Article

Prospective trial of autologous conditioned plasma versus hyaluronan plus corticosteroid for elbow osteoarthritis in dogs

Samuel P. Franklin, James. L. Cook

Abstract — This prospective, randomized, double-blinded trial compared outcomes in dogs with bilateral elbow osteoarthritis (OA) treated with hyaluronan plus methylprednisolone (HA + S) or autologous conditioned plasma (ACP®; Arthrex). An investigator blinded to the treatments graded lameness (0–4) before and 6 months after a single injection with either HA + S or ACP. Clients were blinded to treatment and completed a validated survey before and 1, 6, 12, and 24 weeks after injection. Ten dogs (5 per group) completed all parts of the study. Pre-treatment lameness grades were 1.2 ± 0.97 for HA + S and 1.8 ± 1.1 for ACP and were not different between groups. Post-treatment lameness grades were 0.4 ± 0.55 for HA + S and 0.8 ± 0.64 for ACP with significant ($P < 0.05$) improvement with either treatment but without differences between groups. Client-based assessments demonstrated improvements in activity, lameness, and pain with HA + S and ACP. These data suggest that both treatments have beneficial effects for dogs with bilateral elbow OA.

Résumé — Étude prospective d'un plasma conditionné autologue par opposition à l'hyaluronane et un corticostéroïde pour l'ostéoarthrite chez les chiens. Cette étude prospective, randomisée et à double insu a comparé les résultats chez les chiens atteints de l'ostéoarthrite bilatérale du coude (OA) traitée avec l'hyaluronane et le méthylprednisolone (HA + S) ou un plasma conditionné autologue (ACP^MD; Arthrex). Un enquêteur ne connaissant pas les traitements a évalué la boiterie (0–4) avant et 6 mois après une seule injection soit de l'HA + S ou de l'ACP. Les clients étaient traités à l'insu et remplissaient un sondage validé avant l'injection ainsi qu'aux semaines 1, 6, 12, et 24 après l'injection. Dix chiens (5 par groupe) ont terminé toutes les parties de l'étude. Les grades de la boiterie avant le traitement étaient 1,2 ± 0,97 pour l'HA + S et 1,8 ± 1,1 pour l'ACP et ne différaient pas entre les groupes. Les grades de la boiterie après le traitement étaient 0,4 ± 0,55 pour l'HA + S et 0,8 ± 0,64 pour l'ACP avec une amélioration importante ($P < 0,05$) avec soit l'un ou l'autre traitement mais sans différences entre les groupes. Les évaluations des clients ont démontré des améliorations au niveau de l'activité, de la boiterie et de la douleur avec l'HA + S et l'ACP. Ces données suggèrent que les deux traitements ont des effets bénéfiques pour les chiens atteints de l'OA bilatérale du coude.

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Introduction

Osteoarthritis (OA) of the canine elbow secondary to pathology of the medial compartment is a common problem for which surgical and nonsurgical treatment protocols have been reported. Surgical management of medial compartment elbow diseases fails to prevent onset or progression of osteoarthritis and may not even be superior to non-surgical therapy (1,2). Accordingly, non-surgical therapy will likely remain an important treatment for patients with elbow OA, either as the sole treatment or in conjunction with surgery, and optimization of nonsurgical therapy therefore remains clinically important.

Intra-articular treatment with hyaluronan (HA) is one non-surgical treatment that may prove beneficial in managing

Comparative Orthopaedic Laboratory, College of Veterinary Medicine, University of Missouri — Columbia, 379 East Campus Drive, Columbia, Missouri 65211, USA.

Address all correspondence to Dr. Samuel Franklin; e-mail: sfranklin@uvsonline.com

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dogs with elbow OA. Hyaluronan is purported to increase the viscosity of joint fluid, provide anti-inflammatory and analgesic effects, and be viscoinductive, inducing the production of endogenous synovial fluid (3,4). Numerous randomized, controlled clinical trials have consistently shown alleviation of pain and improved function following treatment of knee osteoarthritis in human patients and use of HA in human medicine continues to grow worldwide (5,6). Similarly, HA has been used for the management of OA in equine patients for many decades (7,8). However, the efficacy of HA for treating dogs with naturally occurring OA remains undocumented (4).

As with HA, a growing body of evidence supports the use of platelet-rich plasma (PRP) products for treatment of several orthopedic disorders in humans and horses including OA (9–14). The effects of PRP are presumed to be a result of anti-inflammatory and anabolic properties attributable to the numerous growth factors and cytokines released from platelet alpha granules (9). Such benefit for treatment of OA has been shown in multiple recent randomized clinical trials in human medicine which compared use of HA and PRP and which showed greater improvement and longer duration of symptom alleviation with use of PRP when treating knee OA (11–14).

The objective of the present study was to compare the effects of intra-articular HA in conjunction with a corticosteroid to intra-articular autologous conditioned plasma (ACP; Arthrex Vet Systems, Naples, Florida, USA) on lameness and function of dogs with chronic elbow OA. Use of a corticosteroid in conjunction with HA was elected rather than use of HA alone because that had been the customary clinical practice at our hospital at the time the study was initiated. Autologous conditioned plasma is a PRP product in human medicine obtained with a commercially available system that has been shown to increase platelet count two-fold while reducing white blood cell concentrations (15). In dogs, ACP has not been shown to increase platelet count above that in whole blood. However, ACP does increase platelet count, platelet-derived growth factor-BB, and transforming growth factor-β1 above that in standard plasma preparations with an almost complete elimination of red and white blood cells (16). We speculate that administration of ACP could still be of clinical benefit associated with the delivery of platelets and their growth factors without the concomitant delivery of erythrocytes and white blood cells. Therefore, we hypothesized that HA plus a corticosteroid (HA + S) and ACP would both be associated with statistically significant and clinically relevant improvements in function and level of pain in dogs with elbow OA. Furthermore, we hypothesized that there would be no significant difference between results with use of HA + S and ACP.

Materials and methods

Dogs that were > 1 y of age that had arthroscopic and/or radiographic evidence of OA in both elbows were eligible to be included in this prospective, randomized, double-blinded clinical trial. All enrolled dogs were failing a non-surgical treatment protocol at the time of enrollment. Three dogs had previous arthroscopic removal of a fragmented medial coronoid process, 2 were in the HA + S group and 1 was in the ACP group. Dogs were only included when fully informed consent was obtained and documented for each patient. Clients received a financial incentive for enrollment in the study in that all costs for examination, injection, and follow-up appointments were paid for by the study and by Arthrex Vet Systems specifically. Dogs with infectious or neoplastic disorders were excluded as were dogs with neurologic or orthopedic disease other than elbow OA as determined by orthopedic and neurologic examination.

Once enrolled, each dog was assessed by the client using a validated subjective assessment survey (17) and evaluated for lameness (Grade 0–4) by 1 surgeon (SPF) as previously described (18) and who was blinded to treatment. The dog was walked and trotted on level ground and up and down stairs; scores were assigned based on the following scale: 0 — no detectable lameness; 1 — mild weight-bearing lameness; 2 — moderate weight-bearing lameness; 3 — marked weight-bearing lameness; and 4 — non-weight-bearing lameness. The dog was then sedated and prepared for aseptic injection of both elbows. Another surgeon (JLC) injected both elbows with either 2.5 mL of ACP or 2 mL (20 mg) of HA (Hylartin-V; Pfizer Animal Health, New York, New York, USA) plus 0.5 mL (20 mg) of methylprednisolone acetate (Novaplus, Pfizer Animal Health), based on a coin flip. The type of injection was recorded as "1" or "2" and not revealed to the client, the first surgeon (SPF), or statistician until the entire study was completed. Lameness grading was repeated by the first surgeon at a 6-month recheck appointment. The clients completed the subjective assessment survey at weeks 1, 6, 12, and at 6 mo post-injection. Clients were not required to return animals for lameness grading on 4 separate occasions for logistical reasons and the 6-month re-evaluation was considered more important than a 1-, 6-, and 12-week re-evaluation. The clients were instructed to continue use of other current therapies (e.g., non-steroidal anti-inflammatory drugs; NSAIDS) as needed and record those given. This approach was taken rather than mandating withdrawal of an NSAID or rigorously standardizing NSAID use in order to assess the efficacy of hyaluronan and ACP as an adjunctive treatment in those patients that were already receiving an NSAID and in order to assess how owners perception of their dog's need for NSAID use would change with use of HA or ACP. Owners were also instructed to allow activities as desired and as tolerated by the dog.

Data were analyzed for statistically significant ($P < 0.05$) differences using a rank sum test to compare differences between groups in client-based assessments at specific time points. A repeated measures analysis of variance (ANOVA) was used to assess changes over time within a treatment group in owner response to specific questions from the survey. T-tests were used to compare the improvement in lameness scores over the 6-month period between the 2 treatment groups. A P-value of < 0.05 was considered significant for all analyses.

Results

Ten dogs (n = 5 in each group) completed all portions of the study. Three patients had previous arthroscopic treatment of medial coronoid disease and all patients were being treated with an assortment of non-surgical management protocols at the time

of enrollment. All patients had been prescribed NSAID medications as part of their non-surgical management protocol but the specific medication, dose, duration of use, and owner adherence to the prescription recommendations were not rigorously controlled. The data are presented as mean ± standard deviation (SD). Pre-treatment mean lameness grades were 1.2 ± 0.97 for HA plus corticosteroid and 1.8 ± 1.1 for ACP and were not statistically different between groups. Post-treatment mean lameness grades were 0.4 ± 0.55 for HA plus corticosteroid and 0.8 ± 0.64 for ACP with each being significantly ($P < 0.045$) less lame than pre-treatment, but not statistically different between groups. With respect to client-based functional assessments over time, statistically significant improvements in scores for activity, lameness, pain, and overall function categories were noted for both groups over the study period with most changes being > 10% in magnitude. The greatest improvements in client-based assessment scores for dogs receiving HA and corticosteroid were noted at 1 wk post-injection for pain and activity and at 12 wk post-injection for lameness. All improvements in client-based assessments for dogs in the group receiving ACP were greatest at 6 wk post-injection. Client-based assessment scores for lameness and pain were significantly ($P < 0.05$) better with ACP than with HA + S at 6 wk post-treatment. No other significant differences were noted between groups. Continued use of other therapies varied widely among clients, but was not subjectively different between groups. Importantly, no side effects were noted with treatment for any patient.

Discussion

These data suggest that ACP and HA plus corticosteroid have perceived beneficial effects for dogs with chronic bilateral elbow OA for up to 6 mo post-injection. This conclusion is tempered by several limitations including lack of a control group. However, numerous randomized controlled trials have demonstrated efficacy of HA in treating humans with OA and we have additional data (unpublished) demonstrating superiority of HA to sham-treated dogs with experimentally induced stifle OA (3,5,19). As a result, we believe both treatments have a clinically relevant benefit as demonstrated by client-assessed improvement of > 10% in many categories and the improvement in lameness scores as assessed by a blinded observer.

The ACP provided greater improvement in a few client-based assessments 6 wk following treatment but otherwise few differences between the tested products were identified. This is in contrast to a few recent randomized controlled trials in human medicine demonstrating superiority and/or greater duration of benefit with use of PRP products compared with HA for treating OA (11–14). Several possible explanations exist for our failure to identify numerous differences between groups in this study including, but not limited to, a lack of power due to insensitivity of the chosen outcome measures or lack of power because few study subjects were enrolled. Similarly, the concurrent use of other modalities (e.g., NSAIDs) may have affected results and masked our ability to identify a difference between groups. Further, although the client-based questionnaire used in this study has been validated to kinetic force plate, a recent study assessing owner and veterinarian evaluation of dogs with forelimb lameness failed to find a reliable correlation between owner and veterinarian assessments and the total support moment ratio generated from kinetic and kinematic data (20). Ideally, our study of HA and ACP would be repeated with an objective outcome measure, such as with use of a pressure sensitive walkway, with a greater number of study subjects, and with rigorous control of other treatment modalities.

Although conclusions that can be drawn from this study are limited for the reasons discussed, the results do provide some evidence that both these treatment modalities can benefit dogs that have failed management of chronic elbow OA. Potentially more importantly, no side effects of treatment were noted for any patient, indicating that intra-articular treatment with HA plus a corticosteroid or ACP for treatment of OA is safe. However, we do recommend that should intra-articular corticosteroids be used that triamcinolone be selected. A previous study in humans demonstrates superiority of treatment with triamcinolone compared to other corticosteroids, some *in vivo* experimental studies in equine patients show beneficial effects of triamcinolone on chondrocyte metabolism, and unpublished data from our laboratory demonstrate significantly less chondrotoxicity of canine cartilage explants when cultured with triamcinolone *in vitro* in comparison to methylprednisolone acetate or betamethasone (21–24). Finally, it should be noted that not all PRP products are equivalent and these data are not necessarily representative of results that could be expected with other PRP systems.

In summary, these data provide some evidence to support use of either hyaluronan plus methylprednisolone acetate or autologous conditioned plasma alone or as an adjunct to other non-surgical or surgical treatment of elbow OA and may be particularly useful for patients which cannot tolerate other disease-modifying osteoarthritis drugs such as NSAIDs. The evidence for efficacy based upon these data are relatively weak because of the study limitations, but the lack of any complications is valuable in justifying their attempted use when other therapies have failed and in justifying further study of these products to more rigorously assess their benefits.

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