Original Article

Effectiveness of disease modifying osteoarthritis agents and carprofen for treatment of canine osteoarthritis

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Abstract

A prospective, randomized, single-blinded study was conducted to evaluate and compare the effectiveness of disease modifying osteoarthritis agents (DMOAAs) and carprofen by using force plate gait analysis and orthopaedic assessment score (OAS) in osteoarthritic dogs. Forty dogs with hip and/or stifle osteoarthritis (OA) were assigned randomly into four treatment groups: PCSO-524, treated with a marine-based fatty-acid compound; GC-ASU, treated with a combination of glucosamine-chondroitin sulphate and avocado/soybean unsaponifiables; CPF, treated with carprofen; and CPF-PCSO, treated with a combination of carprofen and PCSO-524. Each group received the therapeutic agent orally for four weeks. Peak vertical force (PVF), OAS, haematology and blood chemistry values were evaluated before treatment, and on the second and fourth weeks post-treatment. No significant effect was found in the PVF, OAS and blood values among the four treatment groups. Analyses within groups revealed significant increase in PVF among the PCSO-524, CPF and CPF-PCSO groups ($p < 0.05$). OAS showed significant decrease in the PCSO-524, CPF and CPF-PCSO groups ($p < 0.05$). Average BUN in the CPF group increased significantly ($p < 0.05$). PVF negatively correlated with OAS with $r = -0.39$ ($p = 0.014$), $r = -0.49$ ($p = 0.001$) and $r = -0.48$ ($p = 0.002$) before treatment and on the second and fourth weeks post-treatment, respectively. Even though increased PVFs were demonstrated within the PCSO-524, CPF and CPF-PCSO groups, the greatest improvement was demonstrated in the CPF-PCSO group. The preliminary results imply the clinical benefits of PCSO-524 in combination with carprofen in the treatment of OA.

Keywords: chondroitin, dogs, force plate, glucosamine, NSAIDs, PCSO-524

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Introduction

Osteoarthritis (OA) is considered one of the important causes of chronic pain in dogs, according to the United Kingdom practitioners' survey (Bell et al., 2014). Pathological changes leading to OA are the sequelae of the imbalance between synthesis and degradation of the cartilage matrix, and consist of cartilage degradation, synovial membrane inflammation, subchondral bone sclerosis and osteophyte formation (Burnett et al., 2006). Cartilage damage causes pain and inflammation. The end stage of OA may lead to disability. These painful condition and disability not only diminish patients' quality of life, but also increase the need for long-term medical care. Multimodal management of OA consists of medical therapy, weight reduction, nutritional management, rehabilitation and surgery (Perea, 2012).

Non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed commonly for the relief of osteoarthritic pain (Edamura et al., 2012; Ameye and Chee, 2006) and have been recommended as the treatment of choice for OA (Sanderson et al., 2009). NSAIDs exert their effects via inhibition of the cyclooxygenase (COX) pathway, which inhibits the synthesis of prostaglandin E_2 (PGE_2), which is a potent inflammatory mediator (Sanderson et al., 2009). Long-term use of NSAIDs has shown a better therapeutic effect than short-term use because of their ability to inhibit the apoptosis of chondrocytes by reducing nitric oxide (NO^-) synthesis (Innes et al., 2010), however it has been reported to induce some adverse effects in 2.6% to 34% of the canine patients (Roush et al., 2010). Disease modifying osteoarthritis agents (DMOAAs) such as glucosamine and chondroitin sulphate (GC), avocado soybean unsaponifiables (ASU) and the marine-based fatty-acid compound PCSO-524 may be able to reduce joint inflammation, slow cartilage degradation and promote the repair of articular cartilage (Wang et al., 2004).

PCSO-524 is a rich source of long-chain polyunsaturated omega-3 fatty acids (omega-3). It contains eicosatetraenoic acid (ETA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which promote reduction in leukotriene and prostaglandin production through lipooxygenase (LOX) and cyclooxygenase (COX) pathways. The compound is extracted from the New Zealand green-lipped mussel (*Perna canaliculus*) by a method that uses supercritical carbon dioxide (Wolyniak et al., 2005; Treschow et al., 2007). PCSO-524 may be a useful therapeutic agent to alleviate exercise-induced muscle damage and inflammation (Mickleborough et al., 2015) and potentially provide a therapeutic effect for OA patients (Zawadzki et al., 2013).

According to *in vivo* studies, the combination of glucosamine and chondroitin sulphate could prevent chemically induced synovitis, stimulate cartilage metabolism and inhibit cartilage degradation in dogs (Canapp et al., 1999; Johnson et al., 2001). ASU is the total fraction of unsaponifiables of avocado and soybean oils. ASU has shown a chondroprotective effect by preventing subchondral bone remodeling and resorption in dogs (Boileau et al., 2009). In addition, an *in vitro* study reported that the combination of GC and ASU could reduce PGE_2 production, which permitted a reduction in the dose of NSAIDs (Grzanna et al., 2011).

Currently, the effectiveness of OA treatment with GC, ASU and PCSO-524 is still controversial. In addition, there is no strong evidence to prove the advantages of using PCSO-524 alone, or PCSO-524 in combination with NSAIDs, for the treatment of OA in canine patients. There is a need for more randomized controlled trials, with unbiased patient evaluations, to prove the efficacy of DMOAAs for the treatment of canine osteoarthritis. All of these led to our hypothesis that the combination of PCSO-524 and carprofen yields a therapeutic effect that is superior to the use of carprofen or DMOAAs alone for the treatment of canine osteoarthritis.

Materials and Methods

Study design: A prospective, block-randomized, single-blinded clinical trial in client owned dogs was conducted as a hospital-based study at the Kasetsart University Veterinary Teaching Hospital, Thailand. The study protocol was approved by the Committee for the Ethical Care of Animals of the Kasetsart University. Upon a voluntary agreement to participate in this study, dogs' owners gave their written consent prior to receiving random treatment allocation.

Inclusion and exclusion criteria: Canine patients with a history of hindlimb lameness, regardless of gender and breed, two or more years old, weighing between 18 to 50 kg were recruited into the study. Inclusion criteria of the studied dogs were 1) dogs with clinical and radiographic evidences of hip and/or stifle OA and 2) dogs whose haematology and blood chemistry values remained within normal limits. Exclusion criteria were dogs having a primary neurological deficit or dogs with a history of orthopaedic surgery or other systemic diseases, as well as being pregnant or lactating bitches. Withdrawal of previous medication was applied before enrollment in this study. Washout periods were two weeks for NSAIDs and nutraceuticals and four weeks for corticosteroid and injectable sodium-pentosan polysulphate. Use of other medicines or supplements was not permitted during this study.

Randomization and blinding procedures: The dogs were classified into two categories according to the severity of their OA condition, mild to moderate and severe, based on their lameness scores and articular pain scores (Table 1) according to Moreau et al. (2003). Dogs in the severe group were dogs having a lameness score of ≥ 3 and an articular pain score of the hip and/or stifle joints of ≥ 3, whereas dogs in the mild to moderate group were dogs having a lameness score of ≤ 2 and an articular pain score of the hip and/or stifle joints of ≤ 2. The severity of OA was used as a blocking factor in the randomization process to ensure essentially equal distribution of the severity in all four treatment groups. All evaluators were blind to the treatment assignment. Medications were dispensed by a veterinarian who was not involved in the patient

evaluation procedure, and were prescribed in their original forms, to which the owners were not blind.

Drugs and dosing procedures: There were four treatment groups (10 dogs per group). Group 1 (PCSO-524) received PCSO-524 (two capsules, q12hr PO) for four weeks. Each PCSO-524 capsule contained PCSO-524 50 mg, olive oil 100 mg and d-Alpha-tocopherol 0.225 mg. Group 2 (GC-ASU) received glucosamine-chondroitin sulphate and avocado/soybean unsaponifiables (one tablet, q12hr PO) for four weeks. Each chewable GC-ASU tablet contained glucosamine HCl 900 mg, chondroitin sulphate 350 mg and ASU 90 mg. Group 3 (CPF) received carprofen (2.2 mg/kg, q12hr PO) for four weeks. Group 4 (CPF-PCSO) received a combination of carprofen (2.2 mg/kg, q12hr PO) and PCSO-524 (two capsules, q12hr PO) for four weeks. The patients were scheduled for three visits: before treatment, and on the second and fourth weeks post-treatment.

Table 1 Scoring system for subjective orthopaedic assessment (Moreau et al., 2003)

Clinical parameter	Scoring system	Score
Lameness	Stands, walks and trots normally	**0**
	Stands normally, slight algetic gait when trotting	**1**
	Stands normally, slight algetic gait when walking	**2**
	Stands normally, evident algetic gait when walking	**3**
	Stands abnormally, evident algetic gait when trotting	**4**
Articular mobility for the hip joint	No limitation of movement or crepitus	**0**
	10 to 20 per cent decrease in range of motion, no crepitus	**1**
	10 to 20 per cent decrease in range of motion, with crepitus	**2**
	20 to 50 per cent decrease in range of motion	**3**
	More than 50 per cent decrease in range of motion	**4**
Articular mobility for the stifle joint	No limitation of movement or crepitus	**0**
	10 to 20 per cent decrease in range of motion, no crepitus	**1**
	10 to 20 per cent decrease in range of motion, with crepitus	**2**
	20 to 50 per cent decrease in range of motion	**3**
	More than 50 per cent decrease in range of motion	**4**
Articular pain for the hip joint	No sign of pain	**0**
	Mild pain (dog turns head in recognition)	**1**
	Moderate pain (dog pulls limb away or wants to move away)	**2**
	Severe pain (dog vocalizes and becomes aggressive)	**3**
Articular pain for the stifle joint	No sign of pain	**0**
	Mild pain (dog turns head in recognition)	**1**
	Moderate pain (dog pulls limb away or wants to move away)	**2**
	Severe pain (dog vocalizes and becomes aggressive)	**3**

* Scores for the three clinical parameters were added to produce a composite score.

Patient evaluations and outcome variables

Force plate gait analysis: Improvement in weight bearing capacity of the affected limb was determined by increased ground reaction force in vertical direction (peak vertical force, PVF) measured by force plate. Computer-assisted force plate gait analyses were performed by the use of biomechanical strain gauge dual force plates (Model OR6-6; Advanced Mechanical Technology, Watertown, MA) embedded permanently side by side in the middle of a 10-meter-long walkway. The dogs trotted across the dual force plates by the same handler without interference. Six infrared video cameras were used to detect the speed of the dogs. Linear movement and velocity of the reflective target attached on the leash were captured and analysed by the motion analysis system (Motion Analysis Corporation, Santa Rosa, CA). The same range of velocity was maintained throughout the study for each dog. Variations of the velocity were kept as minimal as 0.5 m/sec (Figure 1).

Figure 1 Measurement of PVF using force plate gait analysis

Signals from the dual force plates were acquired and processed by proprietary software (Cortex 4.0; Motion Analysis Corporation, Santa Rosa, CA) to measure the ground reaction force in terms of peak vertical force (PVF). PVF in kilogram-Newton units was normalized with respect to the subject's body weight (%BW). A trial was valid when the dog trotted with its ipsilateral forelimb followed by the hindlimb as it struck the force plate. PVF of the affected limb derived from the first four valid trials of each dog in each evaluation time was averaged and used as a representative value of the visit in the statistical analyses. Improvement in clinical signs was indicated by an increase in PVF.

Alteration of the PVF values over time was adjusted with reference to their pre-treatment values for each treatment group. The adjusted PVF values were expressed in terms of mean changes in weeks two (W2) and four (W4) in proportion to the pre-treatment (W0) PVF values. The calculations were as the following equations:

Adjusted $PVF_{(W0)} = 100 \times (PVF_{(W0)} - PVF_{(W0)}) \div PVF_{(W0)}$

Adjusted $PVF_{(W2)} = 100 \times (PVF_{(W2)} - PVF_{(W0)}) \div PVF_{(W0)}$

Adjusted $PVF_{(W4)} = 100 \times (PVF_{(W4)} - PVF_{(W0)}) \div PVF_{(W0)}$

Orthopaedic assessment scores (OAS): Gait observation and complete orthopaedic examination were performed by the same veterinary orthopaedic surgeon. The subjective orthopaedic scoring system used in this study has been described previously by Moreau et al. (2003) as shown in Table 1 with modification. Improvement in clinical signs was indicated by a decrease in OAS.

Statistical analysis: Repeated measurement analyses by the use of a general linear model were carried out to assess treatment effects (SPSS 18, SPSS Inc., Chicago, IL, USA). A significant level was set at 5% ($\alpha = 0.05$). The Bonferroni adjustments were used for multiple comparison ($\alpha = 0.05$). Demographic and pre-treatment data were compared between groups by Pearson chi-square for breed, sex and severity of OA. The analysis of variance (ANOVA) was performed to confirm insignificant effects of duration of disease, age, BW, PVF and OAS at the pre-treatment time. The Kruskal Wallis test was used for comparison between groups and the Friedman test was used for comparison within group for non-normal distributed data. A significant level was set at 5% ($\alpha = 0.05$). The Pearson correlation was used to study correlation between PVF and OAS in each evaluation time.

Results

Animals: A total of 49 dogs were initially enrolled in this study. Nine dogs were excluded during the study period due to the following reasons: pacing gait characteristics (n = 3), pregnancy (n = 1), loss of follow-up (n = 1), physical illness unrelated to the treatment (n = 2), diarrhea (n = 1), and inconsistent speed during force plate evaluation (n = 1). At the end of the study, 40 dogs (10 dogs in each group) remained for the statistical analyses. Among these patients, there were 18 males and 22 females. The breeds included Golden retrievers (n = 27), Labrador retrievers (n = 7), Siberian husky (n = 3) and cross-breed (n = 3). The average age and weight were 6.8±2.89 years old and 33.69±6.78 kg (mean±SD), respectively. Twenty-six dogs were classified as having mild to moderate OA, whereas 14 dogs were graded as having severe OA. Among these 40 canine patients, 36 had bilateral hindlimb lameness associated with OA of the hip and/or stifle.

The pre-treatment values including the severity of clinical signs ($p = 0.932$), BW ($p = 0.191$), age ($p = 0.972$), breed ($p = 0.590$), sex ($p = 0.076$), joints affected and side ($p = 1.000$ and 0.528), duration of lameness ($p = 0.474$), OAS ($p = 0.929$) and PVF ($p = 0.275$) were not significantly different among the four treatment groups. The demographic data are presented in Table 2.

Kinetic force plate gait analysis: peak vertical force: The repeated measurement analysis (comparison between groups) demonstrated a non-significant effect of the treatment on the PVF values ($p = 0.171$) among the four treatment groups. The interaction effect was insignificant. The comparison within group revealed significant increases in the PVF values during the one-month treatment compared with the pre-treatment values in the PCSO-524, CPF and CPF-PCSO groups, but not in the GC-ASU group (Table 3).

The Bonferroni method was used to perform multiple comparison to test significant increases in the PVF values between evaluation times. On the second week post-treatment, the PVF values of the PCSO-524, CPF and CPF-PCSO groups were significantly greater than those at pre-treatment ($p = 0.031$, 0.028 and 0.001, respectively). Changes in mean PVF of 4.37±4.28, 2.58±2.48 and 4.39±2.56 %BW (mean±SD) were detected in the PCSO-524, CPF and CPF-PCSO groups, respectively. On the fourth week post-treatment, the PVF values of the PCSO-524, CPF and CPF-PCSO groups were significantly greater than their pre-treatment values ($p = 0.026$, 0.001 and 0.001, respectively) with mean changes of 3.88±3.66, 4.23±2.33, 5.36±2.98 %BW (mean±SD), respectively. There were non-significant increases in the PVF values between pre-treatment and at week two, as well as between pre-treatment and at week four in the GC-ASU group with mean changes of 2.53±3.00 ($p = 0.077$) and 1.88±6.83 %BW ($p = 1.000$) (mean±SD), respectively. There were insignificant alterations of PVF between week two and week four for all treatment groups ($p = 1.000$, 1.000, 0.379 and 0.980, respectively). The adjusted PVF values versus evaluation times as previously described were demonstrated schematically in Figure 2. The repeated measurement analysis demonstrated a non-significant effect of velocity in this study ($p = 0.229$). Multiple comparison within the groups revealed non-significant differences in the velocity between evaluation times among the four treatment groups.

Orthopaedic assessment score : The repeated measurement analyses demonstrated non-significant effects among the four treatment groups on OAS ($p = 0.990$). The interaction effect was insignificant. The

comparison within group by the Bonferroni test (Table 4) revealed significant decreases in OAS at week four compared with before treatment in the PCSO-524 (p = 0.023), CPF (p = 0.048) and CPF-PCSO groups (p = 0.029), but not in the GC-ASU group (0.334).

Correlation between PVF and OAS: At each evaluation time, the PVF values negatively correlated with OAS. The Pearson correlation coefficients of -0.39 (p = 0.014), -0.49 (p = 0.001) and -0.48 (p = 0.002) were detected at pre-treatment, and two and four weeks post-treatment, respectively.

Table 2 Demographic variables at pre-treatment of the 4 treatment groups

Variable	PCSO-524	GC-ASU	CPF	CPF-PCSO	P-value
Number of dogs	10	10	10	10	
Severity of clinical sign					0.932
- Mild to moderate	7	6	7	6	
- Severe	3	4	3	4	
Body weight* (kg)	32.75±2.17	30.99±1.33	37.47±1.95	33.54±2.77	0.191
Age* (years)	6.5±1.2	7±0.8	7±0.7	6.6±0.97	0.972
Body condition score					0.055
- 2/5	1	1	0	0	
- 3/5	6	7	2	5	
- 4/5	0	1	4	5	
- 5/5	3	1	4	0	
Breed					0.590
- Golden retriever	8	8	4	7	
- Labrador retriever	1	1	4	1	
- Siberian husky	1	0	1	1	
- Cross-breed	0	1	1	1	
Sex					0.076
- Male	6	7	3	2	
- Female	4	3	7	8	
Joint affected					1.000
- Hip	10	10	10	10	
- Stifle	1	1	1	1	
Side of affected joint					0.528
- Unilateral	1	0	2	1	
- Bilateral	9	10	8	9	
Duration of signs* (months)	5.3±2.57	1.6±1.19	1.8±1.21	2.9±1.79	0.447
OAS	6.9±0.78	6.2±0.85	6.8±1.03	6.5±0.52	0.929
PVF* (%BW)	61.83±3.17	58.02±2.95	54.16±5.03	63.95±3.37	0.275

* Mean±SD

Table 3 Comparison of PVF values at pre-treatment (week 0), week 2 and week 4

	Time	PCSO-524	GC-ASU	CPF	CPF-PCSO	P-value
PVF	Week 0 (%BW)	61.83±10.04	58.02±9.32	54.16±15.92	63.95±10.64	0.171
	Week 2 (%BW)	66.20±10.77	60.55±9.74	56.74±16.34	68.34±10.55	
	Mean change±SD	4.37±4.28	2.53±3.00	2.58±2.48	4.39±2.56	
	P-value	0.031*	0.077	0.028*	0.001*	
	Week 4 (%BW)	65.71±10.28	59.90±8.51	58.40±16.12	69.31±9.22	
	Mean change±SD	3.88±3.66	1.88±6.83	4.23±2.33	5.36±2.98	
	P-value	0.026*	1.000	0.001*	0.001*	

* Multiple comparison using the Bonferroni test with p-value < 0.05

Table 4 Comparison of OAS values at pre-treatment (week 0), week 2 and week 4

	Time	PCSO-524	GC-ASU	CPF	CPF-PCSO	P-value
OAS	Week 0 (points)	6.90±2.47	6.2±2.70	6.8±3.26	6.5±1.65	0.990
	Week 2 (points)	5.7±2.98	5.6±2.84	5.6±2.07	5.9±2.38	
	Mean change±SD	-1.2±1.62	-0.6±2.01	-1.2±2.04	-0.6±1.90	
	P-value	0.131	1.000	0.289	1.000	
	Week 4 (points)	5.2±2.49	5.0±2.75	5.2±2.44	5.1±2.47	
	Mean change±SD	-1.7±1.57	-1.2±2.15	-1.6±1.71	-1.4±1.35	
	P-value	0.023*	0.334	0.048*	0.029*	

* Multiple comparison using the Bonferroni test with p-value < 0.05

Haematology and blood chemistry values: The repeated measurement analysis demonstrated non-significant effects among the treatment groups on pack cell volume (PCV), white blood cell count (WBC), platelet count, blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALK) and the albumin:globulin ratio (A:G ratio) with p-values equaling 0.623, 0.291, 0.419, 0.122, 0.147, 0.845 and 0.441, respectively. The comparison within group using the Bonferroni adjustment revealed significant increases in BUN in the

CPF group at week two (p = 0.031) and week four (p = 0.003) when compared with before treatment. The Kruskal Wallis test revealed insignificant differences in the ALT values between the treatment groups at pre-treatment, week two and week four with p-values of 0.239, 0.130 and 0.058, respectively.

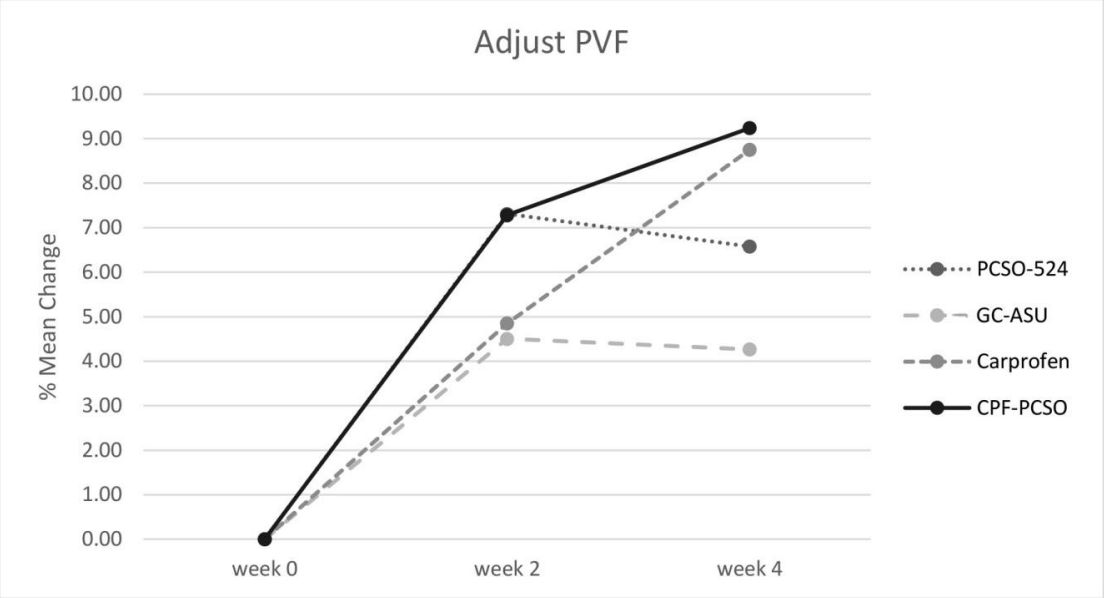

Figure 2 Comparative treatment effect of all treatment groups between pre-treatment (week 0), week 2 and week 4

Discussion

The dogs in the PCSO-524, CPF and CPF-PCSO groups showed significant improvement in the PVF values and OAS after one month of treatment. The significant improvement in OAS was consistent with the changes of PVF. These may indicate the benefits of these agents for the treatment of OA-induced pain and lameness in the studied dogs. The results obtained from this study were consistent with a previous study (Hielm-Bjorkman et al., 2009[a,b]). Eicosanoid biosyntheses via cyclooxygenase (COX) and lipoxygenase (LOX) pathways are of particular clinical relevance especially in osteoarthritis, where the inflammation and pain are predominant. For this reason, NSAIDs remain the treatment of choice for osteoarthritis because these agents can inhibit COX thereby impairing the conversion of arachidonic fatty acid to prostaglandins and thromboxanes. The omega-6 arachidonic fatty acid is incorporated into the phospholipid bilayer of the cell membrane. Under inflammatory stimulation, this omega-6 arachidonic fatty acid is metabolized to yield several potent inflammatory mediators that include 2-series prostaglandins, thromboxanes and 4-series leukotrienes. An increased intake of omega-3 fatty acids including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) has been shown to reduce the omega-6:omega-3 ratio in the phospholipid layer of the plasma membrane. This may alter the process of eicosanoid metabolism to produce the less-potent eicosanoids including 3-series of prostaglandins and thromboxanes and 5-series of leukotrienes (Zawadzki et al., 2013; Calder, 2015). Recently, the novel lipid mediators derived from EPA and DHA namely resolvins, maresins and protectins have been identified. These endogenous molecules are biosynthesized from COX and LOX pathways using EPA and DHA as substrates. The anti-inflammatory properties of these lipid derived mediators have been extensively researched in both *in vitro* and *in vivo* models (Calder, 2015; Norling and Perretti, 2013). The main constituents of PCSO-524 are EPA and DHA, which may be able to modify the omega-6:omega-3 ratio in the body. Additionally, PCSO-524 contains eicosatetraenoic acid (ETA), an omega-3 polyunsaturated fatty acid that has a chemical structure similar to arachidonic acid. It is possible that joint inflammation is reduced because ETA may inhibit competitively the active binding site of an enzyme that utilizes arachidonic acid as substrate (Zawadzki et al., 2013; Doggrell, 2011).

Even though significant increases in PVF were demonstrated in the PCSO-524, CPF and CPF-PCSO groups, the greatest improvement was demonstrated in the CPF-PCSO group. This implies the beneficial effects of PCSO-524 in combination with carprofen. NSAIDs and PCSO-524 may exert their effects in a common pathway of arachidonic acid. Both agents may work synergistically to alleviate joint inflammation and pain. A trend of reduction in the change of PVF at the end of the study was observed in the PCSO-524 group. This may be due to random fluctuation occurring in our study between week two and week four. Fluctuations of the omega-6:omega-3 ratio in the serum of osteoarthritic dogs consuming a diet rich in omega-3 fatty acids have been reported in a multicenter study previously (Roush et al., 2010). However, the overall changes of PVF in each group may be better demonstrated in a long-term study. The composite scoring system used in this study (Moreau el al., 2003) yielded a negative correlation with PVF. The significantly negative correlation of PVF and subjective OAS found in this study confirmed the usefulness of this orthopaedic grading system in the absence of force plate gait analysis.

A non-significant increase in PVF and a decrease in subjective OAS during the one-month treatment period were demonstrated in the GC-ASU group. The chondro-protective and synergistic effects of GC-ASU have been reported in several studies, including the reduction in PGE_2 production and the amelioration of cartilage degradation (Jerosch, 2005; Boileau et al., 2009; Grzanna et al., 2011). The dose of GC in our study might have been insufficient to improve the clinical signs of OA. In addition, the one-month duration of treatment might have been too short for any anabolic effects of these agents to exert. The recommended therapeutic doses of glucosamine hydrochloride and chondroitin sulphate for the treatment of canine osteoarthritis have been reported in a considerably wide range of 25-50 mg/kg/day and 15-40 mg/kg/day, respectively (Moreau et al., 2003; McCarthy et al., 2007). A previous study revealed that at least 70 days of treatment might be necessary to demonstrate the effectiveness of glucosamine hydrochloride and chondroitin sulphate in the treatment of OA (McCarthy et al., 2007).

According to the FDA records of the adverse events associated with the use of NSAIDs, the most common side effects occurred in the gastrointestinal tract (64%), kidney (21%) and liver (14%) (Hampshire et al., 2004). The current study found a significant increase in the BUN value of the CPF group, however the BUN values of all the dogs involved in the study varied within the normal range. One dog in the CPF-PCSO group had watery diarrhea after receiving medications for three days. After withdrawal and administration of a symptomatic treatment, the gastrointestinal disturbance subsided. This patient also developed the episode of diarrhea after the second session of PCSO-524 treatment. Therefore, the dog was excluded permanently from the study. The adverse gastrointestinal effects are found commonly in patients who receive high-dose omega-3 fatty acid supplementation. Undigested fatty acids pass into the small intestine, where they become a substrate for bacteria, resulting in secretory diarrhea (Lenox and Bauer, 2013). This gastrointestinal side effect is treatable.

It is well accepted that the most cost-effective options are the prevention of OA and the timely diagnoses before OA condition becomes progressive otherwise the medical and/or surgical treatments will be very costly and may involve complications (Wheaton et al., 2011; Losina et al., 2014). The estimation of cost benefit of the treatment in OA patients depends on the benefit gain from the treatments, the increases in the patients' quality of life, owner perception and satisfaction as well. However, the owner assessment score and satisfaction were not performed in this preliminary study. Future studies should include a questionnaire to assess owner's satisfaction and patient's quality of life to obtain a better conclusion relevant to the cost-effectiveness. The goals of OA treatment are to reduce pain and inflammation, prevent or slow down degeneration of the cartilage, and support or restore joint functions. To achieve the treatment goals, multimodal management of OA including the combinations of medical therapy, nutritional management, rehabilitation, weight reduction and surgical treatment has been widely used (Case et al., 2011).

In conclusion, the greatest improvement in clinical signs was demonstrated in the CPF-PCSO treatment group. This may imply the beneficial effects of PCSO-524 in combination with carprofen. During the one-month study, there were no serious adverse effects detected in any of the treatment groups. A future study may prospectively investigate changes in biochemical and biomarker variables, including serum fatty acid and PGE_2 levels. Long-term aggregated data from the effect of a greater dosage and a larger sample size should also be further explored.

Acknowledgements

The authors would like to thank Ms. Julaporn Pooliam, the research assistant of Clinical Epidemiology Unit, Faculty of Medicine Siriraj Hospital, Mahidol University, for valuable comments and suggestions about statistical analyses. We would like to extend our thanks to the Pharmalink International Limited for partial research funding. Moreover, we would like to express our special thanks to the Faculty of Veterinary Medicine, Kasetsart University and the Kasetsart University Veterinary Teaching Hospital for equipment and technical supports in this research.

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บทคัดย่อ

การเปรียบเทียบประสิทธิภาพของโภชนเภสัชและคาร์โปรเฟนในการรักษาโรคข้อเสื่อมในสุนัข

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การศึกษานี้จัดเป็นการวิจัยแบบไปข้างหน้า จัดเข้ากลุ่มการศึกษาโดยวิธีสุ่มและปกปิดผู้ประเมินผลลัพธ์ มีวัตถุประสงค์เพื่อประเมินและเปรียบเทียบผลของการใช้โภชนเภสัช (disease modifying osteoarthritis agents: DMOAAs) และยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ (NSAIDs) ชนิดคาร์โปรเฟนในการรักษาโรคข้อเสื่อมในสุนัข วัดผลด้วยวิธีการวิเคราะห์การเคลื่อนไหวด้วยแผ่นวัดการกระจายน้ำหนักที่เท้าและการประเมินระดับคะแนนทางออร์โธปิดิกส์ ทำการสุ่มสุนัขที่มีปัญหาข้อสะโพกและ/หรือข้อเข่าเสื่อมจำนวน 40 ตัวเข้ากลุ่มการทดลอง 4 กลุ่ม ได้แก่ กลุ่มสารสกัดกรดไขมันจากหอยแมลงภู่นิวซีแลนด์ (PCSO-524) กลุ่มกลูโคซามีน-คอนดรอยตินซัลเฟต-สารสกัดจากอโวคาโดและถั่วเหลือง (GC-ASU) กลุ่มคาร์โปรเฟน (CPF) และกลุ่มที่ให้คาร์โปรเฟนและ PCSO-524 ร่วมกัน (CPF-PCSO) โดยแต่ละกลุ่มจะได้รับยาโดยการกินนาน 4 สัปดาห์ ทำการประเมินผลด้วยการวัดแรงปฏิกิริยาสูงสุดที่เท้ากระทำในแนวตั้งฉากกับพื้น (PVF) การประเมินระดับคะแนนทางออร์โธปิดิกส์ (OAS) และการตรวจประเมินทางโลหิตวิทยาและชีวเคมี ณ เวลาก่อนการรักษา และที่ 2 และ 4 สัปดาห์หลังการรักษา การเปรียบเทียบประสิทธิภาพของการรักษาระหว่างกลุ่มการทดลองพบว่าค่า PVF, OAS และค่าทางโลหิตวิทยาและชีวเคมีไม่มีความแตกต่างอย่างมีนัยสำคัญ การเปรียบเทียบภายในกลุ่มการทดลองจากการตรวจประเมินก่อนการรักษา และที่ 2 และ 4 สัปดาห์หลังการรักษาพบการเพิ่มขึ้นของ PVF และการลดลงของ OAS อย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบกับก่อนการรักษาในกลุ่ม CPF, PCSO-524 และ CPF-PCSO ($p < 0.05$) นอกจากนี้ ยังพบว่าค่าเฉลี่ย BUN ในกลุ่ม CPF มีค่าเพิ่มขึ้นอย่างมีนัยสำคัญ ($p < 0.05$) ในการประเมินผลแต่ละครั้งพบว่าค่า PVF มีความสัมพันธ์ในเชิงผกผันกับค่า OAS อย่างมีนัยสำคัญทางสถิติที่ $r = -0.39$ ($p = 0.014$), $r = -0.49$ ($p = 0.001$) และ $r = -0.48$ ($p = 0.002$) ก่อนการรักษา และที่ 2 และ 4 สัปดาห์หลังการรักษา ตามลำดับ แม้ว่าจะพบการเพิ่มขึ้นอย่างมีนัยสำคัญของ PVF ในกลุ่ม PCSO-524, CPF และ CPF-PCSO แต่กลุ่มที่มีการเพิ่มขึ้นของค่า PVF สูงสุดคือกลุ่ม CPF-PCSO ซึ่งอาจบ่งชี้ว่าการให้ PCSO-524 ร่วมกับคาร์โปรเฟนมีแนวโน้มให้ผลการรักษาที่ดีที่สุดในสุนัขโรคข้อเสื่อมในทางคลินิก

คำสำคัญ: คอนดรอยติน สุนัข แผ่นวัดการกระจายน้ำหนัก กลูโคซามีน ยาต้านการอักเสบที่ไม่ใช่สเตียรอย PCSO-524

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