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ORIGINAL RESEARCH

Prospective Clinical Evaluation of Intra-Articular Injection of Tin-117m (^{117m}Sn) Radiosynoviorthesis Agent for Management of Naturally Occurring Elbow Osteoarthritis in Dogs: A Pilot Study

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Purpose: To evaluate the clinical effects of an intra-articular injection of ^{117m}Sn-colloid for management of canine grade 1 or 2 elbow osteoarthritis (OA).

Patients and Methods: This was a prospective study in 23 dogs with grade 1 or 2 elbow OA. An orthopedic examination and elbow radiographs were performed to confirm the presence of OA. Dogs were randomly assigned to receive unilateral intra-articular (IA) injection of low-dose (LD: 1.0mCi, n =8), medium-dose (MD: 1.75mCi, n =6), or high-dose (HD: 2.5mCi, n =9) of ^{117m}Sn-colloid. The primary outcome measure was peak vertical force (PVF) from force-plate gait analysis and secondary outcome measures included the Canine Brief Pain Inventory score (CBPI) and elbow goniometry. The CBPI was evaluated at pretreatment and then monthly post treatment for 1 year, and goniometry and PVF were evaluated at pretreatment, and at 1, 3, 6, 9 and 12 months post treatment.

Results: PVF improved at 3, and 9 months compared to pretreatment values in the HD group. CBPI scores improved at most of the time points in all dose groups. There was no significant difference in elbow goniometry between treated and untreated elbows. There were no self-reports of any adverse effects of the injection by the owners and none were noted by the examining veterinarian at the time of regularly scheduled re-evaluations.

Conclusion: ^{117m}Sn IA injection was free of any obvious adverse effects, improved CBPI scores, and increased weight bearing in limbs with elbow OA providing preliminary evidence that ^{117m}Sn may be beneficial in the management of elbow OA in dogs. Although ^{17m}Sn appeared to be effective for management of elbow OA in these dogs, this pilot study has inherent limitations; therefore, future studies with larger numbers and with placebo group are needed.

Keywords: osteoarthritis, Radiosynoviorthesis, Tin-117m (^{117m}Sn), CBPI, goniometry, peak vertical force

Introduction

Canine elbow osteoarthritis (OA) is a common sequela from elbow dysplasia.[1] Elbow OA is a progressive joint disease characterized by decreased joint range of motion, pain, cartilage destruction, and osteophyte formation.[1,2] Treatment is mainly palliative and current strategies often consist of medical management including NSAIDs, analgesics, nutraceuticals, weight control, physical rehabilitation, and changes in activity level.[1–3] Although daily use of NSAIDs may reduce

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OA pain, these agents have the potential to cause or exacerbate renal, gastrointestinal, and hepatobiliary disorders.[4] In addition, it may not be practical for some owners to administer daily medications. Surgery often fails to prevent progression of OA and may not provide superior outcomes to medical management.[5,6] Salvage procedures such as elbow replacement have inconsistent outcomes and a high complication rate.[1,7,8]

Nonsurgical management will likely remain a viable treatment option for dogs with elbow OA; therefore, optimization of current nonsurgical options and development of new innovative nonsurgical treatments are important. The use of intra-articular (IA) injections including platelet-rich plasma, dextrose prolotherapy, autologous protein solution, or stem cells has been reported for OA treatment with mixed results.[9–12] Larger clinical studies are needed to fully understand the effects of these therapies on dogs with OA.

Synovitis precedes development of radiographic OA changes in humans and dogs.[2,13,14] It is characterized by marked hyperplasia and permeability of the synovial lining, overexpression of proinflammatory cytokines, infiltration of inflammatory cells, production of degradative enzymes, and synovial neovascularization and proliferation.[15] Inflammation sensitizes peripheral neurons in synovial tissue, resulting in joint pain.[16] Marked synovitis precedes structural changes in the progression of OA and early intervention targeting joint inflammation, prior to radiographic changes, can delay or prevent chronic arthritic changes.[15] Low-dose radiation therapy has direct anti-inflammatory effects on the synovium.[17] A small study of 5 dogs with elbow OA concluded that use of single-low-dose radiotherapy may have short-term clinical benefits.[18]

As synovitis is strongly implicated in OA pathogenesis, surgical and nonsurgical synovectomy (synoviorthesis) have been used to alleviate human synovitis symptoms.[19] Another reported method to relieve synovitis is via radiosynoviorthesis (RSO), which involves IA injection of low-energy ionizing radiation to induce apoptosis and ablate inflamed synovial cells.[20] Use of this therapy has been reported in humans to treat synovitis in an effort to prevent, delay, or limit arthritic changes.[20] Radiosynoviorthesis, primarily involving yttrium-90 (^{90}Y), erbium-169 (^{169}Er), and rhenium-186 (^{186}Re), is an accepted outpatient therapy for treatment of early-stage chronic synovitis in humans with rheumatoid arthritis, psoriatic arthritis, hemophilic arthritis or OA.[20,21] The success rate of RSO reported by Zuderman et al was 89% for rheumatoid arthritis and 79% for OA in humans.[22] Tin 117m (^{117m}Sn) homogeneous colloid was specifically developed to avoid the serious outcomes following treatment with high-energy beta emitters.[23] Tin 117m colloid is a non-beta emitter with lower energy from which the conversion electrons have a therapeutic distance of activity of only 300 microns (0.3 mm).

Despite its many advantages, RSO is seldom performed in veterinary medicine, with limited reports including use of ^{177}lutetium-labeled zirconia in dogs and ^{117m}Sn homogeneous colloid in rats.[24–26] In a recent prospective safety study of 5 dogs, blood, urine, feces, and organ scintigraphy counts showed that >99% of ^{117m}Sn activity was retained in the elbow joint for approximately 6–7 weeks.[23] There were no adverse effects, and post-mortem evaluation revealed no joint damage. These findings, combined with the potential for protracted clinical improvement after a single IA injection, justify further evaluation of ^{117m}Sn for the management of canine OA. The authors designed the current study to assess the value of IA ^{117m}Sn for pain management in dogs with naturally occurring elbow OA. Specifically, the authors aimed to quantify changes in peak vertical force (PVF) from force plate gait analysis as the primary outcome measure and canine brief pain inventory (CBPI) scores and elbow goniometry as secondary outcome measures, at multiple timepoints for one year after a single unilateral IA injection of ^{117m}Sn in dogs with grade 1 or 2 elbow OA. By limiting the study to unilateral elbow injection, the opposite leg is a source of comparison data. The hypothesis was that IA ^{117m}Sn-colloid treatment is associated with clinically relevant beneficial effects in dogs with elbow OA.

Patients and Methods

Study Design

The study was designed as a long-term longitudinal and prospective study using serial measurements in dogs. The study protocol was approved by the Institutional Animal Care and Use Committee and informed client consent was obtained prior to study enrollment.

Inclusion Criteria

A convenience sample of 23 dogs was used in this study. No sample size calculation was performed. Dogs were eligible if they were, ≥8kg, at least 1 year of age, had a visible forelimb lameness or pain localizable to one or both elbows, had radiographic evidence of grade 1 or 2 OA in one or both elbows based on international elbow

working group (IEWG) classification,[27] had no clinically detectable abnormalities including pain in any other joint in the forelimbs, had no comorbid condition likely to preclude a 1-year survival, and had no surgical procedure on any leg in the past 4 months or received any joint injections previously. Elbow OA grading was performed by a single board-certified radiologist. All images were calibrated, and osteophyte size was prioritized over trabecular pattern. Dogs with orthopedic disease affecting either hind limb were considered eligible as long as there was no visible lameness present in any of the hind limbs. Dogs being treated with nutraceuticals and/or medications such as NSAIDs were eligible provided they still had lameness or pain localizable to one or both elbow/s.

Study Protocol

Initially, information was collected from dog owners including signalment, duration of OA, and type and duration of current medications/supplements. Owners also completed the CBPI.[28,29] After meeting initial evaluation requirements, all dogs received a baseline assessment within 30 days of treatment prior to study participation. Dogs had a physical examination, and the following variables were obtained: CBC, serum biochemistry, urinalysis (UA), bilateral elbow radiographs, bilateral elbow goniometry and PVF using force plate gait analysis. These parameters were also collected post-treatment at 1, 3, 6, 9, and 12 months. Bilateral elbow radiographs were performed at the 12-month follow-up exam. Treatment included a unilateral IA injection of ^{117m}Sn in the elbow that was determined to be the source of observable lameness or was more painful when observable lameness was not noted. Dogs were randomly assigned to one of the three ^{117m}Sn dose groups (normalized based on body surface area, Supplementary Table 1): low dose (LD): 1.0 mCi (millicuries) or 37 MBq (MegaBequerel), medium dose (MD): 1.75mCi or 64.75 MBq and high dose (HD): 2.5mCi or 92.5 MBq, using a computer-generated randomized table. Observers and owners were masked to the dose group except the radiologist who injected the colloid.

Primary Outcome Measures

Force Plate Gait Analysis: PVF

Both sites used the same model force-plate (OR6-WP -1000, Advanced Medical Technology Inc, Newton, MA) and commercially available force-plate analysis software. Data logging (100Hz, Acquire version 7.3, Sharon Software Inc, Dewitt, MI) was triggered by a force of 5N on the force plate. Five successful trials at a velocity of 1.5–2.5m/sec and acceleration of 0.9 to −0.9m/sec^2 were recorded for each leg. Dogs were acclimated and trained to walk across the force plate during the pretreatment gait trial. Trained handlers walked the dogs for all testing. PVF (N/kg) was recorded and normalized to body weight and the mean value of five trials was used for statistical analyses. Body weight distribution % (BW-D %) between the forelimbs was calculated according to the formula: $BW\text{-}D\% = PVF_T/(PVF_{UT} + PVF_T) \times 100\%$, where PVF_T = mean PVF of the treated leg, and PVF_{UT} = mean PVF of the contralateral untreated leg.

Determination of Positive Response Based on PVF

A positive response was defined as ≥5% increase in mean PVF at a single time point in the treated leg[29–34] at months 1, 3, 6, 9, and/or 12 compared with baseline (0 month) for each individual dog evaluated on the force plate.

Secondary Outcome Measures

CBPI

Owners completed the CBPI[28,35] scores at initial evaluation and then monthly from 1 through 12 months except for the 2nd month post treatment. The same individual was required to complete the survey each time. Owners did not have access to their previous scores at each follow-up visit.

Elbow Goniometry

A single boarded surgeon from each site performed a physical/orthopedic examination. Elbow goniometry was performed using a standard two-arm plastic goniometer as previously described.[36]

IA ^{117m}Sn-Colloid Injection

Dogs were anesthetized, positioned in dorsal recumbency, and the medial aspect of the elbow to be injected was aseptically prepped. The homogeneous ^{117m}Sn-colloid (Synovetin OA®, Exubrion Therapeutics, Buford, GA) was injected into the joint as previously described.[23] After completion of the injection, dogs were recovered from anesthesia and discharged the following morning. Instructions for care and handling with regards to the radioisotope were provided to the owners. All disposables coming in contact with ^{117}Sn were disposed of following all State Regulatory Commission guidelines. Tin 117m is a non-beta emitter in which "radiation burns" do not occur. The low-energy characteristics of the therapeutic

conversion electrons are very different from the higher energy beta emitters (^{90}Y, ^{169}Er, ^{186}Re) commonly used in human RSO.[20] As mentioned, elbow injection doses of Tin 117m were based on a chart based on body surface area (Supplementary Table 1) to allow clinicians to adhere to the ALARA (as low as reasonably achievable) principle. Previous studies in both laboratory rats and dogs in which histologic sections were obtained have shown that even with higher doses of homogeneous Tin 117m colloid, "beta burns" did not occur.[23,25] Standard industry precautions were taken when handling homogeneous tin colloid as with any unsealed radiation source as prescribed by the Nuclear Regulatory Commission.

Data Analysis

Data analyses were performed using JMP Pro 15.0 (SAS Institute Inc., Cary, NC). All continuous parameters were presented as mean ±SD and assessed with a repeated measure ANOVA with a mixed effect model was used with time as the fixed effect and each dog as the random effects with the variance compounds covariance structure within each dose group and within treated or untreated elbow. Kenward-Roger approximation was used to determine the degrees of freedom in the model. A contrast hypothesis was performed at each time point against baseline. Assumptions of these models (linearity, normality of residuals, and homoscedasticity of residuals) and influential data points were assessed by examining standardized residual and quantile plots, and the normality of residual was confirmed with the Shapiro–Wilk test. Ordinal subjective variables at each time point were presented as median (range). Due to small sample size, the data was combined and compared with baseline and untreated elbow using a Wilcoxon signed-rank test. The outcomes of positive response among 3 groups were evaluated with Fisher's exact test. Significance was set at $P < 0.05$.

Results

Demographic characteristics of the study population are shown in Table 1. One dog in the LD-group received a much lower dose, about 40% lower than the prescribed dose of 117mSn-colloid, so that dog was excluded from the study. Another dog (female intact) from the HD-group was excluded because the owner reported the dog had rough play with two other large housemate dogs and was very sore in the front limbs especially on the treated limb at the one-month recheck and the same dog was bred later during the three-month recheck. The exclusion of these 2 dogs resulted in a total of 21 dogs in our study population. Duration of arthritis and type of medical management are shown in Supplementary Table 2. All dogs had visible unilateral lameness except 3 dogs (2 had bilateral grade 1 OA and 3rd one had bilateral grade 2 OA). No adverse effects were observed on physical/orthopedic examination or reported by owners, and no clinically significant laboratory findings were noted related to the IA injection of ^{117m}Sn at regularly scheduled re-evaluations.

Both PSS and PIS significantly improved at all timepoints except for the 10-month (PSS) and the 10- and 11-month (PIS) (Table 2) scores compared to baseline. No significant differences were noted in QoL scores.

In the HD group for elbow extension there was a trend in improvement (approaching significance) in the treated leg at 6, and 9 months, respectively, compared to baseline (Table 3). Elbow extension also increased in the untreated leg at 9-month in the HD group and at 6-month in the MD group. In 1 dog from the MD-group, baseline force-plate data for the treated leg was missing and this dog died secondary to GDV after its 3-month evaluation. In 1 dog from the LD-group, five successful repeatable trials during force-plate data collection could not be obtained at the baseline evaluation. These 2 dogs were not included in the force plate data analysis. This resulted in a total of 19 dogs for force plate data analysis. The mean peak vertical force improved in the treated leg in the HD group by 5.4%, 12.0%, 10.1% and 12.3% at 1, 3, 6, and 9 months, respectively, compared to baseline. This increase was statistically significant at the 3- and 9-month time points. The mean PVF was significantly lower (by 9%) in the untreated leg at the12-month time point compared to baseline (Table 4). In the HD group, the mean BW-D% for the treated leg improved compared to baseline and this improvement approached significance at 3- and 9-month time points (Table 4).

Based on the criteria mentioned above for a positive response, 17 of 19 dogs (89.5%) had a positive response (Table 5). There was no significant difference between the three dose groups for positive responses.

The radiographic OA scores significantly increased both in treated elbows and untreated elbows at 12-month recheck compared to pretreatment scores (Table 6). There was no significant difference in OA score change from baseline between treated and untreated elbows at the time of the 12-month evaluation for all dose groups (Table 6).

Table 1 Demographic Characteristics for 21† Dogs with Naturally Occurring Elbow OA Based on ^{117m}Sn Dose Group

Dose Group	Breeds	Sex (n)	*Age in years	*Weight in kgs	*BCS Out of 9	OA Grade (T)	OA Grade (UT)
LD	Beagle mix	F/S=3	3[a] (1–11)	32.2[b] (23.1–57.2)	5[c] (4–7)	2 (L)	2
	Dogue de Bordeaux	M/N=4				1 (R)	2
	Golden Retriever Mix					2 (R)	1
	Labrador Retriever					1 (L)	1
	Labrador Retriever					2 (L)	1
	Mix					1 (R)	1
	Newfoundland					1 (L)	0
MD	American Bulldog mix	F/S=3	2.5[a] (1–12)	28.0[b] (19.6–66.82)	4.5[c] (4–7)	2 (L)	2
	German Shepherd	M=1				2 (R)	2
	Golden Retriever	M/N=2				1 (L)	2
	Great Dane					2 (R)	2
	Labrador Retriever Mix					2 (R)	2
	Labrador Retriever Mix					1 (R)	1
HD	Bulldog/Dalmatian mix	F/S=5	3[a] (2–10)	24.2[b] (17.5–40.2)	5[c] (4–6)	1 (L)	1
	German Shepherd	M=1				1 (L)	1
	Irish Soft Coated Wheaten Terrier	M/N=2				1 (R)	2
	Labrador Mastiff Mix					1 (L)	1
	Labrador Retriever					2 (R)	1
	Labrador Retriever					2 (L)	2
	Mix					1 (R)	1
	Rhodesian Ridgeback mix					1 (R)	1

Notes: †One dog in the LD-group received a much lower dose, about 40% lower than the prescribed dose of ^{117m}Sn-colloid, so that dog was excluded from the study. Another dog (female intact) from the HD-group was excluded because the owner reported the dog had rough play with other two large housemate dogs and was very sore in the front limbs especially on the treated limb at one-month recheck and the same dog was bred later during the three-month recheck. *Data is presented as median (range). [abc]Same superscript between groups indicate no significant difference for age, weight and BCS, respectively.

Abbreviations: HD, high dose; MD, medium dose; LD, low dose; T, treated leg; UT, untreated leg; F/S, female spayed; M, male; M/N, male neutered; BCS, body condition score.

Discussion

The ability to use RSO as a localized treatment with lasting results and no systemic adverse effects could make it a valuable therapeutic option for veterinary patients with OA. In our study, the use of IA ^{117m}Sn in dogs with elbow OA resulted in clinically relevant beneficial effects lasting for up to 9 months-based on force plate data with statistically significant improvement at 3 and 9 months post-injection and trending towards improvement (approaching significance) at 6 months post injection. The beneficial effects lasted for 1-year post injection based on CBPI data. This duration of RSO response is similar to what has been reported in humans where the response can last for a few months to several years.[17]

Radiosynoviorthesis (RSO) has been successfully used in human medicine for more than 60 years in many countries, particularly in Europe where it was first described and where its use conforms to guidelines published by the European Association of Nuclear Medicine.[22,37–39] RSO

Table 2 Canine Brief Pain Inventory (CBPI) Scores for 21 Dogs[†] with Elbow OA at Pretreatment and at Each Time-Point Post Treatment. Values are Presented as Median (Range)

[‡]CBPI Item	PT	1mo	3mo	4mo	5mo	6mo	7mo	8mo	9mo	10mo	11mo	12mo
[a]PSS sum	14 (4–25)	13* (0–29)	8* (0–21)	6* (0–18)	4* (0–24)	4* (0–22)	8* (0–23)	6* (0–24)	8* (0–30)	10 (0–26)	8* (0–30)	6* (0–23)
[b]PIS sum	20 (0–49)	13* (0–46)	7.5* (0–42)	5.5* (0–31)	6* (0–41)	3* (0–42)	9* (0–43)	8.5* (0–43)	11.5* (0–43)	12 (0–43)	12 (0–49)	9* (0–47)
CBPI total sum	37 (8–70)	30* (1–75)	14.5* (0–63)	10* (0–49)	10* (0–63)	5* (0–64)	17* (0–66)	15* (0–67)	20.5* (0–64)	22 (0–68)	20 (0–79)	16* (0–70)

Notes: [‡]CBPI is a two-part owner questionnaire that evaluates the Pain Severity Score (PSS, questions 1–4) and Pain Interference Score (PIS, questions 5–10) associated with daily activities. [a]Range 0–10 (no pain, extreme pain). [b]Range 0–10 (does not interfere, interferes completely). *Significant difference compared to pretreatment. [†]Due to small sample size the CBPI scores are combined for all dose groups (21 dogs).
Abbreviation: PT, pretreatment.

has been an accepted outpatient therapy for treatment of early stage chronic synovitis in rheumatoid arthritis, psoriatic arthritis, hemophilic arthritis and OA patients for decades.[39–41] Current standards in human clinical practice generally take a conservative approach by recommending initial treatment with front-line therapies including

Table 3 Evolution of Elbow Extension, Flexion and Range of Motion from Baseline to Month-12 in Treated and Untreated Elbows in 21 Dogs with Elbow OA for All Three ^{117m}Sn Dose Groups. The Means of Three Values for Elbow Extension and Flexion Were Recorded Bilaterally. The Data is Summarized as Mean ± Standard Deviation (SD)

	Dose	PT	1mo	3mo	6mo	9mo	12mo
Sample size	HD MD LD	8 6 7	8 6 5	8 5 5	5 5 3	3 3 4	6 3 4
[‡]Extension $_{Treated}$	HD MD LD	158 ±4 163 ±10 158 ±12	160 ±6 158 ±14 158 ±4	160 ±6 166 ±7 156 ±5	165 ±4 p = 0.0527 166 ±7 162 ±4	168 ±7 p = 0.0508 163 ±18 164 ±5	161 ±9 162 ±11 164 ±4
[‡]Extension $_{Untreated}$	HD MD LD	162 ±3 161 ±6 161 ±10	163 ±2 161 ±10 164 ±2	159 ±5 168 ±5 159 ±7	162 ±7 169 ±5 p = 0.0738 163 ±6	169 ±2 p = 0.0565 166 ±8 161 ±5	158 ±7 165 ±13 163 ±8
[‡]Flexion $_{Treated}$	HD MD LD	30 ±9 35 ±16 39 ±9	27 ±8 33 ±9 40 ±12	27 ±10 35 ±13 41 ±12	28 ±5 37 ±17 42 ±17	24 ±4 32 ±8 36 ±7	34 ±11 36 ±17 43 ±19
[‡]Flexion $_{Untreated}$	HD MD LD	29 ±10 35 ±16 33 ±7	27 ±8 31 ±9 35 ±8	25 ±8 33 ±9 36 ±8	31 ±7 39 ±12 37 ±7	29 ±9 32 ±10 32 ±2	32 ±8 28 ±7 37 ±9
[‡]ROM $_{Treated}$	HD MD LD	127 ±10 128 ±17 120 ±18	134 ±12 125 ±22 117 ±14	133 ±15 132 ±19 115 ±8	136 ±8 129 ±21 120 ±15	144 ±11 131 ±26 128 ±8	127 ±19 127 ±27 121 ±17
[‡]ROM $_{Untreated}$	HD MD LD	134 ±8 125 ±17 128 ±15	136 ±8 131 ±18 129 ±7	134 ±12 135 ±12 123 ±8	132 ±13 130 ±16 126 ±7	140 ±11 134 ±18 129 ±3	127 ±13 137 ±20 126 ±11

Notes: [‡]Elbow extension, flexion and range of motion are reported in degrees.
Abbreviations: HD, high dose; MD, medium dose; LD, low dose; PT, pretreatment; ROM, range of motion.

Table 4 Evolution of PVF and BW-D% from Baseline to Month-12 in Nineteen[†] Dogs with Elbow OA for All Three ^{117}Sn Dose Groups. The Data is Summarized as Mean ± Standard Deviation (SD)

Parameters	Dose	PT	1mo	3mo	6mo	9mo	12mo
Sample size	HD	8	7	8	8	8	4
	MD	5	5	5	5	3	3
	LD	6	6	6	6	4	2
[‡]PVF $_{Treated}$	HD	9.3 ±1.5	9.8 ±2.1	10.4 ±1.8* p = 0.0301	10.2 ±1.4 p = 0.0655	10.4 ±1.2* p = 0.0262	9.2 ±0.9
	MD	9.9 ±3.3	10.4 ±3.7	9.9 ±3.6	9.6 ±2.6	10.9 ±1.4	10.0 ±1.4
	LD	9.7 ±1.7	9.7 ±1.0	10.1 ±1.4	10.4 ±2.0	9.3 ±2.5	10.7 ±0.5
[‡]PVF $_{Untreated}$	HD	11.2 ±0.8	11.0 ±1.5	11.3 ±1.3	11.3 ±1.0	11.3 ±1.0	10.3 ±1.5* p = 0.0244
	MD	10.8 ±1.8	10.9 ±3.0	10.2 ±1.6	9.5 ±2.2	11.3 ±2.5	9.8 ±0.9
	LD	10.8 ±1.6	10.6 ±1.8	11.3 ±1.5	11.0 ±2.1	10.3 ±2.5	10.7 ±0.4
BW-D %	HD	45 ±3	47 ±7	48 ±6 p = 0.0872	47 ±3	48 ±3 p = 0.0592	47 ±4
	MD	47 ±7	48 ±5	47 ±9	50 ±2	49 ±2	50 ±2
	LD	47 ±4	48 ±3	47 ±2	49 ±1	47 ±3	50 ±2

Notes: *Significant difference compared with pretreatment values. [‡]PVF reported as N/kg. [†]In 1 dog from the MD-group, baseline force-plate data for the treated leg was missing and this dog died secondary to GDV, so there was no follow-up available after its 3-month evaluation; in 1 dog from the LD-group, five successful repeatable trials during force-plate data collection at time of baseline could not be obtained. These 2 dogs were not included in the force plate data analysis.
Abbreviations: HD, high dose; MD, medium dose; LD, low dose; PT, pretreatment; PVF, peak vertical force; BW-D %, body weight-distribution %.

systemic NSAIDs, glucocorticoids, and local joint therapies such as corticosteroid and hyaluronic acid injections prior to RSO.[37] However, in patients that either respond poorly or have adverse side effects following these traditional therapies, RSO is a useful option that should now be considered in veterinary medicine. Traditional veterinary arthritis therapies when successful are oftentimes less costly than RSO using homogeneous tin colloid (^{117m}Sn). It can become costly when these initial traditional therapies cannot successfully manage elbow osteoarthritis and alternatives such as stem cell or platelet-rich plasma therapies are considered. The treatment in our study was evaluated specifically to manage canine arthritic elbows because oftentimes traditional veterinary arthritis therapies are not successful in dogs with elbow OA.[1,2,4,9–12]

The patients in this study were treated with homogeneous tin colloid (^{117m}Sn) containing microparticles (diameter 1.5 to 20.0 microns) of the radioisotope tin 117m (^{117m}Sn). These microparticles when injected into a joint are engulfed by intra-articular macrophages, which are killed by apoptosis due to the tin 117m conversion electron (CE) radiation.[41] Admittedly, we had limited short-term evaluation for any adverse effects related to ^{117m}Sn injection. The absence of any adverse effects in the present study and in a previous experimental study, is most likely due to unique characteristics of ^{117m}Sn.[23,25,26] Tin 117m emits abundant conversion electrons, low-energy particles with a short, non-diminishing penetration range of approximately 300μm in tissue. Other radionuclides that emit beta particles result in variable tissue penetration and can result in damaging irradiation of adjacent non-target tissues.[20] ^{117m}Sn has a ½ life of nearly 14 days, providing an ideal duration of effect spanning several ½ lives to achieve therapeutic results and to enable short-term stability during storage and handling. Studies in rats and colony bred dogs have confirmed the safety of structures within the joint (cartilage, bone) and adnexal structures following IA injection with homogeneous tin colloid (^{117m}Sn).[23,26] In addition to conversion electrons, ^{117m}Sn emits γ radiation, which is non-therapeutic but readily detectable by scintigraphy. In humans, the risk of infection after IA RSO is very small (1:35,000) and septic arthritis is uncommon.[20] Similarly, none of the dogs in our study developed any infection related to ^{117m}Sn IA injection. Overall, in humans RSO has very low rate of adverse effects.[41] Joint flare ie more pain and joint effusion due to intensification of inflammation (radiosynovitis) within 2–4 weeks after RSO is the most common adverse effect.[20] This may be considered a natural course of the treatment due to rapid and extensive synovial necrosis when using higher energy beta-emitters. In humans, the joint flare from radiosynovitis is the main reason

Table 5 Dog Number, ^{117m}Sn Dose Group, and Treatment Outcome in 19 Dogs Undergoing Force-Plate Analysis

Dog No. (Number of Follow-Up Visits)	117mSn Dose Group	Treated: % of Follow-Up Visits Indicating Positive Response	Untreated: % of Follow-Up Visits Indicating Positive Response	Treatment Outcome[a]
1 (5)	HD	40%	0%	PR
2 (5)	LD	0%	40%	no PR
3 (5)	HD	40%	0%	PR
4 (5)	HD	20%	20%	PR
5 (3)	MD	33%	0%	PR
6 (5)	MD	80%	0%	PR
7 (3)	LD	33%	0%	PR
8 (5)	MD	40%	40%	PR
9 (5)	LD	40%	0%	PR
10 (3)	MD	0%	33%	no PR
11 (4)	HD	75%	75%	PR
12 (3)	LD	100%	67%	PR
13 (4)	LD	25%	25%	PR
14 (4)	HD	100%	0%	PR
15 (4)	HD	50%	0%	PR
16 (5)	HD	100%	100%	PR
17 (3)	HD	100%	0%	PR
18 (4)	LD	25%	25%	PR
19 (5)	MD	60%	80%	PR
Total 19 dogs	8HD 5MD 6LD			PR = 17/19
		Number of dogs showing positive response for 1 time point: HD (8/8) = 100% (67.6–100) MD (4/5) = 80% (37.5–96.4) LD (5/6) = 83.3% (43.6–97)	Number of dogs showing positive response for 1 time point: HD (3/8) = 37.5% (13.7–69.4) MD (3/5) = 60% (23.1–88.2) LD (4/6) = 66.7% (30.0–90.3)	
		Number of dogs showing positive responses for 2 time points: HD (7/8) = 87.5% (52.9–97.8) MD (3/5) = 60% (23.1–88.2) LD (2/6) = 33.3% (9.7–70.0)	Number of dogs showing positive responses for 2 time points: HD (2/8) = 25% (7.1–59.1) MD = 2/5 = 40% (11.8–76.9) LD (2/6) = 33.3% (9.7–70.0)	

Notes: [a]Positive response in the individual dog was defined as ≥ 5% increase in mean PVF at a single time point in the treated leg at months 1, 3, 6, 9, and/or 12, compared with baseline.

Abbreviations: LD, low dose; MD, medium dose; HD, high dose; PR, positive response.

Table 6 Radiographic OA Scores for Treated and Untreated Elbows for Study Dogs with Elbow OA at Pretreatment and at 12-Month Recheck. The 12-Month Radiographs Were Available for 18 Dogs

	PT Median (Range)	12-Month Median (Range)	P value for Comparing OA Grade at PT and 12-Month Time Points	P values for Comparing Progression of OA Between T and UT Elbows
OA score for T elbow	1 (1–2)	2 (1–3)	0.0010	0.726
OA score for UT elbow	1 (0–2)	2 (0–3)	0.0039	

Abbreviations: T, treated leg; UT, untreated leg; PT, pretreatment; OA, osteoarthritis.

to consider co-injection of steroids. Routinely steroids are co-injected into large joints (shoulder, knee, and hip) because radiosynovitis is common in these joints.[20] Even though canine joints are much smaller than human joint but this should be taken into consideration in dogs also in future studies involving RSO of these large joints.

Both PSS and PIS significantly improved at all time points except for PSS at 10 months and for PIS at 10 and 11 months which were not statistically significant compared to baseline, but these scores were still improved compared with baseline. A caregiver placebo effect may have played a role in improvement of CBPI as this effect has been shown to occur approximately 57% of the time for pet owners evaluating their dogs with lameness from osteoarthritis.[34] In addition to this a lack to control group makes this measure less ideal compared to force plate gait analysis to determine outcome. However, it would be implausible to expect a placebo effect to persist for the 1-year duration of the study. In addition, the CBPI has been shown to allow reliable quantification of the owners' assessment of the severity and impact of clinically relevant chronic pain-related behaviors with the dog in its normal environment.[28,29] The QoL item (poor, fair, good, very good, excellent) is a stand-alone item and is used initially as a criterion validity assessment in the validation of the severity and interference scores.[35] It takes very large changes in pain scores to elicit a change in the QoL category, which could be a potential reason why we did not see any significant improvement in this category.[35] In future studies, QoL as an outcome measure should be better approached with a global assessment of change over time (ie, much worse, worse, same, better, much better).

Goniometry is an economic and simple measurement of joint angles used to objectively assess joint function.[42] Mean elbow extension improved by 7 degrees at 6-month and by 10 degrees at 9-month follow-up time point in the treated elbow in the HD-group. However, mean elbow extension also increased in the untreated leg by 7 degrees at 9 months in the HD group and by 8 degrees at 6 months in the MD group. Therefore, our results indicate that there was no significant difference in this outcome measure between treated and untreated elbows.

The force-plate gait analysis is an established objective gold standard for quantification of leg function and pain in dogs with appendicular joint OA.[29] It is considered to provide an accurate and unbiased assessment. However, without a placebo treatment group, we are unable to know if other external factors influenced the dogs in a way that may have resulted in improved leg function. A caregiver placebo effect as mentioned above does not exist for appropriately acquired force plate gait analysis. In addition, in a randomized, blinded, placebo-controlled cross-over study where every dog received tramadol or carprofen or placebo during the study period, the authors found no change in PVF over a 10-day period in the placebo group.[33] Additionally, in our study the untreated opposite leg served as a source of comparison data. The improvement noted in PVF in our study is larger than what has been previously reported.[29,32,33]

One of the limitations of this pilot study was a small sample size. Another limitation was the lack of a placebo or control group; however, OA is a progressive disease. The lack of any therapy for osteoarthritis would not have been acceptable for an ethical committee for running a control group for up to 1 year. While using client-owned dogs is a strength of the study, it is also a limitation. Studies of naturally occurring OA in dogs are associated with potential confounding factors, such as the potential for owner errors in study compliance and variations in the home environment. However, this is the environment in which the agent will be used and assessed by veterinarians and owners. Dogs were allowed to continue previous medical management (NSAIDs or other analgesics) during the study. It is possible that use of these medications could have biased our results. Ideally, dogs would have all been taken off of medical management and undergone a washout period before enrollment. The authors elected to allow dogs to be continued on any previous medications for multiple reasons: to avoid increasing pain should the IA injection fail to control pain, to provide pain control in the untreated leg, to allow the study to be clinically relevant, and for the study to be reflective of the general canine population with OA. Future studies might include more stringent exclusion criteria. We focused on the elbow joint for consistency; it would be interesting to know the effects of this treatment on other arthritic joints.

The safe use of any radioisotope requires documented training by veterinarians and support staff. There is a recommended licensing, treatment and post-treatment caretaker instruction process published by the US Nuclear Regulatory Commission for the safe use of ^{117m}Sn in the US.[43] Unlike I-131 and Tc 99m radiation quarantine is not indicated for ^{117m}Sn as it is not excreted in any appreciable amount. Instead, ^{117m}Sn is retained within the joint and is

eventually cleared by the lymphatics to the liver as microparticles of inert (nonradioactive) tin.[23,25,26] However, there are gamma emissions that must be measured at 1 meter post treatment to determine the amount of interaction with a patient by household members. All household members are to monitor and follow their interactions within 3 feet (from treated joint(s) to center of torso) prescribed by written instructions for 2 weeks. For dogs in which there is an extended close association (sleeping in the same bed, sitting beneath an occupied office chair or in one's lap > 4 hrs daily) there could be a longer period of abstaining from these behaviors for up to 4–6 weeks following ^{117m}Sn radiosynoviorthesis.[43,44] All patients can return to normal activities and interactions with anyone beyond 3 feet immediately post treatment.[43,44]

Clinical response to RSO is usually expected to have some "lag phase" that can last from weeks to months.[20] In humans, the effect in the knee is seen as soon as 4 weeks.[20] In the current study, improvement was noted in dogs at 1-month evaluation, similar to humans. In humans, the full therapeutic impact of RSO can take 4–6 months and duration of response depends on already existing joint damage.[20] Similarly in our study full therapeutic effect as shown by significantly improved objective measurements such as PVF (and improvement in BW-D% approaching significance) was achieved at 3 months post treatment. Advanced-stage OA and pre-existing joint damage are negative outcome predictors of RSO in humans.[45] Thus, the best responders would be patients with limited joint damage or the patients with large amounts of inflammation/effusion rather than advanced degenerative changes. Our study population included dogs with mild to moderate (grade 1 to 2) degree of OA and, as in human studies, a good clinical response was noted. Future studies in dogs with advanced OA are indicated to evaluate the effects of IA ^{117m}Sn in those cases.

In conclusion, IA injection of ^{117m}Sn improved CBPI scores and increased weight-bearing associated with elbow OA, providing preliminary evidence that ^{17m}Sn is beneficial in the management of elbow OA in dogs. This localized therapy with protracted results can be considered as an adjunct to other nonsurgical or surgical treatments or as a stand-alone therapy for elbow OA and might be useful for patients that cannot tolerate traditional OA medications such as NSAIDs. Although ^{17m}Sn appeared to be effective for the treatment of elbow OA, this pilot study has inherent limitations; therefore, future studies with larger numbers of dogs and with placebo group are needed.

Ethics Statement

The study protocol was approved by Institutional Animal Care and Use Committee (Protocol #16-008) and the Radiation Safety Office of the Louisiana State University (site A) and Medical Director Board and Radiation Safety Committee of Gulf Coast Veterinary Specialists (site B). All dogs were client-owned and written consent was obtained before study enrollment. This study adhered to veterinary care best practice guidelines.

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Disclosure

Dr Andrews reports grants from Exubrion Therapeutics, during the conduct of the study. Dr Lattimer reports grants from Exubrion Therapeutics, during the conduct of the study. Dr Lattimer, however, had a career long interest in therapeutics of this type and has participated in privately and publicly funded work that employs radiopharmaceuticals and devices. None of this work has been done in the last several years except that associated with the parent project to this work. The study was funded by Exubrion Therapeutics, Buford, GA, USA. Drs. Aulakh, Hudson, and Fabiani are advisory board members for Exubrion Therapeutics and receive a small honorarium for consultation. All authors declare no other conflicts of interest related to this report.

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