Intra-Articular Administration of a Synthetic Lubricin in Canine Stifles

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Abstract

Objective The aim of this study was to evaluate the functional, systemic, synovial and articular changes after intra-articular administration of a synthetic lubricin within healthy canine stifles.

Study Design A prospective randomized blinded placebo-controlled study composed of 10 dogs equally divided into either a treatment group (intra-articular synthetic lubricin injection, $n = 5$) or control group (saline, $n = 5$). Clinical (orthopaedic examination, gait observation, gait analysis), biochemical (complete blood count and biochemistry profile) and local tissue outcomes (joint fluid analysis, joint capsule and articular cartilage histopathology) were evaluated over a time period of 3 months.

Results No significant differences between the treatment group and control group were identified with regard to baseline patient parameters. No clinically significant orthopaedic examination abnormalities, gait abnormalities, biochemical alterations, joint fluid alterations or histopathological alterations were identified over the course of the study.

Conclusion The synthetic lubricin studied herein is both biocompatible and safe for a single administration within the canine stifle joint. Further research is necessary to evaluate the clinical efficacy of the synthetic lubricin in canine osteoarthritic joints.

Keywords
- osteoarthritis
- biocompatibility
- dogs
- stifle

Introduction

Osteoarthritis is the most common joint disease diagnosed in dogs and poses considerable challenges to canine welfare.[1] While there are many inciting causes, osteoarthritis is an irreversible process leading to permanent joint pathology that negatively impacts an animal's quality of life through lameness, pain and decreased activity.[2,3] Current treatment options, such as non-steroidal anti-inflammatory drug therapy, weight loss, joint supplements and physiotherapy, focus on palliation of clinical signs but have little to no effect on disease progression.[2,3] Salvage procedures such as total joint replacement, arthrodesis or arthroplasty are a last resort for severe osteoarthritis, each with its own associated serious complications.[4–11] Conversely, orthobiologic products, such as mesenchymal stem cells, bone marrow aspirate concentrate and platelet-rich plasma products, aim to restore structure and function and show promise as safe

received
December 10, 2020
accepted after revision
August 16, 2021

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0041-1736189.
ISSN 0932-0814.

treatments for osteoarthritis in humans and certain veterinary species; however, there is little evidence of their efficacy in the treatment of canine osteoarthritis.[12–14]

One reason that current osteoarthritis interventions do not alter disease outcomes is that their mechanisms of action do not address the mechanical necessity of joint lubrication. The three main lubricating constituents of synovial fluid are hyaluronic acid, surface-active phospholipids and proteoglycan-4, also known as lubricin, which contribute to joint lubrication in an additive and independent manner.[15] The surfaces of articular cartilage in a healthy joint are lubricated by synovial fluid that function in both the hydrodynamic mode (i.e. light normal load and fast speed) and in the boundary mode (i.e. heavy normal load and slow speed). Both hydrodynamic and boundary modes of lubrication are needed to prevent articular cartilage degeneration through the mitigation of load bearing and frictional forces experienced at joint surfaces.[16,17] Specifically, when the surfaces of cartilage are in close proximity ('boundary mode'), there can be direct cartilage–cartilage contact, which leads to cartilage damage, inflammation and the progression of osteoarthritis.[16,17] The natural lubricant for cartilage in the boundary mode is lubricin.[18] Lubricin is a glycoprotein that tightly binds to the articular cartilage surface via its C-terminus region, while its hydrophilic oligosaccharides retain water at the cartilage surface, preventing cartilage-cartilage contact.[19] The chondroprotective role played by lubricin is compromised with age and in injured or diseased joints via decreased production, thereby likely propagating cartilage damage and disease progression.[20,21]

Unfortunately, the manufacture of lubricin is both difficult and labour intensive.[22] Recently, synthetic mimetics of lubricin were developed that mimic its structural composition, and have been shown to provide similar properties to natural lubricin *in vitro*.[19,23] In addition, the use of synthetic lubricin to limit the progression of osteoarthritis in a rat anterior cruciate ligament transection model was recently demonstrated.[24] Based on the documented *in vivo* benefit of this class of synthetic lubricin, along with benefits showed by previous studies utilizing recombinant lubricin,[22] further research is warranted to establish both the biocompatibility of synthetic lubricin within healthy canine patients and its potential clinical use for the treatment of osteoarthritis.[25–30]

The specific aims of this study were to determine the systemic and local effects of a single intra-articular injection of a synthetic lubricin on the local tissue environment (joint fluid analysis, joint capsule/cartilage histology), functional outcome (orthopaedic examination and gait analysis) and systemic biochemical changes (complete blood count [CBC] and serum chemistry analysis).

Materials and Methods

Experimental Design

This study was approved by the Institutional Animal Care and Use Committee (Protocol #2015–0017). Ten healthy adult Beagle dogs were randomly assigned into a treatment group (synthetic lubricin) or control group (saline) ($n = 5$ per group) (►**Table 1**). Prior to the study, physical and orthopaedic examination by two board-certified veterinary surgeons, orthogonal view radiography of the stifles, CBC and serum chemistry analysis were performed. Gait analysis was conducted for each dog to establish an animal-specific baseline 1 week prior to the intra-articular injection. Each dog was trotted across a pressure-sensitive walkway (Tekscan Walkway 2.0, Boston, Massachusetts, United States) at a natural velocity between 1.4 and 2.3m/s for a total of five valid passes assessing a minimum total of 15 footfalls per each hindlimb.[31] The system was calibrated and equilibrated prior to the study according to manufacturer guidelines. Passes on the walkway were considered valid if they were within 0.3 m/s of the mean speed of the baseline data collected and video imagery confirmed appropriate body posture and direction with foot strikes falling within the recording area of the walkway.[31,32] A symmetry index (SI) for peak vertical force (PVF) was then derived from the hindlimb data as previously described (SI = PVF [limb of interest]/PVF [contralateral limb]).[33]

Table 1 Tabular representation of baseline patient parameters and randomization of treatment group

Dog	Age (y)	Sex	Body weight (kg)	Treatment	Side	Pre-injection radiographic findings	Note
1	3.9	Male	10.35	Lubricin	Left	No abnormal findings	
2	6.6	Male	11	Saline	Left	No abnormal findings	
3	2.4	Male	11.5	Lubricin	Right	No abnormal findings	
4	4.5	Male	11.5	Saline	Right	No abnormal findings	Non-weight bearing lameness at 6 hours post-injection
5	5.2	Male	15	Lubricin	Right	Bilateral mild stifle effusion	
6	5.8	Male	10.3	Saline	Left	No abnormal findings	
7	3.7	Male	11.9	Lubricin	Right	No abnormal findings	
8	5.9	Male	12.5	Lubricin	Right	No abnormal findings	
9	3.9	Male	11.4	Saline	Left	No abnormal findings	
10	2.4	Male	13.0	Saline	Right	No abnormal findings	

Intra-Articular Injection

One week following baseline gait analysis, each dog was sedated with intravenous injection of dexmedetomidine (20 µg/kg). Joint tap was performed aseptically from the lateral side of both stifle joints by a board-certified surgeon, confirming aspiration of joint fluid, and 1 mL of synthetic lubricin (3 mg/mL) or 1 mL of saline was aseptically injected into one randomly selected stifle joint through the same needle of joint tap (►**Table 1**). Randomization was generated by a coin flip for each dog and the administrator was blinded to the contents of the syringe. Aspirated joint fluid was submitted for cytological analysis. Sterile synthetic lubricin was prepared in sterile phosphate-buffered saline (saline) as previously described.[23] Concentration of synthetic lubricin (3 mg/mL) was chosen based on a preliminary study that demonstrated the coefficient-of-friction of the synthetic lubricin was equivalent to or lower than native lubricin at the range between 1 mg/mL and 10 mg/mL.[23] Volume of injection (1 mL) was chosen based on the clinical experience of stifle injection (of other agents) in Beagle size dogs. Sedation was reversed with intra-muscular injection of atipamezole (200 µg/kg). Gait observation and orthopaedic examination were repeated at 6 hours, 24 hours, 48 hours, 1 week, 1 month, 2 months and 3 months post-injection. Evaluators were blinded to the treatment group. Gait analysis was repeated at 24 hours, 48 hours, 1 week, 1 month, 2 months and 3 months post-injection. Complete blood count and serum chemistry analysis were repeated at 3 months post-injection.

Joint Fluid Analysis and Biopsy

Joint fluid was aseptically collected from the lateral side of both stifles before treatment administration as described above and at 1- and 3 months post-injection after the gait analysis respectively. Joint fluid cytology was interpreted by a blinded board-certified clinical pathologist. Biopsy samples were aseptically collected by a board-certified surgeon at the end of this study period (3 months post-injection) from the injected stifle joint. After intravenous injection of dexmedetomidine (20 µg/kg) and butorphanol (0.2 mg/kg), dog was positioned in dorsal recumbency, a stab skin incision was made with #15 blade medial to the patellar ligament and a 2 mm biopsy punch was used to obtain joint capsule and articular cartilage from non-weight bearing area of medial condyle. A biopsy punch was advanced directly into the joint toward the centre of the medial condyle, from a stab skin incision made medial to the patellar ligament, approximately one third the distance from the distal apex of the patella to the tibial tuberosity. Collection of both joint capsule and articular cartilage was confirmed for each dog. Joint capsule and cartilage specimens were separated, and placed in 10% neutral buffered formalin, embedded in paraffin and stained with haematoxylin and eosin for routine histology respectively. Histopathological grading of joint capsule and cartilage was conducted respectively by a blinded board-certified pathologist as previously described.[24]

Statistical Analysis

The Shapiro–Wilk test was used to evaluate age and body weight for normality. Normally distributed data were reported as mean ± standard error and non-normally distributed data were reported as median and range. Age and body weight were compared using Student's *t*-test between groups. D'Agostino normality testing was used to assess normality for SI data. For repeated measures data that were not normally distributed, a non-parametric Friedman's analysis was utilized, while one-way analysis of variance with repeated measures was utilized for normally distributed data. Dunn's post hoc testing was used to assess differences from baseline for all time points for SI when significances were noted. A p-value of less than 0.05 was considered significant.

Results

The mean age was 4.4 (±0.46) years. The mean body weight was 11.8 (±0.44) kg (►**Table 1**). There were no significant differences in age ($p = 0.672$) and body weight ($p = 0.390$) between groups. Prior to the injection, there were no abnormal findings based on clinical and orthopaedic examination for all 10 dogs. Nine dogs had normal stifle radiographs as evaluated by a board-certified radiologist. In dog 5, there was bilateral mild intracapsular increases in soft tissue opacity, suggestive of mild stifle effusion (►**Table 1**). This dog was included in the study.

Post-injection, no abnormalities were reported on physical and orthopaedic examinations in nine dogs at all times evaluated. There was no lameness, swelling, discharge, crepitus, pain, instability or decreased range of motion noted in these nine dogs. In dog 4 that received the saline injection in the right stifle, a non-weight bearing lameness of the right pelvic limb at 6 hours post-injection was reported; however, there was no swelling, discharge, crepitus, pain, instability or decreased range of motion noted in this dog at this point (6 hours post-injection), and there was no lameness, swelling, discharge, crepitus, pain, instability or decreased range of motion noted in this dog at and after 24 hours post-injection (►**Table 1**). On gait analysis, SI were near 1.0 (symmetric) in all dogs pre- and post-injection (►**Fig. 1**). At all times tested, there were no significant differences ($p > 0.05$) in SI between the saline- and synthetic lubricin-treated groups (►**Fig. 1**). Over the course of 3 months, there were no significant changes in SI of each dog ($p > 0.05$). In addition, there were no significant changes ($p > 0.05$) in SI in both groups over the 3-month study period (►**Fig. 1**).

Complete blood count and biochemistry panel prior to treatment and at 3 months post-injection indicated no clinically significant abnormalities (►**Supplementary Table S1** [online only]). Microscopic joint fluid analysis showed no obvious cytological abnormalities in all dogs prior to, 1-month post-treatment or 3 months post-treatment (►**Supplementary Table S2** [online only]). There were occasional reports of blood contamination. No cytological abnormalities were interpreted as samples with low nucleated cellularity, no atypical cells or infectious microorganisms and no evidence of infection, inflammation or neoplasia. There were no significant findings for the 3-month post-treatment joint capsule and articular cartilage biopsies,

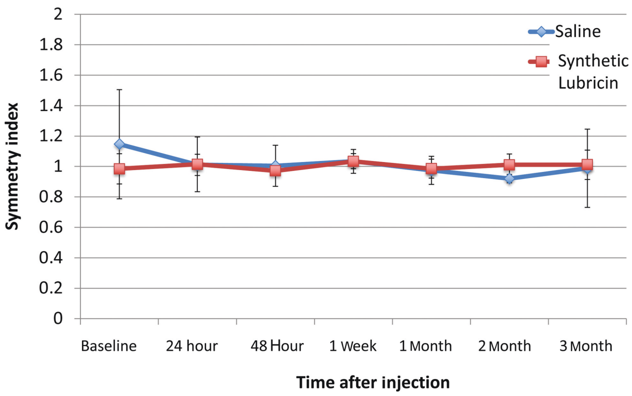

Fig. 1 Symmetry index (SI) of patients undergoing intra-articular injection of either saline ($n = 5$) or synthetic lubricin ($n = 5$) across various time points. A SI of 1 is equivalent to symmetrical weight bearing of each hind limb. There was no significant difference in SI between group ($p > 0.05$). There was not significant difference in SI among time points in each group respectively ($p > 0.05$).

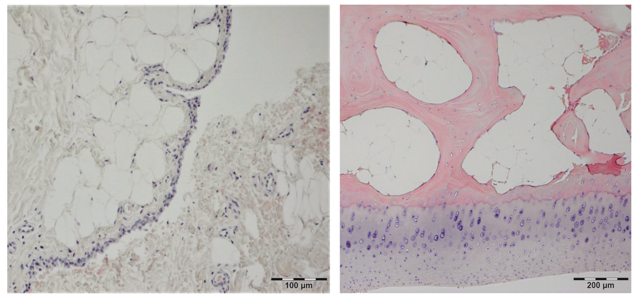

Fig. 2 Left: representative histopathological slide of joint capsular tissue 3 months post-injection of synthetic lubricin from dog 3 (haematoxylin and eosin stain, original magnification x200). Right: representative histopathological slide of articular cartilage obtained from the medial femoral condyle 3 months post-injection of synthetic lubricin from dog 5 (haematoxylin and eosin stain, original magnification x100). No abnormal findings were noted.

with subjective gradings of normal in all samples (►**Fig. 2**) except for the joint capsule biopsy of dog 9 that was determined to be non-diagnostic due to its insufficient size and composition (►**Supplementary Table S2** [online only]). Histological analysis of the cartilage showed the presence of normal chondrocytes, zones of mineralized cartilage within normal limits and normal subchondral trabecular bone composed of compact lamellar osteoid lined by quiescent osteoblasts in all samples (►**Fig. 2**).

Discussion

This study demonstrated that the single-dose injection of synthetic lubricin (volume: 1 mL, concentration: 3 mg/mL) into healthy canine stifle joints did not cause any detectable adverse effect up to 3 months post-injection based on the evaluation of clinical function, the local tissue environment and systemic biochemical parameters. Lubricin, a mucinous glycoprotein, plays a chondroprotective role as a normal constituent of synovial fluid.[16] Recently, a library of biomimetic polymers with structural facets similar to human lubricin was synthesized. Specifically, a mimetic diblock copolymer that represents a synthetic mimetic of lubricin was developed and discovered to have lubricating properties equivalent to lubricin.[23] Lubricin is highly conserved across species.[16,34] This current study is the first to confirm the biocompatibility and biosafety of a single-dose injection of this synthetic lubricin in dogs.

Articular cartilage surfaces are lubricated by native synovial fluid, which provides hydrodynamic and boundary mode lubrication.[16] Targeting joint lubrication for the mitigation of osteoarthritis is not a novel concept, as intra-articular injections of hyaluronic acid have been utilized to restore the hydrodynamic mode of lubrication in affected joints. Relative ease of isolation and the production of authenticated cost-effective hyaluronic acid materials have contributed to its early clinical adoption with comparison to lubricin.[35] Despite promising *in vitro* results demonstrating lubricating efficacy, hyaluronic acid injection alone has not been proven to prevent progressive degenerative changes.[15,17,29,36,37] Furthermore, *in vitro* studies have demonstrated that hyaluronic acid does not possess the same lubricating capacity, specifically in boundary mode conditions as lubricin.[38] The theory that the replacement of the mechanical mechanism of boundary mode lubrication by intra-articular injection makes lubricin an attractive candidate to mitigate the progression of osteoarthritis.[39]

Lubricin's lubricating ability comes from its structure, made up of a mucin-like lubricating domain and a cartilage-binding block.[23] The mucin domain contains dense hydrophilic oligosaccharides, while the terminus binds the molecule to the cartilage surface. When bound, the hydrophilic sugars attract and retain water near the surface, which then allow for many lubricin molecules to aggregate and form a network of mucins near the cartilage surface. Lubricin is highly conserved across species, and the lubricating capacity of lubricin has been established for articular cartilage surfaces and numerous materials.[16,34] The creation of the synthetic mimetic of lubricin aims to replicate these functional domains.[16,19,23] In theory, this synthetic lubricin would provide a similar lubricating ability as native lubricin that separates surfaces and enables movement during high-pressure, high contact, near zero-articulating speeds.[19,26,39] Given the documented downregulation of lubricin production in diseased joints, this makes synthetic lubricin an attractive and practical option for the treatment of osteoarthritis.[16,20,21] Synthetic lubricin used in this current study has been shown to lubricate cartilage or other materials such as bone effectively, robustly and reproducibly under boundary mode conditions, and is hypothesized to be as effective as native lubricin in osteoarthritic joint.[23] Although this current study confirms the biocompatibility and biosafety of a single dose injection of synthetic lubricin, further research demonstrating its efficacy in the treatment of osteoarthritis is necessary.

The limitations of this study include the lack of evaluation of efficacy in the treatment of osteoarthritis, relative low number of subjects, lack of quantitative analysis of joint fluid cytology, lack of blood test and histology during the acute phase and lack of radiographic evaluation at the end of the study period. Although the result did not show significant differences between two groups, this study is underpowered with only five dogs enrolled in each group. There were some values outside the reference range in the blood tests, clinical significances of which were not determined. One dog that received the saline injection showed a transient non-weight bearing lameness at 6 hours post-injection, cause of which was not identified. This study also did not determine effective dose range nor retention period of the injected material.

To the best of our knowledge, this study is the first to investigate a non-surgical strategy to address mechanical mechanism of osteoarthritis progression in dogs. A recent experimental study has demonstrated a significant chondroprotective efficacy of a cost-effective synthetic lubricin.[24] The results of this current study demonstrated a high degree of safety for a single-dose injection of this specific synthetic lubricin, which establishes the basis for future large-scale clinical trials in dogs.

Authors' Contribution

KH designed, directed and performed the project. AB performed the experiment and organized the data. DL organized the data and wrote the manuscript. BGC conducted histopathological analysis. EB performed the experiment and organized the data. UK and SYK designed the experimental model and analysed the data. HR conceived the original idea, devised the project and planned the experiments. DP conducted sample preparation, worked out the technical details and contributed to the interpretation of the results.

Funding

This study was supported by Center for Advanced Technology (CAT), State of New York and the National Institutes of Health under Award Number R01 AR066667 (to DP). This work made use of the Cornell Center for Materials Research Facilities supported by the National Science Foundation under Award Number DMR-1719875.

Conflict of Interest

DP is listed as an inventor on various patents assigned to Cornell University that are associated with materials disclosed in this manuscript. There is no financial or other conflict of interest of any author related to a company or product used in the report. This study was never presented at any meetings.

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