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ORIGINAL INVESTIGATION

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Clinical effectiveness and safety of intraarticular administration of a ^{117m}Tin radiocolloid (Synovetin OA^{TM}) for treatment of early and intermediate grade osteoarthritis of the elbow in a dose finding study conducted in 44 dogs

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Abstract

Osteoarthritis of the elbow joint secondary to elbow dysplasia is common in dogs. Intraarticular radionuclide injection is thought to suppress both synovitis and inflammatory pain mediators in the joint which are not directly addressed by current treatments. This dose-finding investigation was a longitudinal, prospective, experimental parallel group, post-test study with repeated measures. Forty-four dogs, with low to intermediate-grade osteoarthritis, received a single injection into their most clinically affected elbow joint and were randomized into three treatment cohorts; 37 MBq, 64.75 MBq, or 92.5 MBq (normalized to the body surface area of a 22 kg dog) of ^{117m}Sn radiocolloid. Dogs were assessed monthly by owners, using the canine Brief Pain Inventory (cBPI), and at 1, 3, 6, 9, and 12 months intervals by investigators. Positive responses to treatment were observed by both owners and clinicians in all dose groups with the medium dose group having the highest and most durable response rate based on cBPI scores. The results of this study support the use of ^{117m}Sn radiocolloid as a primary treatment of osteoarthritis in low to intermediate-grade osteoarthritis of the canine elbow.

KEYWORDS
coronoid, radiosynoviorthesis, synovectomy

1 | INTRODUCTION

Osteoarthritis (OA) is frequently secondary to elbow dysplasia, a common disorder affecting dogs, with four of the 5 most common American Kennel Club registered breeds having an incidence of 10% or greater.[1,2] Fragmentation of the medial coronoid process has been documented as the most common cause, although incongruity of the humeral-ulnar joint and ununited anconeal process are also common causative factors.[3,4] These skeletal maturation disorders result in joint inflammation cartilage injury leading to OA onset at an early age. Pain severity and rate of arthritis progression is related to the severity of the inflammation and can be modified by the dog's

Abbreviations: ABVP, American Board of Veterinary Practitioners; ACVR, American College of Veterinary Radiology; ACVS, American College of Veterinary Surgeons; cBPI, canine Brief Pain Inventory; MBq, megabecquerel; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis.

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age, level of activity, obesity, and genetic profile. [5,6] Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, combined with exercise and weight control, is the current standard for elbow osteoarthritis.[7,8] Surgical procedures ranging from fragment removal to prosthetic implants are inconsistent in reducing lameness.[9,10] Although the dog's pain is often mitigated by NSAIDS or corticosteroids, they typically do not slow, and in some cases may actually promote, progression of the disease while having a number of possible side effects such as liver or kidney damage, immune suppression, and cardiac disorders[11,12]. Progression eventually leads to cartilage destruction and severe mobility restriction.[11–13] Dietary supplements have not been shown to be effective treatments for this disorder.[13,14]

Intraarticular injections of radiocolloids (radiosynoviorthesis) in people have gained acceptance and wide use in Europe for treatment of inflammatory OA with 80% of treatments performed in Germany.[15] but have been rarely employed in dogs. Radioisotopes used include, but are not limited to, ^{90}Yttrium, ^{186}Rhenium, and ^{169}Erbium.[14,15] Both large and small joints have been treated in humans with reasonable clinical efficacy and minimal side effects.[1415] These agents have the benefit of being highly contained within the joint such that a single intraarticular treatment delivers treatment over a period of days and lasting months to years without systemic effects.[1415] Focal irradiation of synovial inflammatory macrophages following phagocytosis of the radiocolloid is thought to have a sustained anti-inflammatory effect due to destruction of these cells, reducing synovial inflammation-mediated degradation of the joint cartilage.[15–17]

^{117m}Tin is a radioisotope that has physical properties that make it attractive for radiosynoviorthesis, with a 14-day half-life and a low dual-energy conversion electron emissions penetrating approximately 0.3mm in tissue.[18] When constituted as an insoluble, micro-aggregate (Synovetin OA®), approximately 99% is retained within the joint, providing a prolonged low-level irradiation to suppress synovial inflammatory cells. ^{117m}Tin also emits an 87% abundant 158 keV photon which is useful for demonstrating localization and retention of the isotope within the joint via scintigraphy as well as detection of leakage outside the joint. This hypothesis has only been tested in laboratory rats and not in a spontaneous disease setting in dogs.

A previous study demonstrated no adverse systemic or joint effects when ^{117m}Sn colloid is injected into the elbow joints of normal dogs.[18] The objective of this study was to test hypotheses that intraarticular injection of ^{117m}Sn colloid (Synovetin OA®) would be a clinically safe and effective treatment of early to intermediate clinical OA of the canine elbow resulting in decreased lameness, and improved quality of life as assessed by dog owners and veterinary clinicians.

2 | METHODS

2.1 | Selection and description of subjects

The study design was a multi-institutional, longitudinal, prospective, experimental parallel group, post-test study with repeated measures. The Animal Care and Use Committees at the University of Missouri, Louisiana State University, and Gulf Coast Veterinary Specialists provided ethical approval. Privately owned dogs were recruited for inclusion in this study. The inclusion criteria were as follows: 1) ≥1 year of age, 2) ≥8 kg body weight, 3) no known comorbid conditions likely to preclude a one-year survival after treatment, and documentable lameness with radiographic evidence of low or intermediate-grade elbow osteoarthritis as determined by a board-certified veterinary radiologist (J.L., American College of Veterinary Radiology [ACVR]) without another known cause for lameness in the leg. Informed owner consent including a commitment to complete a previously validated canine Brief Pain Inventory (cBPI)[19,21] questionnaire monthly for the duration of the study was required as well as to continue any pain medications as prescribed at the time of study entry. Radiographic Grade 1 or 2 OA as defined according to International Canine Elbow Working Group guidelines was used for the preliminary screening of prospective dogs (Figure 1).

2.2 | Data recording and analysis

After owner consent and commitment not to increase pain medication for the duration of the study, owners completed a baseline cBPI and each dog had the following procedures performed: physical examination including lameness evaluation with video recording at a walk and trot before and after manipulation of the elbows, complete blood count, serum chemistry, urinalysis, and radiographs of both elbows. Independent evaluation of lameness and radiographs was made by board-certified veterinary specialists (ACVR, American Board of Veterinary Practitioners [ABVP], or American College of Veterinary Surgeons [ACVS]) as appropriate. Lameness was also evaluated by the dog's owners on a regular basis using the cBPI form. Clinicians were aware that dogs were part of the study but were instructed not to review the case history or previous findings prior to making their evaluations.

Following baseline evaluations and induction of general anesthesia, non-contrast cross-sectional imaging was performed with either magnetic resonance imaging (MRI) plus ^{18}fluorodeoxyglucose positron emission tomography (PET) (21 dogs) or MRI plus CT (23 dogs), according to the standard protocol at each site. Following a presurgical skin preparation, a 22g 1 in. spinal needle was inserted into the selected elbow joint and a small volume of joint fluid was removed. A prescribed activity of ^{117m}Sn colloidal suspension was then injected through the same needle, followed by a 0.5ml bolus of air to clear the tubing and needle.

Dogs were randomly assigned to receive one of three doses of ^{117m}Sn: 37 MBq (1.0 mCi), 64.75 MBq (1.75 mCi), and 92.5 MBq (2.5 mCi)/joint relative to a 22kg dog, adjusted for body surface area relative to the body surface area of a 22 kg dog (44kg dog would get 1.6 times the dose of a 22kg dog) to compensate for marked differences in skeletal size between dogs. The injected volume was typically <0.5 ml. These doses were chosen based on previous pilot studies done in rats which assessed response to treatment versus adverse effects.[24]

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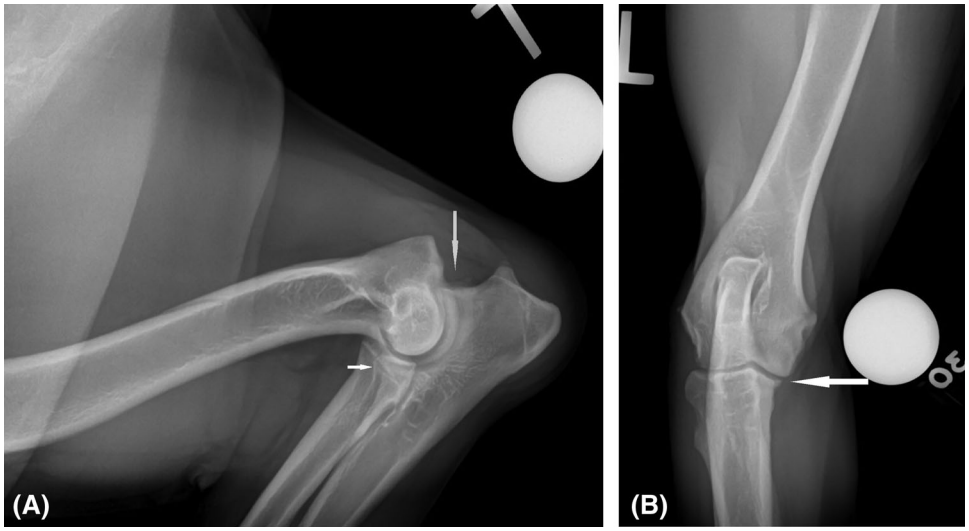

FIGURE 1 Orthogonal radiographic views of the left elbow in a dog. (direct digital capture, CXDI Control Software NE, Canon Inc, Tustin CA, 60kVp, 3mAs). The lateral view illustrates early periosteal proliferation on the anconeal process (large arrow) and rounding/blurring of the medial coronoid process (small arrow). The craniocaudal view illustrates "lipping" of the medial coronoid process (arrow).

Following injection, the dogs were recovered from anesthesia and monitored for evidence of procedural complications. No bandaging or immobilization of the joint was performed as this was shown to be unnecessary in the preclinical studies in dogs and rats where 99% retention was documented without immobilization. During the hospital stay, retention of the isotope within the joint was confirmed by scintigraphic imaging with an Anger camera (lateral view/s of the whole body, 2-minute acquisition, window center 158kV ± 10%) performed 1–3 days after injection. During the in-hospital isolation period, urine, feces, and blood were collected for determination of radioisotope excretion in the urine and feces as well as the amount circulating in blood. Saliva swabs were collected from 13/21 dogs at one site. Following a stay in radiation isolation as required by State or Federal regulations, dogs were released to their owners with appropriate care and handling instructions.

Following release, owners completed a cBPI form monthly. Two other methods of lameness assessment were in-person clinician exam at specified intervals and a remote video assessment. Recheck examinations were performed as described for baseline evaluation at the prescribed intervals of 1-, 3-, 6-, 9-, and 12-months post injection. Each dog was evaluated for lameness at a walk and trot by the admitting clinician before and after manipulation of the elbows for evidence of pain and a video recording of the dog at a walk and trot was made for remote blinded evaluation. Images made at the time of the recheck were evaluated by the principal investigator and graded as static, improved, or worsened relative to both the immediate previous periodic evaluation and the baseline evaluation. Lameness videos, randomly presented with respect to dog and their baseline or follow-up time point, were evaluated on a 6-point scale (Table 1) by two independent consulting veterinarians, (an ACVS Diplomate and a small animal clinician with >40 years of experience).

The cBPI, comprised of Pain Severity Score (PSS), Pain Interference Score (PIS), and Quality of Life (QoL) score, was used to evaluate the owner perception of the effectiveness of the ^{117m}Sn colloid treatment over the 12-month study duration. The cBPI and lameness scores at each recheck evaluation were compared to the baseline values, and those of the most recent visit. The cBPI user guide definition of success, improvement of ≥1 for the PSS, and improvement of ≥2 for the PIS, was used.[18,19] As reported in several other investigations, the assessment of secondary outcome variables included analyses of individual PSS, PIS, and QoL scores.

TABLE 1 Lameness grading scheme

Grade 0	No lameness, walks normally
Grade 1	Slight lameness
Grade 2	Obvious weight-bearing lameness
Grade 3	Severe weight-bearing lameness
Grade 4	Intermittent non-weight-bearing lameness
Grade 5	Continuous non-weight-bearing lameness

2.3 | Statistics

A professional biostatistician with extensive experience in data analysis from clinical trials was paid to design and perform the statistical analysis of the data obtained. Analyses were performed with commercially available statistical analysis software (SAS version 9.3). For each dose group, success was presented as the percentage of elbows meeting the change criteria between baseline and months 1, 3, 6, 9, and 12, and between each visit and the previous visit. For each comparison, possible differences between dose groups were assessed by a generalized linear mixed model assuming a binomial distribution and a logit link. Each model included dose group as fixed effect with site and dose group. Statistical significance was set at $P < 0.05$. When

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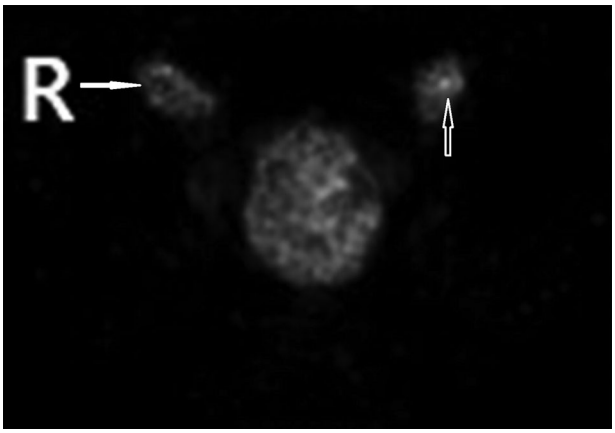

FIGURE 2 Pretreatment axial FDG PET scan (108.41 MBq, whole body scan protocol, matrix;144×144×64, 6.0-minute scan time per bed position, RAMALA 3D reconstruction, C-PET II, ADAC/UGM Medical Systems, Milpitas, CA) indicating increased radiotracer uptake in left elbow (vertical arrow) versus normal uptake in the right elbow (horizontal arrow). These findings mirrored those of the survey radiographs.

statistically significant, comparisons within each dose group at each visit were reported at 95% confidence intervals. No statistical adjustment was applied for multiple comparisons.

Additionally, for the PSS, PIS, and QoL scores, descriptive statistics were calculated for each recheck evaluation compared to the initial evaluation, and to the most recent evaluation. Changes from baseline were assessed by repeated measures analysis of covariance (ANCOVA) modeling. Linear contrast statements were constructed from the models to obtain pairwise comparisons between each dose group at each visit. Within group *P*-values were generated by the paired *t*-test or Wilcoxon signed rank test, depending on the distribution of the data. Statistical analysis of collected data was performed as follows: For effectiveness, tests of statistical significance were completed at a two-sided alpha level of 0.05. For safety, tests of statistical significance were completed at a two-sided alpha level of 0.05.

3 | RESULTS

Forty-four dogs of varying breeds (including 6 chondrodystrophic dogs) and weights (8-70 kg) were enrolled in the study. Forty-one of the dogs completed the study. Two dogs died after the 3-month recheck of unrelated acute medical causes. One dog was dismissed from the study after 6 months due to progressive clinical signs which were attributed to the presence of an initially unrecognized osteochondral defect in the humeral condyle. However, these dogs' safety results were included in the time points for which they were enrolled in the study. Thirty-one of the 44 dogs had inflammatory joint fluid (decreased viscosity, increased neutrophil and mononuclear cell numbers) and 44 of 44 had MRI changes consisting of joint capsule thickening, increased joint fluid volume, and increased synovial stranding indicative of synovial inflammation (Figure 2). Additionally, 21of 21 dogs imaged by ^{18}FDG PET had subjectively increased and altered pattern of intraarticular tracer uptake in comparison to unaffected joints and studies done on normal dogs. (Figure 3)

Fourteen dogs were randomized to the low-dose group, 14 dogs to the medium-dose group, and 16 dogs to the high-dose group. Thirty-seven dogs received a dose within 20% of the intended dose. Scintigraphy confirmed intraarticular injection and retention of the ^{117m}Sn radiocolloid in 43 of 44 dogs (Figure 4). One dog had a periarticular infusion of the test article which remained in the foreleg of the dog. This dog was successfully injected in the contralateral elbow one month later. No adverse side effects or increased elimination of isotope were documented in this or any other dog. No measured clinicopathologic parameters deviated from the normal range in any dog

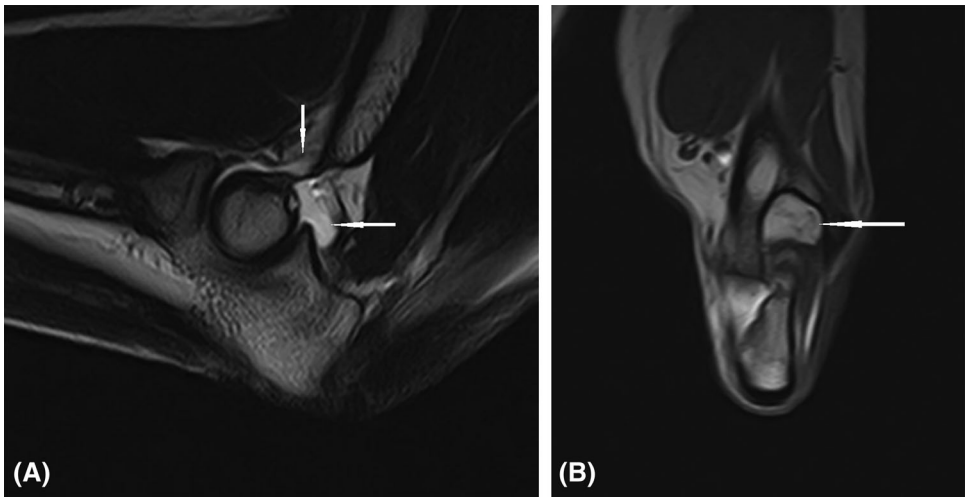

FIGURE 3 A, MRI T2 Sagittal image of a canine elbow demonstrating joint capsule thickening (vertical arrow) and increased synovial fluid volume (horizontal arrow). B, Axial image of the same elbow demonstrating synovial stranding (arrow). (Sternal positioning, Slice thickness 3mm, TR = 5046ms, TE = 120ms, Flip angle 90, number of averages 2, echo train length 13, whole body coil, 2D acquisition, Titan Advantage 3T, Canon Medical Systems USA, Tustin, CA)

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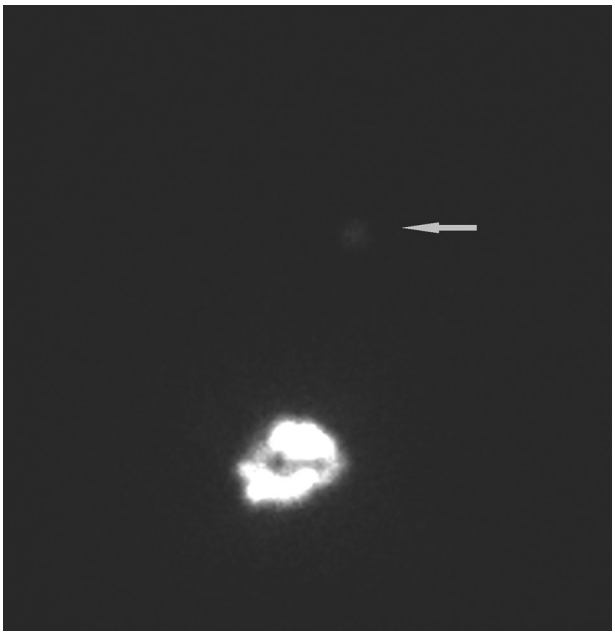

FIGURE 4 Five-day post intraarticular injection lateral scintigraphic image of the right foreleg of a dog, demonstrating long-term retention of the 64.75 MBq 117mSn radiocolloid dose in the joint and slight lymph node uptake (arrow). (scan time 2 min, window center 158kVp, window width ± 10%, LEAP collimator, 256×256 matrix, 35cm × 53cm FOV, no motion correction, Equistand II with Mirage software, Diagnostic Services Middlesex, NJ).

and elimination data based on urine, feces, and blood sampling as well as whole body scintigraphy indicated approximately 99% radionuclide retention in the injected joint as in the preclinical studies.[18] No dog exhibited increased lameness or elbow tenderness in the immediate post-injection period. Only one dog had evidence of oral isotope localization. This dog had been licking the injection site.

Radiographic, CT, MRI, and PET evaluation of the elbows at each time point indicated no significant change in objective or subjective imaging parameters from baseline at any time point between the treatment groups. However, the percentage of animals that were in stable condition was greater in the high-dose group than in the low or medium-dose groups at 1, 3, 6, and 9 months.

Evaluation of the cBPI results indicated no statistically significant overall dose effect. Comparisons to baseline indicated a larger success rate in the medium dose group than the low or high dose group at months 1, 9, and 12. At 9 months, the success rate in the medium dose group was 71.4% compared to 20.0% and 18.2% in the low and high dose groups, respectively. (Table 2). Evaluating the cBPI for change of PSS ≥1 independently with static or improved QoL indicated no statistically significant dose group effect at any visit. Comparisons to baseline showed the greatest improvement in PSS in the medium and high dose groups at 6, 9, and 12 months. (Table 3.). For the PIS, the medium dose group had significant improvement at all time points, the low dose group at 1 and 3 months, and the high dose group at no time point. The QoL score improved significantly only in the medium dose group at 9 and 12 months and in the low dose group at 1 month. (Table 3)

TABLE 2 Baseline comparison using the conventional cBPI analysis. Fractions and percentages represent the number of dogs in that group satisfying the cBPI success criteria. Data presented as percentage success only as results are binary (success versus non-success) and are therefore not assessable by statistical methods

Comparison	Low dose (37.0 MBq)	Medium dose (64.75 MBq)	High dose (92.5 MBq)
Baseline to 1M	2/10 (20.0%)	6/14 (42.9%)	1/11 (9.1%)
Baseline to 3M	4/10 (40.0%)	5/14 (35.7%)	2/11 (18.2%)
Baseline to 6M	4/10 (40.0%)	6/14 (42.9%)	4/11 (36.4%)
Baseline to 9M	2/10 (20.0%)	10/14 (71.4%)	2/11 (18.2%)
Baseline to 12M	3/10 (30.0%)	7/14 (50.0%)	1/11 (9.1%)

Clinician assessment of lameness before and after manipulation at all time points indicated the most consistent and statistically significant improvement in lameness from the baseline in the medium and high dose groups ($P \leq 0.05$). No significant effects in lameness scores were seen when comparing any dose group or time to any other dose group or time in the post-treatment evaluation period. (Table 4). Lameness scoring from the video recordings did not reveal statistical evidence of improvement or worsening of lameness at either the trot or walk for any time point compared to the previous time point or to the baseline evaluation. Likewise, the evaluation of imaging data did not demonstrate either statistically significant improvement or worsening of imaging findings in any of the dogs which completed the study.

4 | DISCUSSION

The results of this study supported our hypothesis that intraarticular injection of the radiocolloid preparation of ^{117m}Sn (Synovetin OA®) into one arthritic elbow would reduce lameness in the view of both owners and experienced veterinary clinicians for the majority of sampled dogs. Analysis of the data also indicated an improvement in quality of life in most cases as assessed by the owners. The moderate dose of radiocolloid resulted in a durable response period of 9 months in more cases than either the high- or low-dose group. However, the response was not universal and the reason for failure was not evident except in one case where a preexisting cartilage defect was not appreciated on the initial imaging.

The pathogenesis of osteoarthritis and the pain arising from it is complex. A major contributing factor in the development and progression of osteoarthritis is joint instability as is usually the case with osteoarthritis of the stifle and hips in dogs.[22] However, elbow joints, even those with medial coronoid disease, anconeal process disease, or joint incongruity, are rarely unstable and often have congruent joint surfaces. In dogs (as in humans), progression of osteoarthritis in stable joints has been shown to be related to ongoing inflammation in the joint, initially incited by the anatomic lesions or minor trauma and then promoted and perpetuated by persistent inflammatory mediators in the joint fluid and synovium that alter the characteristics of the synovial fluid, reducing its cartilage protective function.[6,7]

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TABLE 3 Significant results from cBPI owner survey analysis, Negative values for PIS and PSS indicate improvement in score (less pain severity and pain interference) whereas positive values for QOL indicate improvement in QOL

Parameter	Month	Dose Group	n	Mean	SEM*	Within Group P-value
Pain Severity Score	1M	Medium (64.75 MBq)	14	−1.77	0.59	0.0101*
		High (92.5 MBq)	11	−1.73	0.57	0.0132*
	3M	Medium (64.75 MBq)	14	−2.13	0.65	0.0061*
		High (92.5 MBq)	11	−1.48	0.41	0.0046*
	6M	Medium (64.75 MBq)	14	−2.34	0.81	0.0129*
		High (92.5 MBq)	9	−1.67	0.72	0.0491*
	9M	Medium (64.75 MBq)	13	−3.00	0.70	0.0011*
		High (92.5 MBq)	10	−2.23	0.57	0.0038*
	12M	Low (37 MBq)	10	−1.35	0.50	0.0239*
		Medium (64.75 MBq)	12	−2.33	0.76	0.0110*
		High (92.5 MBq)	11	−2.39	0.50	0.0008*
Pain Interference Score	1M	Low (37 MBq)	10	−2.00	0.57	0.0067*
		Medium (64.75 MBq)	14	−1.73	0.66	0.0207*
	3M	Low (37 MBq)	10	−2.15	0.73	0.0168*
		Medium (64.75 MBq)	14	−2.06	0.65	0.0074*
	6M	Medium (64.75 MBq)	14	−2.27	0.86	0.0202*
	9M	Medium (64.75 MBq)	13	−2.95	0.67	0.0009*
	12M	Medium (64.75 MBq)	12	−2.60	0.96	0.0202*
Quality of Life	1M	Low (37 MBq)	10	0.90	0.31	0.0187*
	9M	Medium (64.75 MBq)	13	1.08	0.40	0.0195*
	12M	Medium (64.75 MBq)	12	0.92	0.38	0.0339*

Standard Error of the Mean

These proinflammatory molecules arise from the synoviocytes and joint macrophages.[6,25] The proinflammatory state may be exacerbated by many conditions including overuse, diabetes mellitus and obesity.[7] Proinflammatory agents have been shown to be present in joints prior to the development of clinical lameness and to promote degeneration of joint cartilage and other structures over time.[7] Cartilage degeneration promotes further production of inflammatory mediators creating a recurring cycle of inflammation and degeneration. This has been documented in canine stifle joints where the presence of inflamed synovium and altered joint fluid has been demonstrated prior to complete cruciate ligament rupture.[25,26]

Local therapies are attractive, having the potential for the treatment of the disease without systemic side effects. Local treatments such as laser therapy, topical administration of pharmaceutical or blood flow-altering agents, and external beam radiation therapy have been shown to be effective for reducing pain and inflammation. However, the effect is transient requiring the dog to return for additional treatments.[27–29] Pharmacodynamic studies of intraarticularly injected anti-inflammatory agents indicate that corticosteroid injections and most other agents undergo systemic translocation within a few hours resulting in transient intraarticular effects.[30–32] Systemic therapies such as NSAIDs and corticosteroids may also have adverse effects on other organs in the body in some dogs. There are also reports indicating accelerated joint deterioration occurring with chronic administration of narcotics.[32] Chemically inert and locally retained agents do not have these concerns.

The concept of using radiation therapy to treat osteoarthritis in animals and humans is not new. Superficial plesiotherapy packs were used to treat arthritic joints in horses in the 1960s.[33] The anti-inflammatory effects of radiation on the joint synovium and suppression of boney proliferation were cited as the rationale for these treatments. Overall, the treatments were well tolerated and resulted in a significant percentage of the horses returning to performance. Radiosynoviorthesis is commonly performed in Europe for treatment of rheumatoid arthritis in humans where thousands of such well-tolerated injections are performed annually with a very low complication rate and a reported success rate of 40–90%.[15,33,34] Injected joints range in size from the hip to the interphalangeal joints. These treatments are not currently employed in North America for a variety of reasons ranging from regulatory resistance to physician bias and unfounded patient fears of radioisotopes. Radioisotopes currently used for radiosynoviorthesis are low to high-energy beta emitters with or without gamma emissions. However, the half-life of some is relatively short to provide the ideal irradiation period of several weeks to promote long-term suppression of synovitis.[34] The 14-day half-life of ^{117m}Sn colloid satisfies this and most of the other prerequisites for a radiosynoviorthesis agent

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TABLE 4 Clinician assessment of lameness at walk and trot before and after orthopedic exam at 9 and 12 months (significant values). Highest (worst) score change for all four parameters was also assessed

Parameter	Month	Dose Group	N	Mean	sEM	Within group *P*-value
Lameness at walk, before orthopedic exam (0-5)	9 M	Medium (64.75MBq)	10	−0.70	0.30	0.0445*
		High (92.5Mbq)	8	−0.75	0.25	0.0199*
	12 M	Medium (64.75MBq)	11	−0.73	0.27	0.0236*
		High (92.5Mbq)	8	−1.00	0.27	0.0027*
Lameness at Trot, before orthopedic exam (0-5)	9 M	Medium (64.75MBq)	10	−0.90	0.35	0.0294*
		High (92.5Mbq)	8	−0.75	1.25	0.0199*
	12 M	High (92.5Mbq)	8	−0.88	0.35	0.0412*
Lameness at walk, after orthopedic exam (0-5)	9 M	Medium (64.75MBq)	9	−0.78	0.28	0.0420*
		High (92.5Mbq)	6	−0.83	0.31	0.0420*
	12 M	Low (37.0MBq)	6	−1.00	0.37	0.0409*
		High (92.5Mbq)	7	−1.14	0.26	0.0047*
Lameness at trot, after orthopedic exam (0-5)	9 M	High (92.5Mbq)	6	−0.83	0.31	0.0422*
	12 M	High (92.5Mbq)	7	−1.00	0.38	0.0382*
Lameness: worse value (largest of the 4 Assessments), i.e. walk Trot, prior to and after the exam	9 M	Medium (64.75MBq)	10	−0.90	0.28	0.0100*
		High (92.5Mbq)	8	−0.63	0.26	0.0492*
	12 M	Low (37.0MBq)	6	−1.00	0.37	0.0409*
		Medium (64.75MBq)	11	−0.64	0.28	0.0455*
		High (92.5Mbq)	8	−0.88	0.35	0.0412*

and localization with in synovial macrophages has been previously demonstrated.[18]

The reason for the better outcome in the medium dose group cannot be elucidated from this study. One possible explanation is that the low dose was insufficient to completely suppress the inflammatory state throughout the joint, whereas the high dose, while suppressing the macrophage-induced inflammation, itself damaged the synovium promoting a renewed inflammatory response. Serial histologic assessment of the synovium was not feasible in these client-owned dogs. The cBPI results agreed with the clinician evaluation and with force plate data from a subset of these dogs (22 dogs) published previously.[36] The three methods of evaluation all indicated an increase in weight bearing and quality of life that lasted 9–12 months for 50% or more of dogs in the medium dose group. This durability of the clinical effect indicated the feasibility of employing this treatment in lieu of or in combination with systemic therapies.

Limitations to this study exist. The clinical evaluation tool (cBPI) used is designed to evaluate the overall effect on the dog and is therefore more suited for the evaluation of systemic therapies. Owners were not asked to discriminate which leg was causing pain or lameness, possibly resulting in a less rigorous evaluation of response in the treated limb. Despite this, a substantial number of the dogs did have a durable positive response in the owners' opinion. Second, the predominantly bilateral nature of elbow disease made it impossible to limit the study to dogs with unilateral disease as would have been ideal. In retrospect, bilateral treatment may have been preferable given the clinical assessment tool used and the subtlety of the imaging changes. Third, this is a relatively small study performed at multiple sites using a standard protocol but differences in execution of the protocol exist. Use of multiple dose groups reduced the power of the study as well and is the likely reason for the lack of significant statistical separation of dose groups and time periods as well as the difficulty in demonstrating significant differences via imaging. The results were not uniformly positive in all dogs but did demonstrate a positive long-term effect in the majority of dogs. The maximum rate of benefit was noted at nine months following treatment with some extending beyond twelve months. Fourth, lack of a standard method of acquiring the video images combined with the subjective nature of the evaluation may have led to the lack of correlation between clinician and owner perceived lameness with the video evaluation. Finally, a control group was not included due to the preliminary nature of the study, and a placebo group was not considered ethical. Rigorous evaluation of a larger and more homogenous group of dogs with bilateral disease using force plate analysis and treatment of both elbows can be explored to confirm the efficacy of the treatment described in this study.

The aim of this study was to demonstrate the benefit and safety of this radiosynoviorthesis agent in dogs with early to moderate arthritis. Dogs with advanced osteoarthritis were excluded from the study because in advanced osteoarthritis there is, by definition, cartilage erosion present which promotes pain and inflammation in affected joints. Radiocolloid therapy is aimed at decreasing synovial inflammation, promoting a healthier joint environment, and slowing the cascade of events leading to cartilage degradation and advanced disease.

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Proper selection of cases for treatment with this agent is critical. The ^{117m}Sn radiocolloid presumably has an anti-inflammatory effect which is less effective once erosion of the joint cartilage exposes the subchondral bone to synovial fluid. This was anecdotally demonstrated in this study by lack of response in the dog with the humeral condylar osteochondral defect. Joint instability, if present, will continue to cause cartilage injury by mechanical abrasion of the cartilage and rapid advancement of the osteoarthritis. Radiosynoviorthesis would therefore be expected to have little utility as a primary treatment of conditions such as ruptured cranial cruciate ligaments, however, a role for treatment of pre-rupture cruciate disease or following surgical stabilization may exist.

Treatment of inflammatory arthritis involving one or multiple joints is the most common use for radiosynoviorthesis in humans. Local therapy with no systemic effects combined with the convenience of a single treatment episode makes this device an ideal primary or adjunctive treatment for inflammatory arthritis not completely controlled by systemic therapy. Injection of multiple joints does not increase side effects because the radiation dose is confined to the treated joint and is not absorbed into the systemic circulation.

Radiation safety is very important when using therapeutic radionuclides. Because the vast majority of the radiation dose from ^{117m}Sn is the result of very short-range conversion electrons and because there is minimal release and excretion of the radionuclide, concerns of environmental contamination or owner exposure to radiation are minimized with this device.[18,36]

In conclusion, findings indicated that intraarticular injection of ^{117m}Sn radiocolloid (Synovetin OA®) in arthritic elbows was well tolerated with no adverse reactions based on clinical examination, owner assessment, clinicopathologic data, and imaging results and was clinically effective for up to one year in 50% of cases. Efficacy and safety were demonstrated in dogs with mild to moderate osteoarthritis in stable elbow joints across multiple clinical settings with durable response in approximately 70% of dogs at 9 months post treatment. Results supported the use of ^{117m}Sn radiocolloid (Synovetin OA®) as a repeatable treatment for a common disorder currently having few effective long-term treatments.

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Category 1

(a) Conception and Design: Lattimer, Selting
(b) Acquisition of Data: Lattimer, Fabiani, Gaschen, Aulakh, Selting
(c) Analysis and Interpretation of data: Lattimer, Aulakh

Category 2

(a) Drafting the article: Lattimer
(b) Revising the article for Intellectual Content: Lattimer, Fabiani, Gaschen, Aulakh, Selting

Category 3

(a) Final Approval of Article: Lattimer, Fabiani, Gaschen, Aulakh, Selting

Category 4

(a) Agreement to be accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Lattimer, Fabiani, Gaschen, Aulakh, Selting

CONFLICT OF INTEREST

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REPORTING GUIDELINE DISCLOSURE

No reporting guideline checklist was used in the compilation of this report.

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