Article

A randomized blind placebo-controlled trial investigating the effects of photobiomodulation therapy (PBMT) on canine elbow osteoarthritis

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Abstract — The effect of photobiomodulation therapy (PBMT) or sham light therapy on pain, nonsteroidal anti-inflammatory drug (NSAID) requirement, and lameness was studied in 20 dogs with naturally occurring elbow osteoarthritis. Dogs (n = 20) were randomly assigned to receive either PBMT (group PBMT; n = 11) 10 to 20 J/cm^2 or a placebo treatment (sham light group S; n = 9) treatment 0 J/cm^2, to both elbows for 6 weeks. Lameness score, pain score, and NSAID dose were recorded by blinded study personnel before and 7 to 10 days after last treatment. Reduction in NSAID dose occurred in 9/11 dogs in the PBMT group, and in 0/9 of group S dogs (P = 0.0003). There was greater improvement in lameness score post PMBT *versus* S therapy (P = 0.001). A greater reduction in pain score was detected in 9/11 parameters in group PBMT ($P < 0.05$). Regularly scheduled PBMT at 10 to 20 J/cm^2 per joint for 6 weeks was successful in improving lameness and pain scores, and in lowering NSAID requirement in canine elbow osteoarthritis patients.

Résumé — Essai clinique randomisé à double insu examinant les effets de la thérapie par photobiomodulation (PBMT) en comparaison à un placebo pour le traitement de l'ostéoarthrite du coude canin. Les effets de la thérapie par photobiomodulation, PBMT (anciennement thérapie au laser froid, thérapie au laser de basse énergie, ou LLLT, abréviation anglaise) ont été évalués et comparés à un placebo lumineux chez 20 chiens souffrant d'ostéoarthrite bilatérale du coude. Les chiens (n = 20) ont été assignés aléatoirement au groupe recevant le traitement au laser (PBMT; n = 11), ou à celui recevant le traitement placebo (S; n = 9). Les deux groupes ont été traités à double insu pendant 6 semaines, recevant soit 10 à 20 J/cm^2 (groupe PBMT) ou 0J/cm^2 (S) pendant 3 à 5 minutes sur chaque coude. Avant (pré) et 7 à 10 jours après chaque traitement (post), la fréquence d'administration et le dosage d'anti-inflammatoire non stéroïdien (AINS), le degré de boiterie, évalué par un clinicien, ainsi que le degré de confort selon l'index d'Helsinki pour la douleur chronique, évalué par le propriétaire, ont été notés. Une réduction du besoin en AINS a été possible chez 9 des 11 chiens du groupe PBMT, tandis qu'aucun chien du groupe S n'a pu réduire sa consommation de médicament (P = 0,0003). Les grades de boiterie se sont améliorés de façon plus marquée chez le groupe PBMT que chez le groupe S (P = 0,001). Il en va de même pour l'index d'Helsinki chez le groupe PBMT pour lequel les propriétaires ont remarqué une amélioration du confort de leur animal pour 9 des 11 paramètres évalués ($P < 0,05$). Ces données suggèrent qu'un traitement au laser pour 6 semaines à un dosage de 10 à 20 J/cm^2 a un effet bénéfique pour les chiens atteints d'ostéoarthrite bilatérale du coude en améliorant leur niveau de boiterie et de confort en plus de diminuer leur besoin en AINS.

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Introduction

Osteoarthritis (OA) is a major cause of debilitation and euthanasia in older dogs. Elbow osteoarthritis is a common sequela to elbow dysplasia, which includes ununited anconeal process (UAP), medial compartment disease (MCD), or medial coronoid process disease (MCPD), osteochondritis dissecans (OCD), and joint incongruity. Medical, interventional, and surgical therapies have been studied, described, and debated (1). As regenerative medicine elucidates more paths to long-term treatments, symptomatic therapy appears to be an important pillar for lameness and pain management.

Photobiomodulation therapy (PBMT), historically referred to as low-level light therapy, low-level laser therapy, or LLLT, is the use of red/near infrared light to stimulate healing, provide analgesia, and reduce inflammation. Cellular targets absorb specific wavelengths of light, initiating intracellular processes that create biologic effects. Photobiomodulation therapy is used within physiotherapy to modulate tissue function without creating a thermal effect (unlike surgical lasers); it is painless, non-invasive, and can be administered in primary care settings (2).

Photobiomodulation therapy mechanisms focus on chromophore cytochrome C oxidase, the terminal enzyme of the mitochondrial electron transport chain. Other chromophores exist in ion channels, opsins, flavins, flavoproteins, interfacial water, and even heat gated ion channels (3). Earlier work proposed reactions which shifted cellular redox potential and *via* mitochondrial signaling affected gene expression, DNA and RNA synthesis (4).

Photons dissociate inhibitory nitric oxide from the cytochrome C oxidase, increase electron transport, mitochondrial membrane potential, and ATP production (5). Light-sensitive ion channels (TRPV1) are activated *via* reactive oxygen species. Changes in cyclic AMP, NO, and $Ca^{2}++$ activate transcription factors (6). Expression of genes results in protein synthesis including anti-apoptotic proteins and antioxidant enzymes, causes cell proliferation and migration, and anti-inflammatory signaling (7). Stem cells and progenitor cells appear to be particularly susceptible to LLLT (8). These changes translate into various tissue effects including wound healing, arthritis, muscular pre-performance enhancement post-injury myopathy (9), bronchial hyperresponsiveness (10), neuropathic pain, traumatic brain/spinal cord injury, and stroke (11).

Clinical results of PBMT depend on parameters of irradiation (irradiance, wavelength, and coherence; Table 1) and light dose (energy, density, time, and interval; Table 2) (2,3,7). If the parameters are less than optimal, a negative therapeutic outcome or a less effective treatment may result. Because PBMT results in a biphasic response wherein lower doses may be more effective than higher doses in some applications (12), there appears to be an optimal dose for each clinical application. Studies using PBMT for human chronic musculoskeletal pain have shown greater effectiveness with treatments delivering higher power densities/irradiance (W/cm^2) and with increase in regularity of treatments (13). Effective wavelengths fall into the "optical window" of 600 to 1070 nm; lower wavelengths (600 to 700 nm) treat superficial tissues and higher wavelengths (780 to 950 nm) treat deeper tissues.

Table 1. Irradiation dose parameters (7).

Irradiation parameter	Irradiation parameters	
	Measurement unit	Description
Wavelength	nm	Therapy lasers operate predominantly in the 700 to 1000 nm range.
Irradiance	$Watts/cm^2$	Also known as intensity or power density, irradiance is the power per cm^2.
Coherence	Spectral bandwidth determines coherence length.	Laser speckle is produced by coherent light. Coherence is important in photobiomodulation interaction with organelles and cells.

Table 2. Light dose parameters (7).

Irradiation parameter	Measurement unit	Description
Energy	Joules (J)	Energy (J) is calculated as: power (W) × time (s).
Energy density	$Joules/cm^2$	Most laser dosages are given in this unit but this could be unreliable as it assumes a reciprocity relationship between time and irradiance.
Irradiation time	Seconds	This is the time to deliver the appropriate energy density.
Treatment interval	Hours, day, or weeks	Different time intervals may result in different outcomes.

Meta-analyses reveal good evidence for PBM effectiveness in treating human rheumatoid arthritis and human knee osteoarthritis (14). There is no randomized, blind, controlled study of PBMT's effect in veterinary patients with osteoarthritis. In this multicenter study, the effect of PBMT or sham light therapy on pain and lameness caused by naturally occurring elbow OA in dogs was studied.

Materials and methods

Study population

This was a multicenter randomized controlled prospective clinical study that was approved by the Clinical Studies Advisory Committee of Ethos Veterinary Health (Woburn and Andover, Massachusetts) and Essex Animal Hospital (Essex, Ontario). All owners received a detailed written description of the study, an explanation of PBMT, and owner consent was obtained for enrollment. Study populations consisted of 20 dogs from the Massachusetts Veterinary Referral Hospital (n = 3), Bulger Animal Hospital (n = 11), and Essex Animal Hospital (n = 6) having elbow OA.

Inclusion criteria included naturally occurring unilateral or bilateral elbow degenerative joint disease, age 2 to13 y, physical examination findings of reduced range of motion and/or pain on extension or flexion of the elbow joint, and radiographs or computed technology examination supporting OA. Dogs would be on nonsteroidal anti-inflammatory drugs (NSAIDs) for > 1 wk, have normal complete blood (cell) count (CBC) and serum chemistry, normal thyroid status, and negative tick serology, no comorbidities, and may have had prior arthroscopy/arthrotomy

of the joints. Use of nutraceuticals (such as glucosamine/chondroitin supplements or omega-3 fatty acids) and other analgesic medications (adequan, tramadol, or gabapentin) was permitted as long as the patient had been receiving these for > 1 wk before entry in the study; doses of these medications could not change throughout the study. Dogs were excluded if they received any elbow joint injections, oral steroids, or opioids orally within 4 wk of start, had clinical neurologic disease or other significant orthopedic disease (such as stifle osteoarthritis), had a history of trauma, nondegenerative elbow disease, or any evidence of neoplastic or systemic disease detected during screening which could confound outcomes.

Randomization

Following a baseline blinded clinician lameness score (15), owner assigned Helskinki Chronic Pain Index score (16), and NSAID frequency/dose recording, dogs were randomly assigned to active laser therapy (group PBMT) or to receive sham laser therapy (group S) *via* a coin toss.

Equipment

Two laser units (CTC-12, Companion Animal Health; LiteCure, Newark, Delaware, USA) were used. The performance/output of all visible and audible indicators of both groups were identical. The only difference was the emission (PBMT) or lack thereof (S) of near infrared light (NIR), capable of a therapeutic effect. The PBMT system used a 12 W gallium aluminum arsenide diode laser emitting 980 nm wavelength light and visible 3.5 mW aiming beam of 650 nm in a continuous wave (CW) form. The S system emitted only the 650 nm wavelength of light. Before initiation and after completion of the study, the output of all units was verified to be within specifications.

Baseline assessments

Patient signalment, dose of all medications (NSAID type, dose frequency), presence of unilateral or bilateral lameness, BCS (body condition score based on a scale of 1–9) (17), weight, and laser unit used (signified laser unit A or B to allow blinding) were recorded. For the **lameness score,** the dogs were walked on a leash for a blinded peer clinician to assign a numerical lameness score according to previous studies (15). If dogs had bilateral elbow disease, lameness was graded on movement of worse forelimb. A score of 0/5 indicated a normal gait with no lameness and a score of 5/5 indicated a severe non-weightbearing lameness at a walk. For **pain score,** owners completed the Helsinki Chronic Pain Index (16). In this questionnaire, several daily life functions (such as attitude, mood, vocalization, ability to rise, run, sleep) were graded on a scale of 0 to 4 most representative of the dog's behavior within the task. In general, lower scores (0 to 1) represented more positive outcomes while higher scores (2 to 4) represented progressively more negative outcomes. Dogs were then randomized into groups to which owners were blinded as confirmed in the consent form.

Treatment schedule

Dogs began twice weekly treatments by blinded technicians at a fluence of 10 to 20 J/cm^2 (using 5 to 10 W power) for PBMT or 0 J/cm^2 to each elbow (regardless of unilateral or bilateral disease). Fluence and radiant power increased incrementally within the range of 10 to 20 J/cm^2 for increasing weight (Table 3). After 3 wk, owners were instructed to reduce NSAID dose by half (frequency constant) and treatments occurred weekly for 3 wk. Owners were queried weekly (by blinded office personnel or technical staff) as to the overall status of the dog (activity, appetite, attitude, mobility, focus on area or limb/foot, and "normality" of life). If the dog's condition was perceived to have worsened, owners could return the NSAID to the original dosage. If the dog was perceived to be in acute or severe pain (lethargy, reluctance to move, overt protectiveness of area, disengagement from normal routine), "rescue" medications (e.g., injectable or oral opioid, intra-articular injection) were administered and the patient was removed from the study. If the dog was static or improved, it remained on the reduced NSAID dose. At the end of the study, the blinded clinician lameness score and Helsinki chronic pain index were obtained; final NSAID type, dose, and frequency were again noted.

Technique of administration and dosage of photodynamic therapy

Protective eyewear was required for treatment sessions. Dogs remained in lateral recumbency allowing treatment of lateral upper elbow and medial lower (prone) elbow. Recumbency was changed and the procedure was repeated on the remaining sides of each elbow. If the animal had excessively long hair, application of a light spray of water to the treatment areas reduced excessive surface heat.

The cumulative fluence delivered to each elbow (10 to 20 J/cm^2) was achieved using 5 to 12 W of power (1 to 2.4 W/cm^2 irradiance dependent on size of dog) delivered at the skin's surface. Doses ranged from 10 J/cm^2 for the smaller dogs (4.5 to 9.0 kg) to 19 J/cm^2 for the larger dogs (> 45 kg). Treatment times ranged from 4.5 to 8 min depending on the size of the patient, total joules for target fluence, power used, and comfort level of the treatment for the patient. For the largest patient, increased power settings resulted in more heat perception during treatment, thus, to reduce this mild discomfort, the power setting was reduced but time of delivery increased to ensure appropriate fluence.

The manufacturer's recommendations were to treat using direct contact of the treatment head; however, due to often painful surfaces with boney prominences, therapy was applied with the hand piece held off the dermis by < 1/2 cm. The aiming beam and head were moved primarily over craniomedial and caudolateral elbow compartments (rate of 2.5 to 7.6 cm/s) using a circumferential alternating proximal to distal movement.

Analysis of data

Pre- and post-treatment lameness scores (15), Helsinki pain index/score (16), and NSAID type dose and frequency were obtained for each dog. Attempts at NSAID dose reduction were treated as a binary outcome ("successful" defined as dogs in which NSAID could be reduced by 50% or more, or "unsuccessful" defined as dogs in which dose could not be reduced, was

Table 3. Photobiomodulation (PBMT) dosage used based on patient weight.

Patient weight range (kg)	Area per elbow (medial and lateral combined) (cm^2)	[a]Dose applied (J/cm^2)	Power (W)	Total joules applied per patient (2 elbows)
0 to 9	125	11	5	1350
9.5 to 18	150	12	5	1800
18.5 to 27	200	13	7	2520
27.5 to 36	250	17	9	4320
36.5 to 45	300	18	10	5400
> 45	350	19	12	5760

[a] Energy density (fluence) is rounded to the nearest whole number.

Table 4. Population demographics for each treatment group of patients.

Group	Breed	Gender	Age (y)	Lameness site	BCS	Body weight (kg)
PBMT	Chow	FS	5.7	L	7	33
	Sheepdog	MN	12.7	B	6	44
	Labrador	MN	9	R	6	37
	Labrador	MN	12.3	R	7	47
	Doberman	M	9.5	B	7	38
	Labrador mix	MN	6.5	B	6	32
	Puggle	MN	6.8	B	5	32
	Great Dane	M	4	B	8	56
	Cocker spaniel	FS	5.6	B	9	13
	Greyhound X Labrador	MN	7.3	R	8	41
	Golden doodle	FS	3.7	L	6	27
Sham	Shepherd mix	FS	7	B	6	41
	Labrador	FS	8.2	L	6	29
	Bull terrier mix	MN	6.3	B	6	27
	Labrador mix	MN	10	R	8	34
	Malamute	MN	6.5	B	7	41
	Dalmation	FS	8.4	L	4	28
	Shepherd	FS	4.2	B	6	38
	Mastiff	MN	4	L	8	43
	Labrador mix	M	2.3	L	5	27

FS — spayed female; M — intact male; MN — neutered male; BCS — body condition score (1 to 9)/9.

reduced by less than 50%, or required an increase or change to another NSAID).

The person carrying out statistical analysis (SM) was blinded to treatment allocation coded as laser units "A" and "B." Analysis was carried out with the software JMP (v.12.0.1.; SAS Institute, Cary, North Carolina, USA). Differences between treatment groups for continuous outcomes (age, weight) were analyzed with non-parametric Wilcoxon rank-sum and Fisher's exact tests for differences in BCS, lameness site, dose reduction, gender, and breed. To account for the paired nature of the non-normally distributed lameness and Helsinki pain scores, differences from baseline after treatments were computed first and then analyzed using the Wilcoxon rank-sum test. Results were frequency (%) for categorical variables (successful dose reduction by at least half), and median/ range for continuous, non-normally distributed outcomes (lameness and Helsinki pain index scores).

Results

Population demographics

Differences in population variables are given in the following paragraphs as frequency (%) for categorical variables (BCS, lameness site, gender, and breed) and as median and range for continuous outcomes (weight, age, and treatment dose).

The distribution of BCS scores was not different among groups: group PBMT had 1 (9%), 4 (37%), 3 (28%), 2 (18%), and 1 (9%) dog with BCS scores 5, 6, 7, 8, and 9, respectively, and group S had 1 (11%), 1 (11%), 4 (45%), 1 (11%), and 2 (22%) dogs with BCS scores 4, 5, 6, 7, and 8, respectively ($P = 0.92$). Gender distribution was as follows: 3 (27%) female spayed, 2 (18%) male, and 6 (55%) male neutered dogs in group PBMT, and 4 (44%) female spayed, 1 (11%) male, and 4 (44%) male neutered dogs in group S ($P = 0.54$). Eleven dogs were treated in group PBMT, 6 (55%) affected bilaterally, 2 (18%) affected in the left only, and 3 (27%) in the right only. Nine dogs were treated in group S: 4 (44%) of those affected bilaterally, 4 (44%) affected left only and 1 (11%) affected right only. The median (range) weight was 37.0 kg (12.7 to 56.0 kg) in group PBMT and 33.7 kg (26.7 to 43.0 kg) in group S ($P = 0.54$). The median (range) age was 6.8 y (3.7 to 12.7 y) in group PBMT and 6.5 y (2.3 to 10 y) in group S ($P = 0.54$). One dog in group PBMT had a prior arthroscopy at ~8 mo. One dog in each of the PBMT and S groups was on tramadol throughout the study, 1 dog in Group S was on monthly Adequan injections, and 2 dogs in the PBMT and 1 dog in the S group were on glucosamine/chondroitin supplements. No doses of any of these medications/supplements changed. Table 4 shows the population demographics.

Table 5. Results for nonsteroidal anti-inflammatory dose reduction in PBMT and sham therapy groups.

Group	Breed	Pre-NSAID drug and dose (mg)	Post-NSAID drug and dose (mg)	Dose reduction
PBMT	Chow	meloxicam (3)	meloxicam (1.5)	yes
	Sheepdog	meloxicam (4.5)	meloxicam (4.5)	no
	Labrador	meloxicam (3.5)	meloxicam (0)	yes
	Labrador	meloxicam (4)	meloxicam (2)	yes
	Doberman	firocoxib (227)	firocoxib (113)	yes
	Labrador mix	carprofen (200)	carprofen (50)	yes
	Puggle	meloxicam (2)	meloxicam (0)	yes
	Great Dane	carprofen (100)	carprofen (25)	yes
	Cocker spaniel	firocoxib (55.7)	firocoxib (0)	yes
	Greyhound × Labrador	carprofen (150)	carprofen (75)	yes
	Golden doodle	firocoxib (55.7)	firocoxib (55.7)	no
Sham	Shepherd mix	carprofen (75)	carprofen (75)	no
	Labrador	carprofen (75)	carprofen (75)	no
	Bull terrier mix	carprofen (50)	carprofen (100)	no
	Labrador mix	aspirin (325)	carprofen 100)	no
	Malmute	aspirin (325)	carprofen (50)	no
	Dalmation	meloxicam (3.3)	meloxicam (3)	no
	Shepherd	firocoxib (227)	firocoxib (227)	no
	Mastiff	carprofen (100)	carprofen (100)	no
	Labrador mix	firocoxib (113)	firocoxib (227)	no

The median (range) therapeutic light was 18 (12 to 19.2 J/cm^2) in group PBMT, and 0 J/cm^2 in group S. Note that for group S, the actual dose of light delivered was 0 J/cm^2 despite a dose of 17.3 J/cm^2 (12.7 to 18 J/cm^2) visibly registering on the sham unit in order to assure blindness in the technician treating the patient.

Treatment effect

A dose reduction by at least 50% of the original NSAID dose occurred in 82% (9 of 11) PBMT dogs, and in 0% (0 out of 9) of the S dogs ($P = 0.0003$). Dose reduction was not successful for 2 dogs in the PBMT group and 9 in the S group. In group PBMT, the dose was reduced by $< 50\%$ for 1 dog, and stayed equal for another dog. In group S, it was not possible to reduce NSAID dosing throughout the study for 56% (5/9) of the dogs, 22% (2/9) of the dogs required increase in dose of NSAID, and 22% (2/9) of the dogs required a change from 325 mg aspirin per day to an alternative NSAID (150 and 50 mg carprofen) to manage their symptoms (Table 5).

Group PBMT showed a median change in lameness score by a decrease of 1 (range: -2 to -1) indicating overall improvement in gait; lameness score did not change in group S ($P = 0.001$). No patients experienced severe pain or required "rescue" medications necessitating removal from the study. A greater improvement in Helsinki pain score was detected in 9 of 11 parameters/daily life functions in group PBMT compared with group S ($P < 0.05$), with the exception of mood ($P = 0.20$) and vocal score ($P = 0.35$), which did not differ between groups before and after treatment (Table 6).

Discussion

In this study, regularly applied PBMT at 10 to 20 J/cm^2 per joint for 6 wk resulted in improved lameness and pain scores, and allowed a reduction in NSAID dose in dogs with naturally occurring elbow OA compared with similar patients receiving sham therapy. These results are consistent with studies examining PBMT effects in the human knee OA (18), experimental tendonitis in sheep (19), and canine cruciate repair pain (20).

Limitations of this study were our inclusion/exclusion criteria reflecting the clinical heterogeneity of elbow osteoarthritic canine patients, use of a small sample size including 1 patient with prior arthroscopy and several patients on pre-existing supportive therapies, inability to standardize pre-existing NSAIDs, possible biologic effects from the sham laser, outcome variables chosen, and alterations from manufacturer's guidelines in treatment of patients in both groups.

One patient in the PBMT group had had arthroscopy. Burton et al (21) saw no significant difference between arthroscopically and conservatively managed dogs. As such we felt justified including this patient. Osteoarthritis was bilateral in several patients, and although unilateral lameness would have reduced confounding variables, canine elbow OA is normally bilateral with unilateral lameness exhibited as the first sign in the degenerative process (1). Identifying truly unilateral disease would have required advanced diagnostic imaging not available in any of the study locations. Since pain management standards (22,23) require that clinical patients be managed for their pain, we did not feel that stopping the administration of any concomitant supportive medications would be ethical. Given that tramadol has been shown to have negligible analgesic effects (23,24) its contribution to analgesia was considered minimal.

Two patients in the S group used aspirin therapy as a treatment for osteoarthritis. Aspirin's analgesic efficacy is supported in the literature (25); however, the 2 patients on aspirin showed signs of decline (increased moderate lameness in 1 patient and overall reduced activity in another) and subsequently were switched to an FDA-approved NSAID (carprofen) because of our inherent trust in the latter. This indeed could have added to inability to reduce NSAIDs given both owners perceived the

Table 6. Clinician lameness scores and Helsinki pain scores immediately pre-treatment (pre-tx), post-treatment (post-tx), and the difference between scores after treatment compared with pre-treatment scores by treatment group.

	[a]PBMT (n = 11)		[a]S (n = 9)		[b]Difference post-tx compared with pre-tx		
Item	Pre-tx	Post-tx	Pre-tx	Post-tx	PBMT	S	P-value[c]
[d]Clinician lameness score	3 (2 to 4)	1 (1 to 3)	3 (2 to 3)	3 (2 to 4)	−1 (−2 to −1)	0 (−1 to 1)	0.001
[e]Helsinki chronic pain index score							
Mood	2 (1 to 3)	1 (1 to 2)	1 (0 to 3)	2 (0 to 2)	0 (−2 to 1)	0 (−1 to 1)	0.20
Play	1 (1 to 3)	1 (0 to 2)	2 (1 to 4)	2 (1 to 2)	−1 (−2 to 0)	0 (−1 to 1)	0.05
Vocalization	2 (0 to 4)	2 (0 to 3)	1 (0 to 2)	2 (0 to 2)	0 (−1 to 1)	0 (0 to 1)	0.35
Walking	1.5 (1 to 3)	1 (0 to 2)	2 (1 to 3)	2 (1 to 3)	−1 (−2 to 0)	0 (−1 to 1)	0.01
Steps	2 (1 to 3)	1 (0 to 2)	3 (1 to 3)	2 (1 to 4)	−1 (−2 to 0)	0 (−2 to 1)	0.02
Running	2 (1 to 3)	1.5 (1 to 3)	2 (1 to 3)	2 (1 to 3)	−0.5 (−2 to 0)	0 (−1 to 1)	0.03
Jumping	3 (1.5 to 4)	1.5 (0 to 4)	3 (2 to 3)	3 (2 to 3)	−1 (−2 to 0)	0 (0 to 1)	0.01
Difficulty lying down	2 (1 to 4)	1 (1 to 2)	2 (0 to 3)	2 (0 to 3)	−1 (−3 to 1)	0 (−1 to 1)	0.04
Rising from down position	3 (1 to 4)	1 (0 to 4)	3 (2 to 3)	3 (2 to 4)	−1 (−2 to 0)	1 (−1 to 1)	0.003
Movement after rest	3 (1 to 4)	2 (0 to 3)	3 (2 to 3)	3 (1 to 4)	−1 (−3 to 0)	0 (−1 to 2)	0.006
Movement after exercise	2 (2 to 4)	2 (1 to 2)	2 (1 to 3)	3 (1 to 4)	−1 (−2 to 0)	0 (−1 to 2)	0.03

[a] Values given are median score followed by range (parentheses).
[b] Values noted are the median and range computed from each individual animal's change in score with negative signs denoting an overall decrease in score post-treatment.
[c] P-values derived from Wilcoxon rank-sum test.
[d] Lameness score criteria (from reference 15): 0 = clinically sound, 1 = barely detectable lameness, 2 = mild lameness, 3 = moderate lameness, 4 = severe lameness, 5 = non-weight-bearing lameness.
[e] Helsinki pain index (modified from reference 16): owners are asked to score on a scale of 0-4 how their dog rates in terms of mood, willingness to play, vocalization in the form of audible complaining such as whining or crying out, willingness to walk, willingness to ascend or descend stairs, willingness to run as in trot or gallop, willingness to jump as into/out of car or up to/down from sofa: ability to lay down, ability to rise from a down position, movement after rest, movement after major/heavy activity or exercise.
PBMT — photobiomodulation treatment; S — sham treatment.

pets improved and may have been less inclined to attempt dose reduction on the new NSAID.

Regarding NSAID "washout periods," pain management guidelines state that in case of an unsatisfactory response to an NSAID, changes may be warranted. However, providing time between administration of 1 NSAID before switching to another ("washout" period) has not been scientifically supported (23). Dowers et al (26) found no evidence that rapid switching between NSAIDs lead to problems in canine patients. The transition from aspirin to carprofen was done with caution as suggested in guidelines (23) and our 2 patients exhibited no signs of gastrointestinal illness, including reduced appetite, vomiting, or diarrhea.

We did not choose to standardize patients incoming or pre-existing NSAIDs for multiple reasons. First, in order for the study to be reflective of the general canine osteoarthritic population, a variety of NSAIDs was prescribed. Second, variation in drug response among individuals (27) does not scientifically support "standardizing" the population. Third, since all patients had entered the study on these medications prescribed by their referring veterinarians, changing medications (without patient decline) may have altered the referring veterinarian-specialist relationship and is generally not in the best interest of the patient or parties involved (28). There appears to be very little evidence for efficacy of one NSAID over another in treatment of canine OA (29).

Randomization was performed to evenly distribute dogs and to control both known and unknown confounding variables of which NSAID choice is one. In group PBMT, 0 (0%), 3 (27%), 3 (27%), and 5 (45%) dogs were treated with aspirin, carprofen, firocoxib, and meloxicam, while in group S, 2 (22%), 4 (44%), 2 (22%), and 1 (11%) dogs were treated with aspirin, carprofen, firocoxib, and meloxicam, respectively. The difference between the initial NSAID allocation was analyzed with Fisher's exact test for a P-value of 0.23. However, the small sample size may have hindered an even randomization. Future studies could consider a larger sample size with blocked enrollment of known confounders. Our study should be considered a proof of concept work that will create interest in larger population research in PBMT.

The term "sham" laser was used to describe the treatment delivered by the light unit which emitted 650 nm of visible light. However, this wavelength of light has been shown to produce a biologic effect (30). However, Anders et al (31), demonstrated no statistical difference in the mitochondrial metabolism of non-treated human fibroblasts *in vitro versus* fibroblasts treated with an aiming beam of this wavelength. Additionally, depth of penetration is related to both wavelength and power. Our sham aiming beam was a 3.5 mW 650 nm wavelength red light. While this beam may have had some effect on the skin surface, penetration to deeper tissues has been shown to be limited.

Further shortfalls of our study center on the outcomes analyzed. The blinded clinician evaluating lameness was a resident or a Boarded diplomat in most cases. For 2 cases, the clinician was an internship-trained emergency doctor in the specialty hospital system. Marques et al (32) noted no significant differences in overall lameness scores in horses reported by equine practitioners and specialists. Evaluation by a clinician throughout the study as opposed to only pre- and post-study may have altered results. However, NSAID reduction has been used as an objective outcome assessment in evaluation of many analgesic therapies including opioid use, loco-regional anesthesia, and nutraceutical and complementary therapies (33). Other objective outcome measures (such as gait or force plate analysis) would no doubt be beneficial in future studies.

Treatment parameters chosen could have contributed to differences between groups. Our treatment plan was based on

scientific principles, and *in vitro* and *in vivo* translation studies for dose optimization. Anders et al (2) showed that once a dose is established and optimized *in vitro,* it should be translated (dose extrapolated) and tested for transcutaneous administration through appropriate tissue depths based on patient size, tissue characterization, and target tissue being treated. Standard doses of 6 to 8 J/cm^2 prescribed for OA did not seem to alter the clinical course of the disease within our daily practice therapies. We surmised this may be due to the severity of OA in such weight-bearing joints as the elbows reflecting more neural and bone (*versus* joint) pathology. Meta-analyses from human medical literature have demonstrated that "higher" fluences and more frequent treatment regimens (34) were beneficial in reducing pain associated with neck, knee, lumbar spine, and temporomandibular disease. We therefore increased the fluences used in treating these dogs. Whether this dose is applicable for other diseases is unknown.

One patient in each group required a "light spray of water" to be applied over the lateral elbow coat before PBMT as per the manufacturer's suggestion, although it should be noted that topical and tissue water content may affect the distribution of laser fluence rate (35). The elbow joint incongruity and degree of pain, especially medially, also required that we deviate from manufacturer's directions of direct application of treatment head on skin, which may explain why higher fluences could be clinically useful in treating elbow OA. Penetration is also not uniform for all tissues. There is a general lack of knowledge in the veterinary literature regarding optimal dosage, treatment schedule, energy density, output, and wavelength of PBMT, all of which add to the heterogeneity of treatment. Our study included various breeds and body conditions (hence elbow sizes and anatomic variations), with variable initial severities of lameness. Some studies have failed to find PBMT effective for large joints, while the results for PBMT for smaller joints seemed to be more clinically positive. These factors may have contributed to differences between our treatment groups.

Within the veterinary literature, PBMT has been shown to accelerate time to ambulation in surgical dogs with myelopathy secondary to disc herniation (36), to improve peak vertical force in post-surgical cranial cruciate disease surgical repair (37) and to aid in healing of sterile granulomatous pododermatitis (38). It has also been determined to not accelerate wound healing in canine patients (39) nor improve recovery related variables when used alone or as part of a rehabilitation protocol for surgically treated intervertebral disc disease (40). Reasons for inconsistent results among studies might include an array of treatment parameters, delivery systems, and similar shortfalls as noted. It is important to examine the possible reasons for the varying results reported when critically evaluating the PMBT studies and outcomes in both veterinary and human literature.

Additional rehabilitative therapies such as low level strengthening exercises and modalities such as therapeutic ultrasound, or transcutaneous electrical stimulation would likely add to the improvement in our patients, as photobiomodulation is often used as a component of comprehensive pain management programs. Photobiomodulation therapy may present a non-invasive, cost-effective, low risk OA treatment option. The data presented provide a framework for future larger-scale research in PBM, and guidance regarding dosage, frequency, and outcomes for this very specific veterinary indication.

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