores compared to baseline values at the final evaluation point were censored. All results were analyzed with IBM SPSS Statistics version 20, and a significance level of $P < .05$ was set.

## Results

The sample included 30 active Police working dogs, with a mean age of 6.9 ± 2.7 years and body weight of 31.0 ± 6.4 kg, representing both sexes (male n = 20; female, 10). Four dog breeds were represented: German Shepherd Dogs (n = 17), Labrador Retriever (LR; 7), Dutch Shepherd Dog (DSD; 4), and Belgian Malinois Shepherd Dogs (2). At the initial evaluation, 9 dogs were classified as having mild OA (3 in CG and 6 in MG), 17 as moderate (6 in CG and 11 in MG), and 4 as severe (1 in CG and 3 in MG),

### Table 2—Time (days) to event probability calculated with Kaplan-Meier estimators and compared with the Breslow test.

<table>
<thead>
<tr>
<th>Clinical metrology instrument</th>
<th>Breslow test</th>
<th>Group</th>
<th>95% CI</th>
<th>Group</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBPI</td>
<td></td>
<td>CG</td>
<td>95% CI</td>
<td>MG</td>
<td>95% CI</td>
</tr>
<tr>
<td>PSS</td>
<td>0.031*</td>
<td>76.9</td>
<td>16.2</td>
<td>137.5</td>
<td>92.6</td>
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<tr>
<td>PIS</td>
<td>0.000*</td>
<td>48.8</td>
<td>22.6</td>
<td>74.9</td>
<td>90.7</td>
</tr>
<tr>
<td>LOAD</td>
<td>0.001*</td>
<td>42.5</td>
<td>63.2</td>
<td>82.0</td>
<td>72.9</td>
</tr>
<tr>
<td>COI Stiffness</td>
<td>0.000*</td>
<td>30.0</td>
<td>9.9</td>
<td>50.0</td>
<td>92.1</td>
</tr>
<tr>
<td>Function</td>
<td>0.019*</td>
<td>50.6</td>
<td>27.4</td>
<td>73.8</td>
<td>93.6</td>
</tr>
<tr>
<td>Gait</td>
<td>0.001*</td>
<td>41.3</td>
<td>19.4</td>
<td>63.1</td>
<td>93.7</td>
</tr>
<tr>
<td>QOL</td>
<td>0.000*</td>
<td>28.1</td>
<td>42.4</td>
<td>85.6</td>
<td>91.9</td>
</tr>
<tr>
<td>Overall</td>
<td>0.006</td>
<td>50.6</td>
<td>25.2</td>
<td>76.0</td>
<td>85.1</td>
</tr>
</tbody>
</table>

*Indicates significance.
See Table 1 for remainder of key.

### Figure 1—Kaplan-Meier curve demonstrating a significant difference between control group (CG) and mesotherapy group (MG) in time (days) for pain interference score (PIS) to return to baseline values.

### Figure 2—Kaplan-Meier curve demonstrating a significant difference between CG and MG in time (days) for Canine Orthopedic Index (COI) to return to baseline values.
Osteoarthritis is the most commonly diagnosed joint disease in veterinary medicine, leading to pain and reduced joint function. Its presentation is highly influenced by several factors, like breed, age, and exercise level. Our results show that this mesotherapy protocol reduced pain levels and improved clinical scores in police working dogs with bilateral hip OA.

OA management is set around controlling symptoms, mainly its pivotal symptom, pain. NSAIDs are an effective treatment for managing canine OA and its clinical signs. Several reports have pointed out strong evidence of the efficacy of different NSAIDs, such as carprofen, meloxicam, or firocoxib, without insufficient evidence to determine if one is superior to others. This study shows that this combination of drugs, administered through mesotherapy, provides significant pain relief in working dogs with bilateral hip OA. The pain relief observed in MG was significantly better than in the CG with both the PIS and PSS from the first evaluation moment posttreatment (+15 days) and remained significant up to the last evaluation moment at +90 days. Also, the Kaplan-Meier test results show that MG scores took significantly longer than the level of defined treatment success. It is known that the overall perception of pain is influenced by all joint composing and surrounding tissues, and this effect in MG may be attributed to the fact that drugs applied through intradermal injection diffuse from the microdeposit created on the skin to all underlying tissues, reaching higher concentration levels than when administered through other routes.

A similar effect was observed with the LOAD, with significantly better results in the MG group after the first 4 treatment sessions (at +30 days) and remaining better up to the last evaluation moment. The time-to-event plots also show that, during the treatment period, most animals did not experience the defined outcome. The LOAD has been compared to force plate analysis as a criterion-referenced standard, and the improvement observed in this study for this score is in contrast with previous reports regarding working dogs. Since MG showed significantly better results than CG with these scores, it is positive information on this treatment modality’s efficacy.

Dimensions of the COI showed different degrees of variation. The ones related to functional performance (function and gait) showed better results in MG than CG. Function scores improved at the first follow-up evaluation, at +15 days, and remained significantly better up to the last evaluation point at +90 days. Significant improvements were only observed with gait after the first 4 weekly sessions, at +60 days. The same was observed in the COI overall score, with many animals not experiencing the defined outcome during the treatment period. Some of these variations, or lack of them, may be related to the nature of the treatment and drugs used. Mesotherapy has been proven to impact pain in dogs and humans significantly, and the improvements observed may be related to decreased pain and, consequently, better ability to perform daily activities. Other dimensions, like stiffness, may require different treatment modalities to improve joint function.

Trainers were not allowed to see previous answers to reduce bias, as we felt that it could influence their responses. A previous study addressing this question concluded that allowing responders to see previous answers may increase treatment effect sizes and, consequently, increase clinical trial power. Additionally, we must take into consideration that the animals included in this study are working dogs, which, on the one hand, means that their musculoskeletal structures are under greater demand than...
those of companion animals. On the other hand, most of the dogs included in this study were treated earlier in life and show fewer radiographic changes than what is expected for companion animals. For these reasons, these results need to be extrapolated to companion animals with caution as they may vary: mesotherapy results may be better in companion animals due to their lower physical demand, or worse, as companion animals are likely to present in a more advanced disease stage.

Of the patients treated, 1 dog in MG vomited. This was the only adverse effect noted, and it has been described before in dogs treated with mesotherapy. The lack of adverse side effects and low systemic concentration means that mesotherapy can be combined with other systemic therapies in cases where different administration routes are not an option due to existing comorbidities. This should be addressed in a future study. This study presents some limitations, namely the use of CMIs as the outcome measures. Even though all CMIs have been validated for evaluating pain and lameness, and the use of several scales may help hinder this limitation, further studies should include objective evaluation methods such as force plate gait analysis or weight-bearing evaluation. Another limitation is related to sample size and frequency of the different hip grades. We selected a convenience sample, so future studies should include a sample size calculation and power analysis. We also chose to include a different number of animals in the groups, although we acknowledge that it may have an impact on the results. Future studies should evaluate the impact of these variables on treatment results. The reason for our decision was that NSAIDs have a well-established effect on OA pain, although we seldom use them as the single treatment for this disease. On the other hand, mesotherapy had not been described in a controlled blind study, so we felt that more information on its use was required. Additionally, it would be interesting to have more animals to evaluate the treatment effect in dogs of different sizes, body conformation, and hip OA grades. Human reports recommend using mesotherapy in patients where NSAIDs are contraindicated. Before making a similar claim in veterinary patients, further studies should also evaluate the pharmacokinetics of the drugs administered through mesotherapy, particularly to assess the potential accidental systemic uptake. In addition, while thiocolchicoside has been authorized in many countries for the treatment of painful muscular disorders, the European Medicines Agency recommended that it should only be used as an add-on treatment for painful muscle contractures and that there should be a restriction on the maximum dose and number of days of treatment when given by mouth or injection. With the protocol reported here, a low dose of thiocolchicoside was used. In addition, human studies have demonstrated that drugs administered through mesotherapy have limited systemic absorption. The use of different/drug combinations in managing OA and other musculoskeletal conditions is also required. Most of the published papers on mesotherapy in animals chose a corticosteroid as the anti-inflammatory drug in the solution used. There are other reports where NSAIDs were used, and in humans, they are the norm. The reason for this difference is not clear. We elected to use an NSAID due to the availability of more references on NSAID use in mesotherapy protocols and to a lower level of potential side effects.

Mesotherapy may be a minimally invasive, cost-effective, low-risk treatment option for canine hip OA since this protocol was able to significantly reduce pain scores and other CMI scores in police working dogs. This reduction in pain scores was significantly superior to meloxicam. Further studies are required to evaluate alternative drugs or drug combinations and their application to different conditions.

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