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A Randomized, Blinded, Placebo-Controlled Study Of BVP-01, A Proprietary Nutraceutical Formulation For The Treatment Of Canine Osteoarthritis

Research Article

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Abstract

Objectives: To examine the efficacy and safety of a proprietary nutraceutical formulation BVP-01 to manage the clinical signs of osteoarthritis (OA) in dogs using a blinded placebo-controlled study.
Introduction: Currently, every fifth dog suffers from OA. OA dogs are usually treated with non-steroidal anti-inflammatory drugs (NSAIDS), but because of their serious side effects, nutraceuticals are used as alternative medicine.
Methods: Dogs were selected from 5 primary accession clinics in New Zealand, and evaluated for clinical signs of OA. Dogs with mild OA were randomly allocated into three Groups: Group 1, BVP-01, Group 2, Placebo for six weeks followed by BVP-01 for next six weeks; Group 3, BVP-01 and Rimadyl (R). Group 4, severe OA dogs were treated with the same medication protocol as Group 3. The dogs were supplemented for 12 weeks. During weeks 7-12, Groups 2, 3 and 4 received BVP-01. The owners assessed the dogs weekly for pain and activity. At 0, 6 and 12 weeks the dogs were clinically examined and were videoed for subsequent kinematic analysis.
Results: Of 74 dogs accepted into the trial, clinical and owner data on 71 dogs and kinematic data on 58 dogs were obtained. Supplementation of dogs with BVP-01 +R (Group 3) resulted in a significant improvement in owner-assessed activity and pain scores at weeks 2 and 3. Supplementation with BVP-01 (Group 1) provided a comparable significant improvement at weeks 9 and 10. Clinical assessment identified that lameness grade was worse in Group 4 at weeks 0, 6 and 12. Groups 1, 2 and 3 had significant improvement in articular pain scores at week 6. Kinematic analysis identified an improvement in limb range of motion at week 12 for Group 3 ($p=0.055$) and there was a trend for improvement in Group 1 ($p=0.079$).
Conclusions And Clinical Relevance: BVP-01 offers an alternative to NSAIDs for the management of mild OA signs in dogs.

Keywords: Osteoarthritic Dogs; Green Lipped Mussel Extract; Deer Velvet Antler Extract, Shark Cartilage, Enzogenol, Rimadyl, Nutraceutical, BVP-01.

Introduction

Currently, about 20% of adult dogs suffer from arthritis. Out of two common forms of arthritis (osteoarthritis, OA; and rheumatoid arthritis, RA), OA occurs with greater frequency. Although any breed of dog can develop OA, large breed dogs (such as German Shepherds, Labrador Retrievers, Newfoundland, Rottweilers, Siberian Huskies, and others) are genetically predisposed for OA and are ~45% likely to develop this disease [21]. OA is as an inflammatory heterogeneous chronic degenerative joint disease (DJD) characterized by progressive degradation of the articular cartilage, osteophyte formation, thickening and sclerosis of the subchondral bone, bone marrow lesions, hypertrophy of bone at the margin, synovitis, synovial fluid effusion, and fibrosis [23]. The pathophysiology of OA is very complex due to the involvement of multiple etiologies including aging, genetics, injury, excessive or lack of exercise, nutritional deficiency, obesity, infection, etc [57, 35, 21, 22]. OA affects the entire joint, including cartilage, bones, nerves and surrounding muscles [52, 36]. It includes a wide array of clinical signs such as limping, immobility, stiffness of joints, crepitus, periarticular swelling, palpable effusion, pain upon manipulation of the joint and lameness [52, 22, 21, 23, 31, 17, 36, 12, 43, 60].

The diagnosis of OA is usually based on physical examination, clinical signs, and radiographic evidence [20, 17, 43, 21, 60]. Bio-

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chemical biomarkers in serum/plasma, synovial fluid and urine have become exceptionally useful in diagnosis and treatment of OA [2, 21-23].

The two main objectives in managing OA include: 1) minimizing joint pain by reducing the inflammation, and 2) slowing the progression of cartilage damage, thereby increasing joint flexibility and enhancing quality of life. Until recently, symptom-modifying drugs such as analgesics (i.e., acetaminophen) and NSAIDS were the preferred choice for OA management in both humans and animals. Unfortunately, NSAIDS have been associated with serious side effects in the renal, hepatic, cardiovascular, and GI systems [42, 44, 3, 48, 29, 46, 53, 6]. During the past two decades, an alternative to NSAIDs has been the use of nutraceuticals [8, 28, 40, 34, 20-23, 43, 13, 60].

In a number of studies, Green lipped mussel (Perna canaliculus) extract (GLME) alone or in combination with other ingredients has been found to be a therapeutically effective and safe nutraceutical for OA dogs [9, 10, 11, 4, 47, 25, 50, 60]. GLME is a source of glucosamine, chondroitin, omega-3 fatty acids, vitamins (C and E), minerals (such as zinc, copper, iodine and manganese), enzymes and peptides/proteins. By having these vital constituents, GLME exerts antioxidative, anti-inflammatory, anti-cyclooxygenase, anti-lipoxygenase, chondroprotective and anti-arthritic activities and retards the degenerative process in cartilage [39, 33, 15, 38, 16, 60].

Recently, there has been interest in the use of deer velvet extract to treat OA. Deer velvet extract contains chondroitin sulfate and the anti-inflammatory pilose antler peptide. In a clinical trial, deer velvet extract was found to improve peak ground reaction force and owner assessed activity score (41). GLME and deer velvet extract (as well as enzogenol and shark cartilage) are components of the nutraceutical BVP-01 marketed to alleviate the signs of OA in dogs.

There have been few randomized clinical trials examining the effect of nutraceuticals on qualitative (e.g. clinical examination and owner perception) or quantitative measures (gait analysis) in dogs with clinical signs of OA [28, 40, 20, 43], and even fewer trials quantifying the effect of GLME [4, 8-11, 15, 47] or deer velvet extract [41]. To the authors' knowledge, there have not been any trials examining the use of GLME and deer velvet extract together in a product or studies involving any product containing GLME, deer velvet, enzogenol and shark cartilage.

We conducted a longitudinal, multi-centric, blinded, placebo-controlled study to examine the effects of a proprietary nutraceutical formulation BVP-01 compared to those of a positive control (Rimadyl™) and negative control (placebo) regimen, in a population of dogs clinically affected with OA. The hypothesis was that owner assessment, clinical examination and kinematic evaluation of parameters of lameness in OA dogs would improve after nutraceutical supplementation in comparison to the placebo Group.

Materials and Methods

Dogs

Dogs were selected from 5 primary accession veterinary clinics located in the lower North Island and upper South Island of New Zealand. Entry into the trial was based on the dogs being in good clinical health but presenting with clinical and/or radiological signs of chronic lameness. Dogs were excluded if they were clinically unhealthy (e.g. kidney or liver disease), presented with complicating clinical conditions such as septic or immune-mediated polyarthritis, or had a history of systemic or intra-articular treatment for lameness with either NSAID's for up to four weeks and/or pentosans, glucosamines, or corticosteroids for up to four months, prior to the commencement of this study. Radiographs were examined by a specialist to exclude dogs with conditions that would be likely to preclude their responding at all to therapy.

Experimental design

This was a blinded randomized trial, except that moderate to severely lame dogs (based on lameness score and clinical evaluation) were immediately allocated to Group 4 by the clinician. Mild to moderately affected dogs were randomly assigned into one of 3 treatment groups:

Group 1: BVP-01 (each tablet contained 175mg GLME, 25mg deer velvet, 100mg shark cartilage, 5mg enzogenol), given in one dose per day as either 1 tablet (small dog BW up to 15Kg), 2 tablets (medium dog 15-30Kg) or 3 tablets (large dog over 30Kg) for 12 weeks.

Group 2: Placebo (starch tablet) for 6 weeks, then BVP-01 for the following 6 weeks at the same dose rate as in Group 1.

Group 3: BVP-01 and Rimadyl™ (Zoetis Animal Health), with a maximum dose of carprofen 2.2mg/kg per os daily for 6 weeks, then only BZS for the following 6 weeks at the same dose rate as in Group 1. Rimadyl™ was offered as a single dose of either a 20mg or 50mg tablet or a combination of tablets based on dog body weight.

Group 4: Moderate to severely lame dogs had the same medication protocol as Group 3.

The study was approved by the PharmVet Solutions Animal Ethics Committee.

Owner assessment

Weekly assessment: The activity level of the dog was assessed weekly by the owner, based on the ability of the dog to perform predefined activities (such as walking, running, climbing up and down stairs, and playing/exercising). The owner assessed the activity using a difficulty scale from 0 (no difficulty) – 4 (cannot perform) and NA (cannot evaluate). The pain associated with these activities was also graded using a 4-point pain scale from score 0 (no pain) – 3 (constant pain irrespective of activity).

Clinical examination

Clinical examinations were performed at the participating clinics on weeks 0, 6, and 12 on each of the study dogs. Clinical assessment consisted of examination of all four legs, grading of the severity of lameness in each of which was scored on a 0 (least) - 4 (severe lameness) point scale. A Total Dog Lameness score (sum of all four legs) was determined by adding the four limb scores.

Articular mobility was scored in each of the four limbs, in the joint which the clinician identified as restricting movement, using a 0-4 point scale in which 0 was normal and 4 was >50% reduced range of motion. The sum of the four scores produced a total articular mobility score.

Articular pain was evaluated in the joints assessed for articular mobility and was scored using a 0-4 point system, in which 0 = no signs of pain and 4 pain causing the limb to be non-weight-bearing at rest. The sum of the four scores produced a total articular pain score.

Kinematics

At the time of the clinical examinations, data were collected for kinematic analysis. Reflective markers (15mm diameter, Oracal Reflective Tape, Orafol Europe GmbH, Oraneinburg, Germany) were placed on the lateral aspect at the following anatomical sites: metacarpophalangeal joint space, metacarpal joint, humeroradial joint, scapulo-humeral joint and the proximal scapula. In the hindlimb the sites for marker placement were the metatarsophalangeal joint, metatarsal joint, femoral-tibial joint, coxo-femoral joint, the tuber coxae and the 12th rib.

The dogs were trotted on a loose lead in a straight line between two cones placed 3m apart on a level even surface. A stationary digital video camera (mini DV cameras) with a 1/1000 shutter rate was placed 2.5-4m perpendicular to and at the center of the path trotted. Data was captured from both the left and the right side of the dog.

The video footage (50Hz) was imported (Pinnacle studio v8.12, Pinnacle Systems Inc, Ca, USA) and digitized within commercial gait analysis software (Ariel Dynamics Inc, Trabuco Canyon, CA). The digitized and processed kinematic data was exported to MS Excel for manipulation. The kinematic data for the forelimb and hindlimb were calculated and analyzed separately, and were based on the ROM of the whole limb. The ROM was the total craniocaudal displacement of the most distal limb marker in relation to the pivot point (marker) in either the shoulder or hip.

Statistical analysis

Data were analyzed using a general linear model. The clinical and owner observation scores were summed for the individual legs to provide a total dog score for the specified assessments of activity, pain and lameness for each limb. Within the model, the examination day and the treatment Group were treated as fixed factors. The dog ID was treated as a random factor.

Kinematic data were analyzed using a general linear model with examination day and treatment groups as fixed factors, dog ID was treated as a random factor, and velocity of the dog was treated as a covariate.

To examine the effect of week and lameness grade, multiple linear regression models with binary coding for the week or assessment and lameness grade were fitted to the percentage change in range of motion of the forelimb and hindlimb.

Data was analyzed within SPSS (Chicago, IL, USA) with a significance level set at $p<0.05$. Data is presented as mean ± standard error (SE) unless stated otherwise.

Results

Dogs

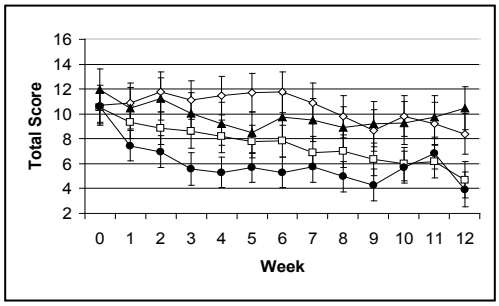
Seventy four dogs were accepted into the trial, and clinical information was obtained from 71 of them. There were 19 dogs in Groups 1, 2 and 3, and 14 dogs in Group 4. The dogs were either not lame (n=9), or lame in one leg (n=25), two legs (n=24), three legs (n=8), or in all four legs (n=5). The group means ± SD for age and weight of Groups 1 to 4 respectively were 8.6 ± 3, 7.1 ± 3.5, 6.9 ± 3.3 and 8.5 ± 3.5 years and 31.1 ± 11.6, 33.7 ± 7.2, 30.4±8, and 37±11 Kg.

Owner weekly assessment

Activity: Total activity score was significantly improved (decrease in total activity score, p=0.024) over the week 0 value in Group 3 by week 2, and by week 9 in Group 1 (p=0.043) (group activity score is the mean of the scores of all the dogs in the group). There was no significant improvement in total dog activity score for Groups 2 or 4 by the end of the 12week observation period (Figure 1).

There was no significant inter-group difference in dog activity at the start of the trial (week 0). Prior to week 6, the activity score for Group 3 was significantly better (i.e. lower score) than that in Group 2 from week 2 onwards. After week 6, when all dogs were on BVP-01, the difference between Group 2 and 3 remained significant until weeks 10 and 11 ($p<0.05$). There was no significant difference between the scores of Group 2 and Groups 1 and 4 prior to, or after week 6, by which time all dogs were treated with BVP-01.

Figure 1. Total dog activity score for difficulty, observed weekly by owners.



□ Group 1 ◊ Group 2 ● Group 3 ▲Group 4

Pain

At week 0 there was no significant difference between groups. A significant reduction in owner assessment of pain compared to week 0 value was observed at week 3 for Group 3 (p=0.005), and by week 10 for Group 1 (p=0.033). There was no significant change from week 0 values for the dogs in Groups 2 or 4 during the period of the study (Figure 2). At week 2, Group 1 had a significantly better pain score than did Group 2 (p=0.038), and this remained significantly less than the Group 2 pain score until week 12.

The dogs in Group 3 were reported to have significantly less pain compared to the dogs in Group 2 from weeks 4-11 ($p<0.05$).

Clinical examination

Lameness: At weeks 0, 6 and 12, total dog lameness score was significantly greater (more severe lameness) in Group 4 than the other three Groups (p=0.014) (Figure 3). There was no significant effect of clinical observation day, and there was no significant interaction of clinical observation day and treatment Group on the total dog lameness score.

Articular Mobility: There was no significant difference in the articular mobility score due to group, clinical examination (weeks 0, 6, 12) or interaction between group and clinical examination (Figure 4).

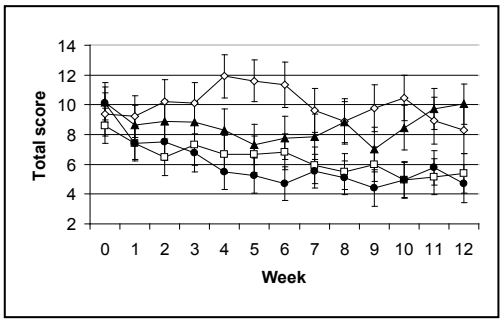
Articular Pain: There were significant differences within treatment groups between weeks 0 and 6, with a significant reduction in articular pain score in Group 1 (p=0.021), Group 2 (p=0.008) and Group 3 (p=0.022), but not Group 4 (p=0.206) (Figure 5). There was no significant change in articular pain score between weeks 6 and 12 for any treatment Group.

Kinematics: Screening of video footage of the 71 dogs at week 0 showed that quality of kinematic outputs was inadequate in one toy breed dog, one long haired retriever, and in three dogs that were missing the shoulder marker and these data were excluded. One clinic did not provide video footage for week 12, resulting in the loss of data of another 8 dogs in week 12, thus restricting longitudinal kinematic analysis to 58 dogs.

Forelimb ROM: Pair-wise comparisons showed that there was no significant effect of week on the % change in forelimb ROM (Figure 6). Some treatment groups had between-week differences that were almost significant. For instance, the improvement in ROM in Group 1 tended to be larger than that in Group 2 (p=0.079). Group 3 tended to have a greater improvement than either Group 2 (p=0.055) or Group 4 (p= 0.084).

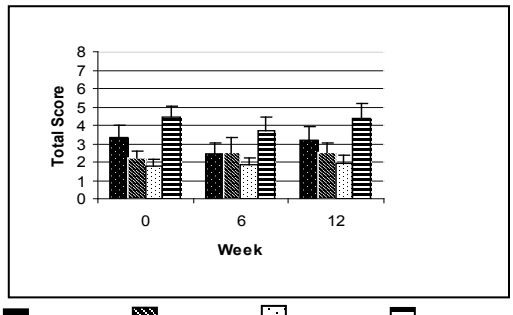
Multiple linear regression of the percentage change in forelimb ROM identified that velocity (0.526±0.037, p=0.001) and clinical

Figure 2. Total dog activity score for pain, observed weekly by owners.



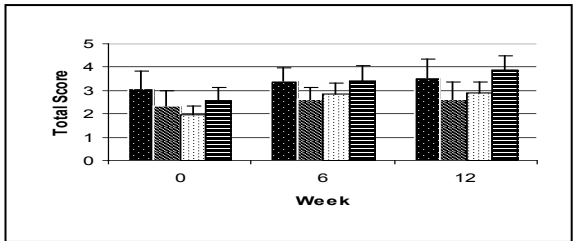
□ Group 1 ◊ Group 2 ● Group 3 ▲ Group 4

Figure 3. Total dog lameness score at scheduled clinical examinations.



Group 1 Group 2 Group 3 Group 4

Figure 4. Total dog articular mobility score at scheduled clinical examinations.



Group 1 Group 2 Group 3 Group 4

examination week ([week 12], 4.2±1.79, p=0.02) were significantly related to the percentage change in forelimb ROM from the week 0 examination. There was no significant effect of clinicians lameness score on forelimb ROM.

Hindlimb ROM: The ROM in the hindlimb was insignificantly less than that observed in the forelimb (39.05±0.32 vs. 40.11±0.35, p=0.025). There was a significant effect with all treatment groups improving in ROM at week 12 (P<0.04), which was less than that observed with the forelimb (Figure 7). There was no significant difference between the treatment groups at either time period.

The same regression model (see above) was fitted to the hindlimb data. In contrast to the forelimb, the only parameter that was significant in the regression model was the velocity (p<0.001). The observation week was close to significance (P=0.074) and the trend was for a 2.9% improvement in gait at the week 12 observation. There was no clear or significant effect of the dog lameness score on the ROM in the hindlimb.

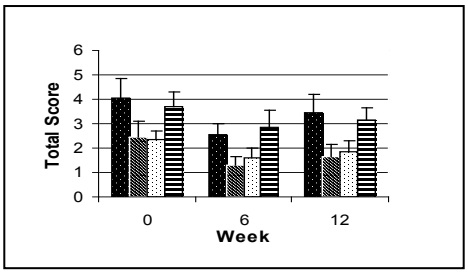
Discussion

In this trial, the 74 dogs recruited represented a heterogeneous cross- section of the domestic canine population. A loss of data from only 3 of the 74 dogs for clinical data for a multi-centred longitudinal trial is more than acceptable. It was unfortunate that the video footage for 8 dogs from a clinic was not obtained as this would have improved the statistical power of the kinematic analysis.

The trial design was aimed at treating the dogs for mild, moderate or severe clinical signs of OA. Dogs with mild to moderate OA were randomly allocated into Groups 1, 2, and 3. Dogs with severe OA were allocated into Group 4. These dogs required immediate medication with a known anti-inflammatory effect, and it would have not been ethical to place them in a trial with a one in three chance of receiving a placebo. The testing of many natural products/nutraceuticals is generally restricted to the use of dogs with mild to moderate clinical signs of OA [20, 58, 31, 17, 12, 43, 60]. The allocation of dogs to Group 4 provided an opportunity to compare responses in dogs with severe OA to mild or moderate OA in regards to severity of disease and responses of dogs to treatment.

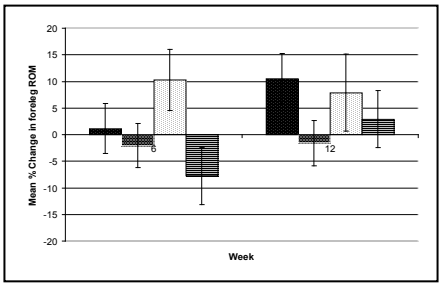
The owners of dogs given Rimadyl™ (R) + BVP-01 (Group 3) and BVP-01 (Group 1) initially reported significant improvement in dog activity and pain scores at weeks 2 and 3 and at weeks 9 and 10, respectively. Most dogs (70%) in Group 1 had positive responses by week 7. It is of interest to note that the improvement observed in Group 3 was maintained after the removal of

Figure 5. Total dog articular pain score at scheduled clinical examinations.



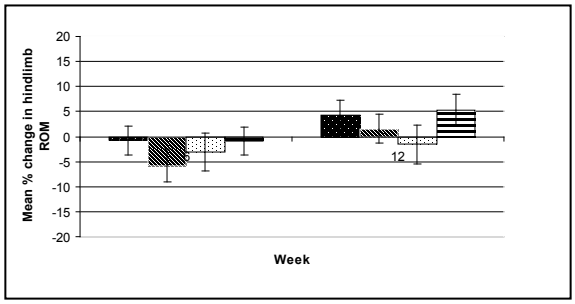
Group 1 Group 2 Group 3 Group 4

Figure 6. Mean percentage change in the forelegs range of motion from week 0 for the four treatment groups.



Group 1 Group 2 Group 3 Group 4

Figure 7. Mean percentage change in the hindlimb range of motion from week 0 for the four treatment groups.



Group 1 Group 2 Group 3 Group 4

Rimadyl™ at week 6. In contrast, clinical examination identified no differences between groups for lameness and articular mobility, with all groups having a reduction in articular pain as assessed by the clinician. It is highly likely that because the clinical signs of OA typically vary in severity over time, the clinical assessments performed every 6 weeks would be less sensitive in detecting what are often subtle changes in clinical signs compared to owners, who observe their dogs daily and most likely give "average" assessments for the week in question.

Kinematic gait analysis has been used in dogs for the assessment of lameness (14, 7, 40). In the present study, significant improvement in kinematic parameters were observed at week 12 in dogs given R + BVP-01 (Group 3) (p=0.055), and improvement was close to statistical significance in dogs given only BVP-01 (Group1) (p=0.079). These improvements in gait were identified after the improvement recorded by the owners of the dogs. This, together with the "average" rather than "One-off" assessments performed by the clinicians (see above), may indicate the sensitivity of the owner assessment to detect early and subtle changes in behavior that may not appear as improvements in gait until later.

It appears that the earliest effect of BVP-01 is the reduction in pain and an improvement in activity level. In many dogs, OA is a chronic affliction that they have endured for months or years, resulting in an abbreviated and cautious gait, due to the presence of pain, the expectation of pain, and changes in tissues which accompany their long-term reduced use. Perhaps it is not until these changes are reduced or reversed that changes in gait become sufficient to be detected by kinematic examination. However, kinematic examination was not frequent enough to determine the exact time at which such changes would first have been detectable.

In the present study, as expected Rimadyl™ in the first 6 weeks of treatment had an almost immediate effect on the perceived assessment of pain and activity, as it has been reported in previous clinical studies with carprofen, meloxicam, or etodolac in OA dogs [7, 43, 37]. In several clinical studies conducted in OA dogs, carprofen (Rimadyl™) has been used: 1) alone for the treatment of OA in dogs [26, 59, 40] as a positive control or in combination with nutraceuticals [37, 25, 18]. In addition to inhibition of COX-1 and COX-2 activities [51], carprofen has been reported to simultaneously reduce progression of morphological changes in cartilage and subchondral bone in OA dogs [45].

In contrast to Rimadyl™, the apparent anti-inflammatory effect of BVP-01 took longer to occur. This is consistent with a longer period required for an anti-inflammatory nutraceutical to have an effect than NSAID's [24, 47, 37, 20, 31, 17, 12, 43, 60]. However, serious adverse effects with the long-term use of the COX inhibiting NSAIDs have been associated with hepatic, renal, cardiovascular and GI systems [42, 44, 40, 3, 48, 29, 46, 53, 6]. The reduction in pain and immobility observed by owners was similar between the BVP-01 alone and R + BVP-01 groups, indicating a similar level of efficacy in pain reduction and improvement in gait between Rimadyl™ and BVP-01. The advantage of BVP-01 is that it could be used for the long-term treatment of dogs with chronic OA without the clinical complications and costs commonly associated with some NSAID's. Findings of the present study suggest that a suitable strategy for dogs with mild OA is to administer Rimadyl™ and BVP-01 concurrently for the first 6 weeks and then continue long-term management with BVP-01 as a standalone treatment to avoid suffering associated with OA in dogs while waiting for BVP-01 to show its effects.

BVP-01 is a unique nutraceutical that consists of green lipped mussel extract (GLME), deer velvet extract, shark cartilage, and enzogenol. GLME is known to have multiple constituents (glucosamine, chondroitin, omega-3 poly unsaturated fatty acids (omega-3 PUFAs), eicosatetraenoic acid (ETA), vitamins, enzymes, peptides, and proteins). Some of these constituents are reported to exert antioxidative, anti-inflammatory, anti-cyclooxygenase, anti-lipoxygenase, chondroprotective, and anti-arthritic activities, in addition to lubricating the joints and retarding the degeneration of cartilage [39, 33, 15, 38, 36, 16, 21, 23, 60]. Recently, Webber et al (2020) demonstrated that Flex Choice™ (Vets Plus Inc., Menomonie, WI, USA), by having GLME, in addition to Boswellia serrata extract, krill oil, hyaluronic acid, astaxanthin, and iron transport tocopheryl polyethylene glycol succinate (IT-PGS), markedly reduced OA associated inflammation and pain in moderately OA dogs.

Since oxidative stress, inflammation, and degeneration of cartilage are major detrimental processes in the pathophysiology of OA, prevention and/or reversal of these processes appear to be the rationale for the use of GLME in OA dogs. Furthermore, GLME is gastroprotective and does not affect platelet aggregation, suggesting that ETA may selectively block the pro-inflammatory COX-2 pathway rather than the physiologically important COX-1 pathway [49, 4]. Many other herbs and nutraceuticals also display COX-1 inhibition but majority of them are either less bioavailable or clinically not proven to be effective. For example, curcuminoids are strong COX inhibitors and inhibit proinflammatory cytokines but their bioavailability is considerably poor. However, we have recently developed a metallic complex of curcuminoids (CurCos-os) which is highly bioavailable and stable. In our upcoming studies, it would be interesting to see if CurCos-os in conjunction with BVP-01 will offer greater anti-OA effects than the NSAIDs.

The extract of deer/elk velvet antlers has been used for treating various diseases and ailments for thousands of years. These extracts are reported to consist of collagen as a major protein, a pilose polypeptide of 68 amino acids, pantocrin, glycosaminoglycans (primarily chondroitin sulfate), and nerve growth factors, which may exert anti-inflammatory, antioxidative, and regenerative activities against OA in dogs, humans and other species [62, 63, 54, 55, 1, 41, 32, 19, 27, 30]. Studies suggest that chondroitin sulfate present in velvet antler mediates anti-OA effects [54, 55]. Reduction of pain and improvement of the myotropic effect and daily activity of OA dogs may be due to the anti-inflammatory, antioxidative, adaptogenic, myotropic and anti-arthritic properties of glycosaminoglycans, pilose peptides and pantocrin present in the velvet antler extract. Recently, in an experimental study in mice, Xie et al. (2019) [61] reported that velvet antler polypeptide may enhance extracellular matrix (ECM) synthesis by down regulating matrix metalloproteinase-13 (MMP13), a disintegrin metalloproteinase with thrombospondine motif 5 (ADAMTS5) and ADAMTS4 (aggrecanase-1) via Wnt/β-catenin signaling pathway, thereby ameliorating signs of OA. Furthermore, pilose polypeptide is also reported to promote chondrocyte proliferation via the tyrosine kinase signaling pathway. In a placebo-controlled double-blind study, Moreau et al. (2004) [41] found that administration of powdered elk velvet antler alleviated the signs of OA and it

was well tolerated in dogs, as observed in the present study with BVP-01.

In BVP-01 supplement, in addition to GLME and deer velvet antler extract, shark cartilage is also a source of chondroitin sulfate, which is proven to ease OA in dogs, humans and horses. Notably, chondroitin sulfate is more effective when given in combination with glucosamine [5, 20-23]. Shark cartilage is also known to boost the immune system, thereby exerting an anti-OA effect. Another important ingredient in BVP-01 supplement is enzogenol, a flavonoid-rich extract from Pinus radiata, which might have exerted anti-OA effect due to its ani-inflammatory, antioxidative and blood circulation promoting properties.

It can be concluded that BVP-01 is a unique nutraceutical that consists of several ingredients and is found to be quite effective against mild to moderate OA in dogs exerting multiple mechanisms, such as anti-inflammatory, antioxidative, immunomodulatory, analgesic, blood circulation promoting, chondroprotective and regenerative activities. Also, BVP-01 is safe and well tolerated by OA dogs. Rimadyl™ treatment for the first 6 weeks eliminated suffering in dogs before BVP-01exerted its anti-inflammatory and anti-arthritic effects.

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