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Evaluation of different substance combinations in a multiple-session mesotherapy protocol for the management of osteoarthritis in dogs: a retrospective study

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OBJECTIVE
To describe the effect of different substance combinations administered through mesotherapy in dogs with hip osteoarthritis.

ANIMALS
104 dogs.

METHODS
In this retrospective study, 4 groups (dogs treated with a combination of lidocaine, piroxicam, and thiocolchicoside [MG]; dogs treated with lidocaine, piroxicam, and Traumeel [TG]; dogs treated with lidocaine, piroxicam, and glucosamine [GG]; and dogs treated with the same combination as in MG combined with a photobiomodulation session [MPG]) were set. For all groups, the same treatment frequency was followed. Response to treatment was measured with the Canine Brief Pain Inventory (divided into pain interference score and pain severity score), Liverpool Osteoarthritis in Dogs (LOAD), and Canine Orthopedic Index (divided into function, gait, stiffness, and quality of life) before treatment and 15, 30, 60, 90, and 120 days after treatment. Cox proportional hazard regression analysis was used to investigate the influence of treatment, age, sex, body weight, breed, and Orthopedic Foundation for Animals score.

RESULTS
Dogs had a mean age of 7.6 ± 3.1 years and body weight of 28.6 ± 5.5 kg. Hip osteoarthritis was classified as mild (4), moderate (70), or severe (30). Greater improvements were observed in MG and MPG. Kaplan-Meier estimators showed MG and MPG had longer periods with clinically significant results. Treatment was the covariable that contributed more frequently to the outcomes observed.

CLINICAL RELEVANCE
The combination used in MG, particularly combined with photobiomodulation, produced longer-lasting clinically significant results.

Keywords: dog, mesotherapy, chronic pain, osteoarthritis, patient-reported outcome measures

Osteoarthritis (OA) is the most commonly diagnosed musculoskeletal disease in veterinary medicine.[1] The disease is particularly impacting in working dogs, their performance, and overall quality of life (QOL).[2] Osteoarthritis is a low-inflammatory chronic disease[3] and is a cause of pain.[4] Managing the disease can be challenging, requiring a multimodal approach.[5] A wide range of approaches have been developed and tried for the management of OA, which speaks to the challenges of successfully managing the disease. Nonsteroidal anti-inflammatory drugs remain the most common first line of approach for the management of OA, with multiple compounds being available.[6] More recently, a growing number of alternative approaches have been described, such as a growing array of oral joint supplements,[7] compounds administered through intra-articular injections,[8–12] biological products,[13–16] photobiomodulation,[17] and more.

Intradermal therapy, commonly referred to as mesotherapy, is a technique used to inject a drug into the superficial layer of the skin.[18] This technique creates a

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small deposit of medication in the skin, with the intent to modulate the drugs' kinetics, slow absorption, and prolong the local mechanism of action.[18] The use of mesotherapy for the management of painful musculoskeletal conditions has been described in humans,[19] horses,[20] and dogs.[21–23] A recent study[24] showed that a multiple-session mesotherapy protocol was superior to an NSAID in the management of hip OA.

Different substances have been described in mesotherapy protocols and for the management of OA. Traumeel is a homeopathic combination formula of 12 botanical and 2 mineral substances with demonstrated anti-inflammatory, anti-edematous, and antiexudative effects.[25] In humans, it has been described as not inferior to NSAIDs in the treatment of epicondylitis, trauma, pain, and other injuries.[26] Its use has been described in horses and dogs.[20,27] Glucosamine has been characterized as a chondroprotective agent due to a modulatory effect on the metabolic activity of chondrocytes. In vitro, it has been shown to have the ability to reduce matrix molecule degradation and enhance its synthesis[28] and is usually administered in combination with chondroitin sulfate, the major glycosaminoglycan found in the cartilage of moving joint surfaces.[29] Reports on the efficacy of these 2 compounds in the management of OA show different levels of clinical improvement,[30] and there is some evidence suggesting that long periods of administration are required.[31]

The purpose of this study was to retrospectively evaluate the effectiveness of different combinations of substances administered in a multiple-session mesotherapy protocol for the management of hip OA in police working dogs.

Methods

This study's protocol was reviewed by the Ethical Review Committee of the University of Évora (Órgão Responsável pelo Bem-Estar dos Animais da Universidade de Évora, process No. GD/21660/2022) and complies with relevant institutional and national guidelines for the care and use of animals as well as the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. All experiments were performed following relevant guidelines and regulations. Written informed consent was obtained from the institution responsible for the animals.

Patient selection

Electronic medical records were searched to identify all dogs with hip OA evaluated by the Canine Veterinary Clinic of the Guarda Nacional Republicana (Portuguese Gendarmerie). To be included in the study, dogs had to be diagnosed with hip OA and show clinical signs of the disease (eg, difficulty rising, jumping, and maintaining obedience positions; stiffness; decreased overall performance; pain during joint mobilization; and reduced range of motion); have radiographic findings consistent with bilateral hip OA (graded via the Orthopedic Foundation for Animals [OFA] scoring scheme); have confirmed absence of any other disease (clearly stated on the medical records, with available copies of additional performed diagnostics); have available results of the Canine Brief Pain Inventory (CBPI; divided into a pain severity score [PSS] and a pain interference score [PIS]),[32,33] the Liverpool Osteoarthritis in Dogs (LOAD),[34] the Canine Orthopedic Index (COI)[35] for the set follow-up evaluations; and have been treated with the treatment frequency set by the Italian Mesotherapy Society[36] (1 weekly session for 4 weeks, followed by 1 session every other week for 3 treatment sessions). Additional inclusion criteria included a body weight of ≥ 15 kg and age > 2 years as well as the absence of any other concomitant treatment.

Identified treatments

For substance combinations to be considered in the study, records of at least 10 animals had to be available. Four combinations were identified: a solution combining 40 mg of lidocaine (Anestesin 2%), 20 mg of piroxicam (Feldene), and 4 mg of tiocolchicoseide (Relmus), for a total dose of 4 mL, based on an identical protocol previously described in dogs[21,22] (MG); a second solution, combining 20 mg of lidocaine (Anestesin 2%), 20 mg of piroxicam (Feldene), and 3 mL of Traumeel,[27] for a total dose of 5 mL (TG); a third solution, combining 20 mg of lidocaine (Anestesin 2%), 20 mg of piroxicam (Feldene), and 3 mL of glucosamine (Viartril-S),[37] for a total dose of 5 mL (GG); and a final solution, combining 40 mg of lidocaine (Anestesin 2%), 20 mg of piroxicam (Feldene), and 4 mg of tiocolchicoseide (Relmus), for a total dose of 4 mL, combined with a photobiomodulation session (MPG) on treatment days. Photobiomodulation was administered with a therapeutic laser (Companion CTC class IV laser; Litecure LLC). Photobiomodulation parameters and the flow chart of the process are presented **(Table 1; Figure 1)**.

Treatment technique

Treatments were administered as previously described.[21,24] A solution volume of 0.1 to 0.2 mL was injected ID at each injection point. Four-millimeter, 27-gauge mesotherapy needles (Mesoram) were used. Injection sites were spaced approximately 2 cm apart 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 the injections, the hair and skin were thoroughly scrubbed with a disinfection solution around the area of interest. Following the treatment frequency set by the Italian Mesotherapy Society,[36] 7 treatment sessions were performed for each dog: on days 0, 7, 14, 21, 35, 49, and 63. Medical records were also checked for possible adverse effects, including nausea, vomiting, diarrhea, mild pain, edema, pruritus, and erythema.[38]

Outcome measures

Several clinical metrology instruments (CMIs) have been developed to evaluate the severity of orthopedic conditions and the response to treatment.[39] Osteoarthritis pain is a multidimensional experience,

Table 1—Photobiomodulation therapy treatment parameters.

	Light parameters (dose)	Notes
Wavelength (nm)	980 (for patients with dark coat color) 980/808 blend (for patients with light to medium coat color)	Blend consists of 80% of 980 nm and 20% of 808 nm
Radiant power (W)	6.5–8	
Irradiance (W/cm^2) at skin surface	4.2–5.2	Depending on patient size, with smaller/thinner patients being treated at lower power, irradiance increased with an increase in power
Fluence (J/cm^2)	14.3–19.5 (average over the treated area)	
Treatment protocol	Continuously moving grid pattern in contact over the area of the greater trochanter at a speed of 2.5–7.5 cm/s, according to manufacturer recommendations	
Treatment area (cm^2)	225	
Treatment time	Between 4 min, 35 s–5 min, and 5 s	

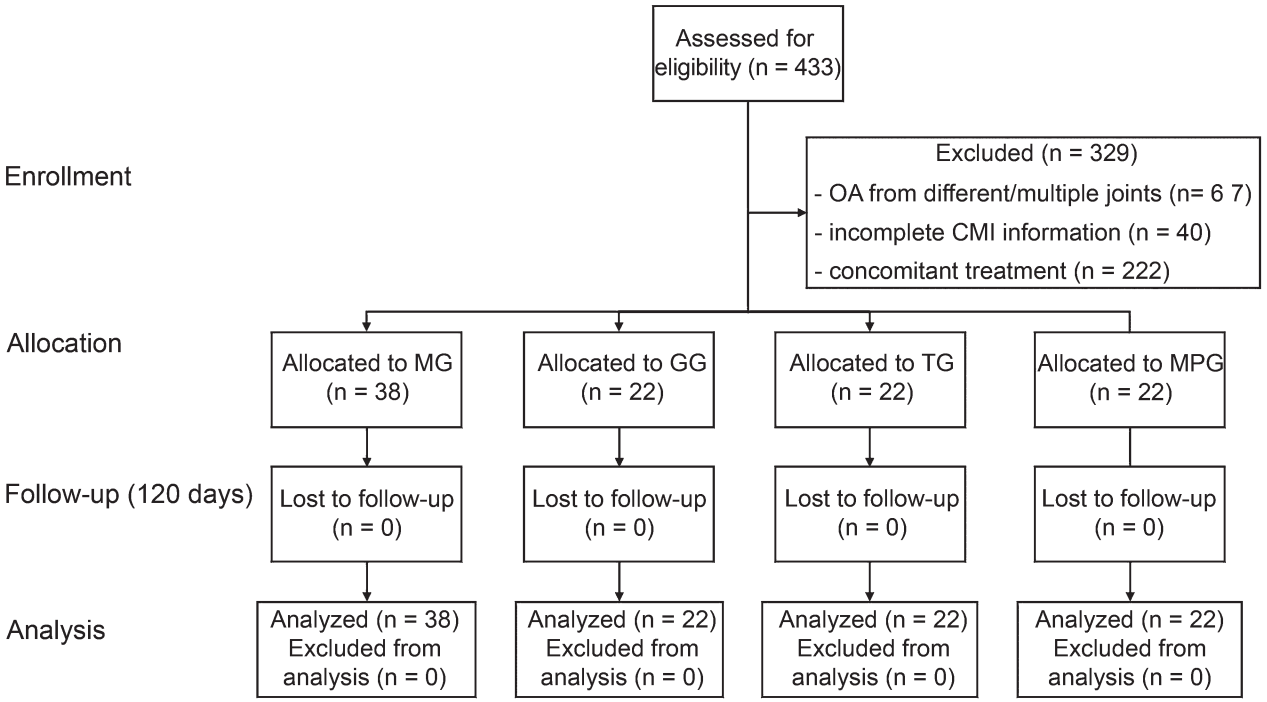

Figure 1—Full study flow diagram. GG = Glucosamine group. MG = Mesotherapy group. MPG = Mesotherapy + photobiomodulation group. TG = Traumeel group.

which encompasses more than just a functional aspect. For that reason, gathering information on several CMIs may help to cover this complex experience. All the considered instruments have been previously validated in their Portuguese versions.[40–43] Response to treatment was measured with the CBPI, LOAD, and COI before treatment (day 0) and at 15 (+15d, after 2 treatment sessions), 30 (+30d, after 4 treatment sessions), 60 (+60d, after 6 treatment sessions), 90 (+90d, after all 7 treatment sessions), and (+120d) days after treatment. The same dog handler completed all instruments for each dog throughout the follow-up period. All patients completed the full evaluation period (120 days).

Statistical analysis

Normality was assessed with a Shapiro-Wilk test. Kaplan-Meier estimators were conducted to generate a time-to-event curve and time-to-event probability. Different outcomes were set for each CMI based on the measures of success that have been set for what constitutes a clinically important difference. With the CBPI, it has been set as a reduction of ≥ 1 in PSS and ≥ 2 in PIS.[44] For the LOAD, a measure of success has been set as a reduction of ≥ 4.[45] For the COI, the success level has been determined only for the overall score, as a reduction of ≥ 3.5.[45] For the dimensions of the COI (stiffness, gait, function, and QOL), success has been set as a reduction of –4 for stiffness, function, and gait and –3

for QOL.[46] Cox proportional hazard regression analysis was carried out to investigate interest variables' influence (age, sex, body weight, breed, and OFA score) on the set events.

All results were analyzed with commercially available software (SPSS Statistics, version 20; IBM).

Results

The sample included 104 active police working dogs, with a mean age of 7.6 ± 3.1 years and body weight of 28.6 ± 5.5 kg, representing both sexes (n = 60 males and 44 females). Four dog breeds were represented: German Shepherd Dog (GSD; n = 46), Labrador Retriever (LR; 23), Belgian Malinois (BM; 16), and Dutch Shepherd (DS; 12). At the initial evaluation, 4 dogs were classified as having mild OA, 70 as moderate, and 30 as severe. No clinically significant differences were observed at day 0 regarding CMI scores, age, body weight, and distribution of breed, age, sex, or OFA grades between groups. Clinical metrology instrument scores in each group are presented **(Supplementary Table S1)**. Differences were observed in pain scores, both PSS and PIS, from the +15d to the +120d evaluations, with MG and MPG showing greater improvements. Worse scores were observed in GG. Similar results were observed in LOAD and COI dimensions. Results of the Kaplan-Meier estimators with each instrument were summarized **(Supplementary Table S2)**. Time-to-event plots for PSS and LOAD are presented **(Figures 2 and 3)**. Better results for more extended periods with the considered instruments were observed in MPG and MG, where a longer period was required for scores to return to the initial evaluation values. No side effects were recorded in either group.

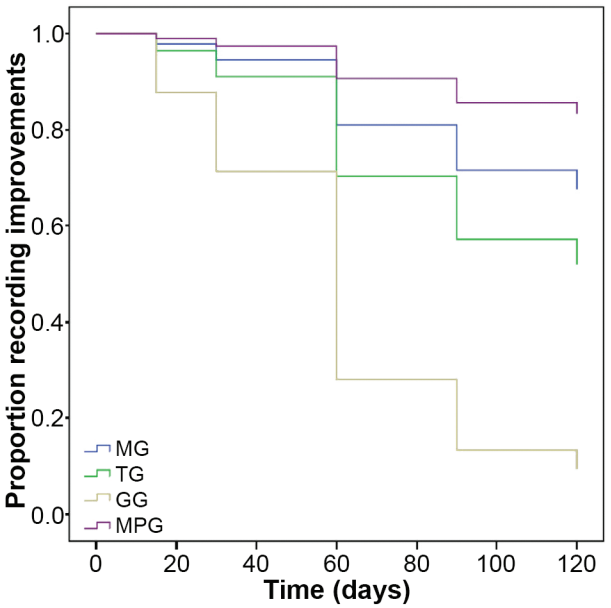

Figure 2—Time-to-event curves demonstrating a clinically significant difference between the GG, MG, MPG, and TG, in time (days) for the improvement in pain severity score to reduce < 1 point ($P < .01$, compared with the log-rank test).

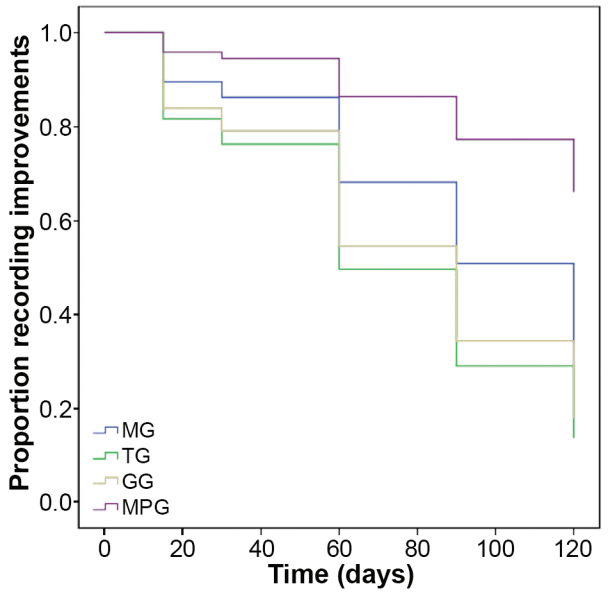

Figure 3—Time-to-event curves demonstrating a clinically significant difference between the GG, MG, MPG, and TG, in time (days) for the improvement in Liverpool Osteoarthritis in Dogs scores to reduce < 4 points ($P < .01$, compared with the log-rank test).

Results of the Cox proportional hazard regression are presented **(Supplementary Table S3)**. Treatment was the covariable that contributed more frequently to the outcomes observed, and for most instruments, it was the only one. The OFA score, particularly in cases of severe OA, also influenced function and QOL scores. Dogs with a severe hip grade had a 5.9- and 3.67-fold probability of recording the set events, compared with dogs with a mild grade. Quality of life was the only outcome measure influenced by breed, with BM and DS showing a lower risk to return to baseline values, compared with GSD.

Discussion

Osteoarthritis management remains a challenge for clinicians. The results from this retrospective study showed that different mesotherapy protocols can improve OA patients' clinical signs, as measured with different CMIs. A previous report[24] showed that a combination of drugs, administered through mesotherapy, provided a superior improvement in OA clinical signs than an NSAID.[24] Currently, the joint is viewed as a complex organ, and it is known that the surrounding tissues, including muscle, tendons, and ligaments, also contribute to the overall experience of OA.[4] The different substance combinations theoretically allow targeting of different tissues, which can contribute to the overall beneficial effect.

A difference was observed in pain relief with the different protocols, with MG and MPG showing greater improvements, both in PIS and PSS. This improvement was observed from the first follow-up and lasted up to the last follow-up (+120d). Also, the Kaplan-Meier test results show that MG took significantly longer to

record the set events. In GG, PSS was the only score to show clinical improvements. A similar finding was observed with the Kaplan-Meier test, with MG and MPG showing longer to record the set events and MPG showing the longest periods. Similar results were observed with the LOAD. Although an improvement has been observed in almost all groups, the beneficial effect started to wear off when treatment sessions were spaced in time (every other week). In MPG, the level of improvement seemed to last longer at a steady level. Photobiomodulation has been shown to have a positive effect in dogs with OA.[17] The increased and longer-lasting improvements observed in MPG can be attributed to the additive effect of photobiomodulation on the mesotherapy treatment. However, the treatment frequency followed in combination with the mesotherapy was different than the one described for the management of OA,[17] and the effect lasted long after the sessions were discontinued. It is possible that, in addition to the effect of photobiomodulation itself, it can also influence the different substances' kinetics, improving their effectiveness. This has to be addressed in future studies.

The changes in the different dimensions of the COI varied between groups and follow-up moments. For stiffness, function, and gait, a clinically significant difference was observed between groups up to the +90d or the +120d follow-up. Some of the differences observed, as with the other instrument, may be related to the substances used. Reports on the efficacy of glucosamine for the management of OA in dogs show different (and sometimes conflicting) levels of clinical improvements.[30] The combination with glucosamine used in GG did not have an impact on PIS levels but did on PSS. Glucosamine may take longer to exert its effect, requiring more administrations and treatment sessions. A limitation of this study is that other measures of clinical assessment, such as joint range of motion and muscle thigh girth, were not assessed. The benefits of glucosamine may be felt in other dimensions of the complex experience that is OA. The effect observed in TG was, as a whole, inferior to that observed in MG and MPG. This fact may be related to the higher volumes of solution that were prepared for this combination and, as the same number of administrations is performed, lower doses of each substance being administered. However, in humans with back pain, lower doses seem to improve clinical signs to a greater extent.[47] This should be explored in future studies.

It is known that the presentation of OA is influenced by a variety of factors, including breed, age, and body weight.[48] We investigated the effect of these variables, in addition to the different treatments, in the different outcomes we set. Treatment was the covariable that contributed to the outcomes observed with all instruments. A decreased probability to experience the set event was observed in MPG, while GG showed higher probabilities when compared to MG. Orthopedic Foundation for Animals scores also influenced function and QOL scores, with dogs with a severe hip grade having a 5.9- and 3.67-fold probability of recording the set events, compared with dogs with a mild grade. This finding stresses the importance of early treatment in OA. Quality of life was the only outcome measure influenced by breed, with BM and DS showing a higher risk to record set events, compared with GSD. This finding is somewhat surprising, as GSDs are usually found to be predisposed to several orthopedic conditions. Even active working GSDs have been described as having worse scores with some instruments than other breeds.[2] Previous reports have described BM and DSs as having significantly higher spontaneous activity levels and lower body condition scores than GSDs.[49] These 2 factors can play a role in the differences observed between breeds, particularly as the QOL score can capture other areas of the OA experience than just the functional and painful signs. In contrast to what is reported, body weight did not influence the outcomes. However, the study population is composed of working dogs, which generally have a good body condition score and are very rarely overweight.

Regarding the completion of CMIs, it has been suggested that responders should be allowed to see previous answers, as it may increase treatment effect sizes and clinical trial power.[50] This information was not available for this study, but, to reduce bias, we usually do not allow handlers to see their previous answers. Although all the instruments used as an outcome measure have been validated, further studies should include objective evaluation methods such as force plate gait analysis or weight-bearing evaluation. We also must keep in mind that this was a retrospective study; for that reason, no sample size calculation was performed, and a different number of animals was included in the groups, which may have an impact on the results. Additionally, since this was a retrospective study, it was not possible to standardize all variables, specifically substance volumes or adding photobiomodulation to the treatment with each substance combination.

Different substance combinations, administered through mesotherapy, can improve clinical signs in patients with hip OA. The combination used in MG, particularly combined with photobiomodulation, seemed to produce better, longer-lasting results, as recorded with different CMIs. Further studies are required to evaluate the application of the technique to different conditions.

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Supplementary Materials

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