Original Article

Ameliorative Effects of Omega-3 Concentrate in Managing Coxofemoral Osteoarthritic Pain in Dogs

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Abstract

The aim of the present study was to investigate the effect of omega-3 concentrate on pain management in dogs with osteoarthritis (OA) at the coxofemoral joint. Totally, 31 dogs with confirmed coxofemoral OA were orthopedically evaluated for pain scores at walk and trot (1-6), joint manipulation (1-3), and examining range of motion (1-4). Besides, blood collection was performed on the first and the last visits. Omega-3 concentrate was orally given to all dogs at one capsule per 10 kg_{BW} since the first visit on a daily basis for four consecutive weeks. On a weekly basis, pain scores were assessed for all dogs. Results exhibited that the pain scores at walk and trot, joint manipulation, and examining range of motion between the beginning and the end of the study significantly declined from 3.0±0.8 to 1.4±0.6 (P<0.001), 2.5±0.5 to 1.1±0.4 (P<0.001), and 3.1±0.4 to 1.5±0.5 (P<0.001), respectively. Considering the blood profiles, hepatic and renal enzymes did not statistically alter during the study as could be seen from ALT (51.76±7.21 vs 46.46±5.16 U/l, P=0.3066), AST (26.68±1.37 vs 27.23±2.08 U/l, P=0.4103), BUN (14.31±1.00 vs 13.31±1.28 mg%, P=0.1456), and CR (0.98±0.0 vs 1.01±0.03 mg%, P=0.8370). In summary, omega-3 concentrate is one of the new decent alternatives to relieve canine coxofemoral osteoarthritic pain. Not only for pain alleviation, but it could also be given to dogs for 4 consecutive weeks since it does not disrupt hepatic and renal functions.

Keywords: coxofemoral osteoarthritis, dogs, omega-3 concentrate, pain score

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Introduction

Osteoarthritis (OA) is one of the most common chronic pains in dogs; approximately 10-12 million dogs in the United States of America undergo OA (Moore et al., 2001). Besides, more than 20% of dogs aged >1 year old suffer from OA. In general, OA is majorly investigated in senile, overweight, and large-breed dogs. Nevertheless, OA can take place in every age, size, and breed of dogs (Johnston, 1997). OA represents synovitis and deteriorates articular cartilage, entailing the complete destruction of cartilage surface. Basically, articular cartilage is composed of chondrocytes and extracellular matrix (ECM), which is principally made up of water, collagen, and proteoglycans (Man and Mologhianu, 2014). Chondrocyte, the only one cell type in articular cartilage, is responsible for sustaining joint homeostasis and ECM degradation. Consequently, OA is caused by the failure to balance synthesis and degradation of ECM (Heijink et al., 2012). It contributes to the overproduction of several destructive and proinflammatory mediators such as free radicals, proteases, and prostaglandins, from chondrocytes, bringing higher catabolism than anabolism rate. Finally, progressive destruction of the articular cartilage takes place (Mortellaro, 2003).

Treatments for OA aim at preventing and controlling clinical signs, together with nutritional management, physical therapy, analgesic and anti-inflammatory drugs, etc. (Roush et al., 2010b). Application of anti-inflammatory agents such as corticosteroid and non-steroidal anti-inflammatory drugs (NSAIDs), is one of the efficient methods of OA remedy. Nevertheless, considerable adverse effects such as gastric ulcer, renal and hepatic failures, and death might be observed from patients treated with anti-inflammatory drugs. In addition, long-term application of corticosteroid and NSAIDs might expedite cartilage degeneration (Henrotin et al., 2005). A number of studies suggest that omega-3 polyunsaturated fatty acid (PUFA) have advantageous effects on rheumatoid arthritis (Calder and Zurier, 2001; Goldberg and Katz, 2007; Roush et al., 2010b).

PUFA can be mainly classified into two groups: omega-3 PUFA and omega-6 PUFA. Both are substrates for producing eicosanoids, which play significant roles in inflammatory control. Eicosanoids produced from omega-6, especially arachidonic acid (AA), are responsible for proinflammation and immunoactivation processes, meanwhile those produced from omega-3, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), inhibit eicosanoid generated from omega-6 (Wall et al., 2010). A number of clinical studies reveal that omega-3 is effective to ameliorate chronic inflammations such as rheumatoid arthritis and inflammatory bowel diseases through the stimulation of immune system by altering eicosanoid production (Calder, 2006; Sijben and Calder, 2007), together with reducing the generation and activities of proteoglycan-degrading enzyme, cyclo-oxygenase-2 (COX-2), and inflammation-inducible cytokines (Curtis et al., 2000). Besides, feeding animals with fatty fish or supplementing fish oil in the feed enhances EPA and DHA in the inflammatory cells, contributing to the decrease in omega-6 product, especially AA; it compromised inflammatory process (Calder and Zurier, 2001). However, comprehensive studies of the application of omega-3 concentrate in coxofemoral osteoarthritic dogs have been scant. Consequently, the aim of the present study was to investigate the effects of omega-3 concentrate on pain management in dogs naturally afflicted with coxofemoral osteoarthritis.

Materials and Methods

Animal intervention in the present study was approved by the Committee of Research Ethics in Laboratory Animals, Mahasarakham University (0007/2558).

Animals and selection criteria: All patients were dogs visiting a veterinary hospital in Bangkok, Thailand, with the client complaint of hindlimb problems such as weakness of hindlimb, difficulty to get up, hindlimbs with non-weight bearing condition, and so forth. Complete physical examination, including orthopedic examination, was conducted by only one veterinarian in all patients to confirm hindlimb abnormalities. In addition, complete neurological examination was performed in order to rule out pain from neurological disorders; those with neurological pain were excluded from the study. Furthermore, all dogs were sent to the imaging unit to confirm OA at both coxofemoral joints via radiography. On the last visit, radiography at the coxofemoral joints was performed again to investigate the condition of the joints. The dogs included in the present study had healthy condition and underwent complete vaccination program, i.e. canine distemper, parainfluenza, parvovirus, infectious hepatitis, infectious tracheobronchitis, rabies, and leptospirosis. Moreover, those acquiring hydrotherapy, acupuncture, vitamins, supplements, and any medication within one month before the study initiated were excluded. Eventually, 31 dogs afflicted with naturally coxofemoral OA, together with owners' consent, were included in the study.

Blood collection: All patients were venipunctured from cephalic or saphenous veins to examine complete blood count and blood chemical profiles. In addition, blood parasite investigation was performed. Those with positive blood parasite result were excluded from the study. Blood chemical profiles investigated were total protein (TP), blood urea nitrogen (BUN), serum creatinine (CR), alanine aminotransferase (ALT), and aspartate transaminase (AST). In order to evaluate an alteration of blood parameters during the study, blood collection was performed on the first and the last visits from all dogs.

Pain evaluations: Individual patients were evaluated for pain severity at coxofemoral joint by the same veterinarian at the same hospital throughout the study. Veterinary orthopedic examinations, including lameness at walk and trot, pain at joint manipulation, and range of motion, were performed at the coxofemoral joints and were reported as pain score. Considering lameness at walk and trot, pain scores

were classified into six grades: 1 = normal walk and trot, 2 = intermittent lameness, 3 = persistent lameness, 4 = non-weight bearing walk, 5 = ambulatory walk only with assistance, and 6 = non-ambulatory walk. According to pain at manipulation of the coxofemoral joint, pain scores were categorized into 3 classes: 1 = no pain, 2 = mild pain (make an effort to withdraw limb against strong manipulation), and 3 = severe pain (abruptly withdraw limb when start touching the joint). Owing to range of motion, pain scores were grouped into 4 indices: 1 = no pain through full range of motion, 2 = pain only at full range of motion, 3 = pain at less than full range of motion, and 4 = pain at any joint manipulation (Black et al., 2008). All dogs were evaluated for pain scores of the three parameters by the same veterinarian on a weekly basis throughout the study.

Omega-3 concentrate administration: Every patient started taking omega-3 concentrate (Omacor®, Banner Pharmacaps Europe BV, the Netherlands) since the first visit with the diagnosis of coxofemoral OA. One soft-gel capsule of omega-3 concentrate (1,000 mg) consisted of 460 mg EPA, 380 mg DHA, and 4 mg alpha-tocopherol. The dosage of omega-3 concentrate was applied by one capsule per 10 kg_{BW} per os (Mueller et al., 2004). All patients obtained omega-3 concentrate orally on a daily basis for four progressive weeks since the first day of the study. Besides, all of them had to visit the hospital every week to acquire pain score assessment at the coxofemoral joints by the same veterinarian.

Statistical analysis: All data were manipulated and analyzed statistically by SAS version 9.0 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics of all dogs were presented as mean±SD. Pain evaluations were scored as 1-6 for lameness at walk and trot, as 1-3 for pain at joint manipulation, and as 1-4 for pain at examining range of motion. The score of each parameter was analyzed for difference among number of visits (1-5) using signed rank test. The blood profiles, i.e. PCV, TP, BUN, CR, ALT, and AST, were tested for normality (proc univariate). Differences in blood profiles between the first and last visits were analyzed using paired *t* tests (for PCV, BUN, and CR) and signed rank tests (for TP, ALT, and AST). $P<0.05$ was considered statistically significant.

Results

Thirty-one patients undergoing naturally coxofemoral OA in this study were 18 male and 13 female dogs. They were 1 Saint Bernard, 2 Bangkaew, 1 Bulldog, 1 Cocker Spaniel, 2 German Shepherds, 10 Labrador retrievers, 5 mixed breeds, 1 Pekingese, 1 Pomeranian, 2 Poodles, 2 Rottweilers, 1 Shih tzu, 1 Siberian Husky, and 1 Yorkshire Terrier. Averagely, mean age and body weight of the patients were 7.4±3.8 years (a range of 0.3-14.0 years) and 24.3±12.6 kg (a range of 5.7-46.0 kg), respectively. In addition, the mean body weight of all dogs from the beginning to the end of the study was consistent: 24.5±14.1, 24.7±14.2, 23.9±13.4, 24.9±14.7, and 24.9±14.8 kg ($P>0.05$) on 1st, 2nd, 3rd, 4th, and 5th visits, respectively.

According to the examination of pain at walk and trot, pain scores from the first to the last visits are demonstrated in Figure 1. The dogs significantly had lower pain score after one week of treatment (3.0±0.8 vs 1.9±0.6, $P<0.001$). Moreover, the alleviation of pain at walk and trot was further found significant between the 2nd and 4th visits (1.9±0.8 vs 1.4±0.6, $P<0.001$). At the end of study, the pain score at walk and trot was 1.4±0.6.

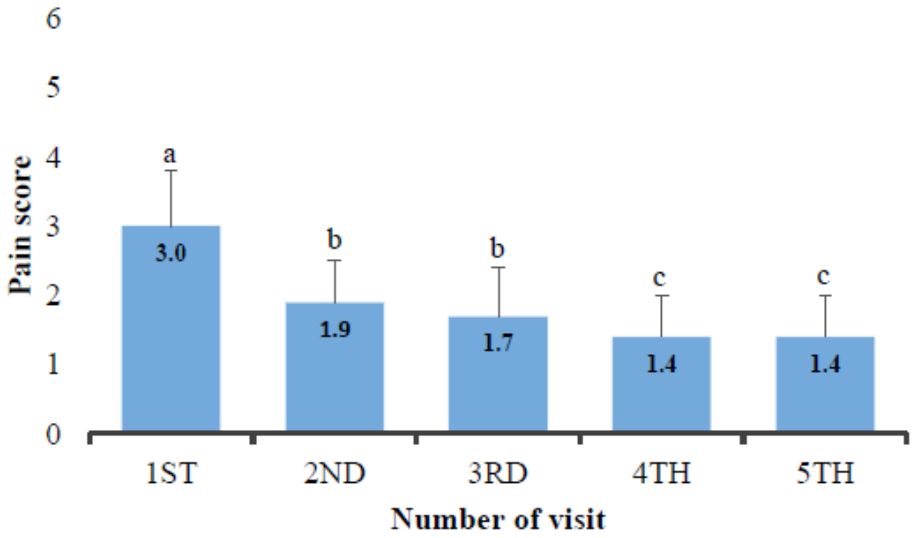

Figure 1 Pain score (mean±SD) at walk and trot of 31 dogs from the first to the last visits. [a,b,c] Different superscripts indicate statistical significance ($P<0.05$).

The investigation into pain at joint manipulation is shown in Figure 2. It was apparently found that the pain score alleviated significantly between the 1st and 2nd visits (2.5±0.5 vs 1.5±0.6, $P<0.001$), as well as between the 2nd and 3rd visits (1.5±0.6 vs 1.2±0.4, $P<0.001$). Finally, the pain score while manipulating coxofemoral joints was 1.1±0.4.

The pain scores after the test for range of motion at coxofemoral joints are displayed in Figure 3. The dogs administered with omega-3 concentrate had continually declined painfulness from the 1st to 3rd

visits (3.1±0.4 vs 2.2±0.4 vs 1.8±0.5, P<0.001) and diminished to 1.5±0.5 at the end of the study.

For the blood examination, results for complete blood count and blood chemical profiles are exhibited in Table 1. PCV and TP slightly increased but were still in normal range. In addition, hepatic and renal enzymes at the end of the study did not statistically differ from those on the first visit, as could be observed from ALT (51.76±7.21 vs 46.46±5.16 U/l, P=0.3066), AST (26.68±1.37 vs 27.23±2.08 U/l, P=0.4103), BUN (14.31±1.00 vs 13.31±1.28 mg%, P=0.1456), and CR (0.98±0.0 vs 1.01±0.03 mg%, P=0.8370). Furthermore, they were still in normal range.

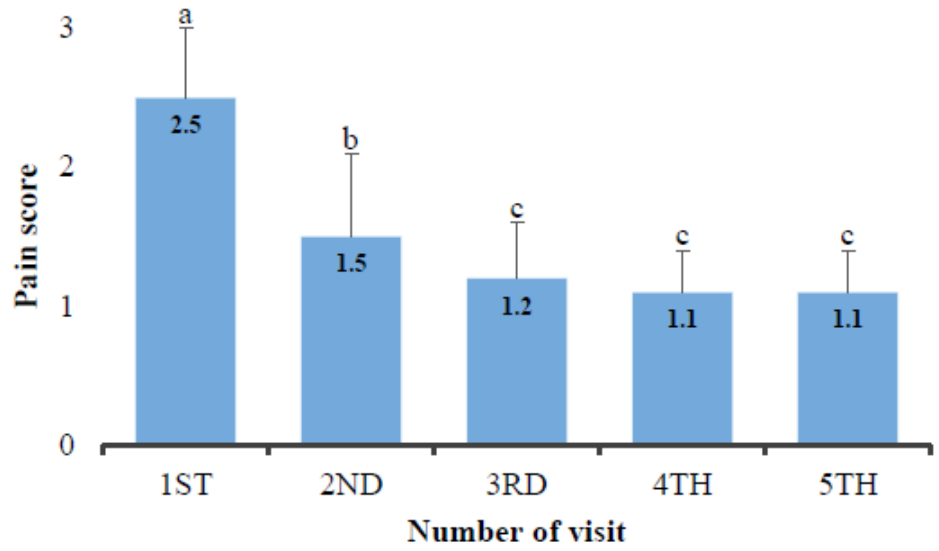

Figure 2 Pain score (mean±SD) at joint manipulation of 31 dogs from the first to the last visits. [a,b,c] Different superscripts demonstrate statistical significance (P<0.05).

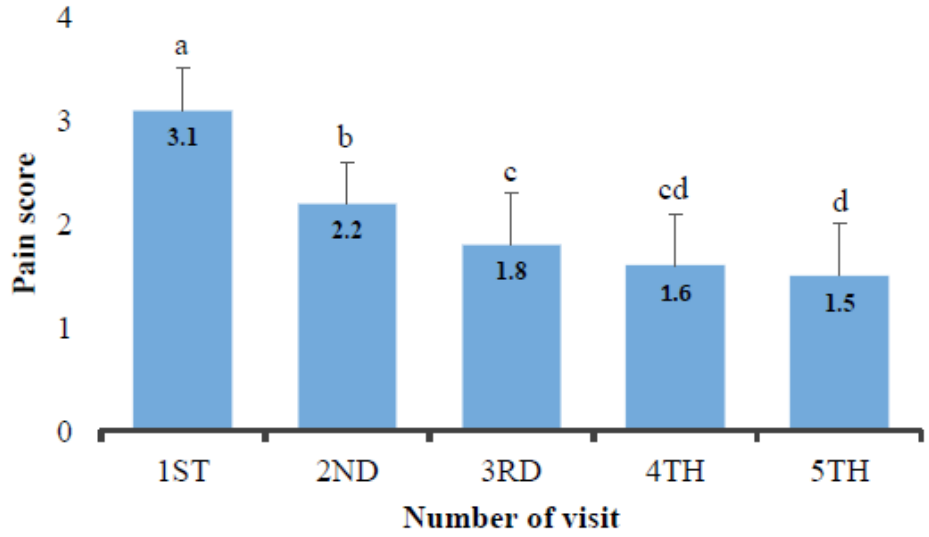

Figure 3 Pain score (mean±SD) at examining range of motion of 31 dogs from the first to the last visits. [a,b,c,d] Different superscripts illustrate statistical significance (P<0.05).

Discussion

The present study demonstrated that omega-3 concentrate was an effective agent to relieve pain at the coxofemoral joints in dogs afflicted with hip osteoarthritis. According to the investigation into painfulness at walk and trot, joint manipulation, and examining range of motion, the pain scores of all parameters significantly declined, especially on the first two visits. The dogs, finally, possessed pain scores of 1.4±0.6, 1.1±0.4, and 1.5±0.5 for pain at walk and trot, joint manipulation, and examining range of motion, respectively. This implies that they had apparent improvement in painfulness at the coxofemoral joints, contributing to the better walk and weight-bearing gesture in this study. Correspondingly, according to a previous study of the supplementation of fish oil omega-3 fatty acid in feed for OA dogs for 90 days, significant weight-bearing improvements were found in those that consumed such feed (Roush et al., 2010a). In addition, its following study demonstrated that dogs with OA fed on omega-3 supplement possessed significantly better ability to rise from resting position, walk, and play than those fed on control feed (without omega-3 addition) (Roush et al., 2010b). Such painfulness diminished because omega-3 PUFA tenanted high potential to lessen OA pathology in the natural scenario as confirmed by physiological

markers such as type II collagen, alkaline phosphatase (ALP), matrix metalloproteinase (MMP), and so on. A study of guinea pigs with natural OA revealed that those fed on omega-3 PUFA had enhanced cartilage glycosaminoglycan, lessened denatured type II collagen, and low MMP-2, which are improved signs of OA (Knott et al., 2011). Moreover, an *in vitro* study of bovine chondrocytes with the existence of omega-3 PUFA, especially EPA, demonstrated less expression of cartilage-degrading enzymes, COX-2, and a number of cytokines stimulating an inflammation (Zainal et al., 2009).

Table 1 Blood profiles (mean±SEM) of 31 dogs naturally afflicted with coxofemoral osteoarthritis on the first and the last visits of omega-3 concentrate administration

Variables	First visit	Last visit	*P*-value	Normal range
PCV (%)	39.06±1.09	41.08±1.19	0.0269	35.0-55.0
Total protein (g/dl)	6.59±0.14	7.14±0.18	0.0023	5.30-7.80
BUN (mg%)	14.31±1.00	13.31±1.28	0.1456	10.00-26.00
CR (mg%)	0.98±0.03	1.01±0.03	0.8370	0.50-1.30
ALT (U/l)	51.76±7.21	46.46±5.16	0.3066	6.00-70.00
AST (U/l)	26.68±1.37	27.23±2.08	0.4103	10.00-43.00

Generally, a traditional and effective treatment of OA is performed with steroid or NSAIDs. In addition, OA is considered a chronic disease; the dogs, accordingly, might be treated to reduce painfulness with steroid or NSAIDs for a long period. Nevertheless, both medications cause considerably adverse outcomes, including ulcerative gastrointestinal tract, renal and hepatic failures, and death. Moreover, cartilage degeneration might be accelerated by the long-term medication of both steroid and NSAIDs (Henrotin et al., 2005). As a result, omega-3 concentrate has been one of the beneficial alternatives to manage pain from OA in a chronical manner. In the present study, the long-term administration of omega-3 concentrate in the dogs with natural OA scantly affected the functions of important organs, especially the liver and kidneys, as could be vividly seen in Table 1. The blood chemical profiles of the patients in this study demonstrated non-significant alteration in hepatic (ALT and AST) and renal (BUN and CR) functions after administering omega-3 concentrate for one month. In addition, they were still in the normal rage of standardized laboratory of a veterinary hospital. For this reason, hepatic and renal failures will not be a matter of concern in the treatment of canine coxofemoral OA with omega-3 concentrate. Not only for the treatment of coxofemoral OA in general dogs, but omega-3 concentrate will also be extensively advantageous to geriatric dogs suffering with OA. Because organ degeneration increases with age, chronic treatment with steroid or NSAIDs in old dogs might accelerate the degeneration or failure of liver and kidneys.

Senile dogs with hypertension and cardiac failure were required to receive a combination of diuretics, angiotensin converting enzyme inhibitor (ACEI), and angiotensin receptor antagonist (ARA) for treatment (Thomas, 2000). A former study revealed that patients requiring NSAIDs for co-treatment during that combination might have worse hypertension and cardiac failure, together with development of renal failure (Kerr et al., 2003). Consequently, it is relatively safe to treat OA in senile dogs with systemic diseases such as hypertension or cardiac failure with omega-3 concentrate instead of NSAIDs during such combination. This is because NSAIDs could exacerbate renal functions to failure. On the contrary, omega-3 concentrate does not damage both liver and renal functions, as obviously seen in the present study, and therefore could be taken for a long period.

Prior to administering omega-3 concentrate, side effects to cardiovascular system and liver functions should considerably be concentrated on since it could induce recurrence of atrial fibrillation. In addition, it might cause elevation of AST and ALT in patients with hepatic impairments. Moreover, dogs with hypersensitivity to omega-3 acid ester and any product component should avoid taking omega-3 concentrate (Truven Health Analytics Inc., 2016). Considering the cost for treatment, omega-3 concentrate used in the current study was available in a bottle consisting of 28 soft-gel capsules. In Thailand, the cost of a bottle is approximately 1,300 Thai baht.

In summary, omega-3 concentrate is the new alternative for the treatment of coxofemoral OA since it yielded ameliorative effects on the dogs with OA at the coxofemoral joints. It could reduce painfulness at the joints as lucidly seen by the successive decrease in pain scores of pain at walk and trot, joint manipulation, and examining range of motion. Moreover, omega-3 concentrate could be given to patients treated with long-term NSAIDs, especially to patients with hypertension and cardiac disease, since it does not disrupt the liver and renal functions.

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บทคัดย่อ

ผลเชิงบวกของโอเมก้า-3 เข้มข้นในการจัดการความเจ็บปวดจากภาวะข้อสะโพกเสื่อมในสุนัข

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การศึกษานี้มีวัตถุประสงค์เพื่อทดสอบผลในการจัดการความเจ็บปวดของโอเมก้า-3 เข้มข้นในสุนัขที่มีภาวะข้อสะโพกเสื่อม สุนัขที่ได้รับการตรวจยืนยันแล้วว่ามีภาวะข้อสะโพกเสื่อมจำนวน 31 ตัวได้รับการตรวจทางออร์โธปีดิกส์เพื่อประเมินคะแนนความเจ็บปวดขณะเดินและวิ่งเหยาะ (คะแนน 1-6) ขณะขยับข้อต่อ (คะแนน 1-3) และขณะตรวจพิสัยการเคลื่อนไหวของข้อต่อ (คะแนน 1-4) นอกจากนี้ ยังมีการเก็บตัวอย่างเลือดในวันแรกและวันสุดท้ายของการศึกษาอีกด้วย สุนัขที่เข้ารับการศึกษาทุกตัวได้รับโอเมก้า-3 เข้มข้นทางการกิน โดยให้กิน 1 แคปซูลต่อน้ำหนักตัว 10 กิโลกรัมทุกวันตั้งแต่วันแรกที่เข้าร่วมการศึกษา และกินต่อเนื่องอีก 4 สัปดาห์ สุนัขทุกตัวได้รับการประเมินคะแนนความเจ็บปวดทุกสัปดาห์จนสิ้นสุดการศึกษา เมื่อสิ้นสุดการศึกษา พบว่าคะแนนความเจ็บปวดขณะเดินและวิ่งเหยาะ ขณะขยับข้อต่อ และขณะตรวจพิสัยการเคลื่อนไหวลดลงจาก 3.0±0.8 เป็น 1.4±0.6 (P<0.001), 2.5±0.5 เป็น 1.1±0.4 (P<0.001) และ 3.1±0.4 เป็น 1.5±0.5 (P<0.001) ตามลำดับ นอกจากนี้ ยังพบว่าเอนไซม์ที่บ่งชี้ถึงการทำงานของตับและไตไม่มีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติระหว่างการศึกษา โดยเห็นได้จาก ALT (51.76±7.21 vs 46.46±5.16 U/l, P=0.3066), AST (26.68±1.37 vs 27.23±2.08 U/l, P=0.4103), BUN (14.31±1.00 vs 13.31±1.28 mg%, P=0.1456) และ CR (0.98±0.0 vs 1.01±0.03 mg%, P=0.8370) โดยสรุป โอเมก้า-3 เข้มข้น ถือเป็นทางเลือกใหม่ในการลดความเจ็บปวดจากภาวะข้อสะโพกเสื่อมในสุนัข นอกจากนี้ โอเมก้า-3 เข้มข้นยังสามารถให้สุนัขกินได้ต่อเนื่องถึง 4 สัปดาห์โดยไม่สร้างความเสียหายต่อการทำหน้าที่ของตับและไต

คำสำคัญ: ข้อสะโพกเสื่อม สุนัข โอเมก้า-3 เข้มข้น คะแนนความเจ็บปวด

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