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A medicinal herb-based natural health product improves the condition of a canine natural osteoarthritis model: A randomized placebo-controlled trial

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ABSTRACT

An oral herb-based natural health product (NHP) was evaluated in the canine natural osteoarthritis model. At baseline, the peak vertical force (PVF, primary endpoint) and case-specific outcome measure of disability (CSOM) were recorded in privately-owned dogs. Dogs (16/group) were randomized to receive NHP formulations or a negative control. The PVF was measured at week (W) 4 and W8. Daily locomotor activity was recorded using accelerometer. The CSOMs were assessed bi-weekly by the owner. The NHP-treated dogs ($n = 13$) had higher PVF at W4 ($p = 0.020$) and W8 ($p < 0.001$) when compared to baseline. The changes at W8 were higher than control dogs ($n = 14$, $p < 0.027$) and consistent with Cohen's d effect size of 0.7 (95% confidence interval: 0.0–1.5). The NHP-treated dogs had higher locomotor activity at W8 ($p = 0.025$) when compared to baseline. No significant change was observed for the CSOM. The NHP improved the clinical signs of osteoarthritis in this model.

1. Introduction

Osteoarthritis (OA) is by far the most common human musculoskeletal disease, affecting millions worldwide (Lawrence et al., 2008). The prevalence of OA in dogs is also high, particularly in geriatric animals, being estimated to be five times that observed in mature adults (Shearer, 2011). In dogs, OA results mainly from traumatic insults to the cranial cruciate ligament (CCL), and hip or elbow dysplasia (McLaughlin, 2001; Roush, 2001). Cascades of biological and biomechanical events then merge to induce and perpetuate structural changes at the level of the entire joint, which, as in humans, lead to crippling pain, disability and poor quality of life (Cook, 2010; Johnston, 2001; Madsen and Svalastoga, 1994; Martinez, 1997; Martinez and Coronado, 1997).

Naturally-occurring models of OA have been proposed to accelerate the development of human therapeutics (Pelletier et al., 2010), and a recent review of experimental data underlined the high translationability of outcomes obtained from canine OA models, in particular the response to treatment (Moreau et al., 2013). Undertaking a trial in privately-owned dogs afflicted by natural OA would provide preclinical data and additional evidence on the therapeutic potential of new compounds under development. Of note, the potential of several therapeutic approaches has been tested in different randomized controlled trials (RCTs) in the canine natural OA model using force platform gait analysis as an outcome measure of pain-related functional impairment. These tested compounds include non steroidal anti-inflammatory drugs (NSAIDs) (Budsberg et al., 1999; Moreau et al., 2003, 2007), therapeutic diets (Moreau et al., 2012b; Rialland et al., 2013; Roush et al., 2010) as well as natural substances (naturaceuticals) used to restore or maintain good health status (Hielm-Bjorkman et al., 2009; Moreau et al., 2004, 2012a). The latter therapeutic class is considered by the authors as natural health products (NHPs) which originate from plants, fruits and vegetables, animals, microorganisms and marine sources.

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Currently, no effective therapy seems able to alleviate the clinical signs of OA in humans or dogs. As relief of pain and the preservation of joint structure cannot be claimed with certainty for currently approved treatments, there is a need for effective strategies to improve the condition of afflicted patients.

Medicinal herbs have long been used in traditional medicine and there is considerable evidence that such NHP and their derivatives may play beneficial roles in OA (Mobasheri, 2012). *Harpagophytum procumbens*, also known as devil's claw, is a South African plant which includes harpagoside as one of its major biologically active phytochemical compounds. A large body of evidence supports the efficacy of harpagoside and related extracts in alleviating symptoms of OA in humans (Gagnier et al., 2004). Resin extracts from the *Boswellia serrata* tree have been demonstrated to be effective in alleviating the clinical signs of OA in humans (Kimmatkar et al., 2003) and dogs (Reichling et al., 2004). Active phytochemical compounds isolated from *Ribes nigrum* leaves showed anti-inflammatory properties *in-vivo* in chrondrocyte assays (Garbacki et al., 2002), while its seed oil was an effective treatment for active rheumatoid arthritis (Leventhal et al., 1994). *Salix alba* extracts have recently been reported to have *in-vitro* chondroprotective properties in primary canine articular chondrocyte culture (Shakibaei et al., 2012). These extracts seem also to be potent in counteracting low back pain in humans (Gagnier et al., 2007). In rodent models of inflammation, an extract from *Tanacetum parthenium* demonstrated antinociceptive and anti-inflammatory effects (Jain and Kulkarni, 1999). Classified as a herb, bromelain is a digestive enzyme found in the stem and the fruit of *Ananas comosus*. This herb has been shown to have anti-inflammatory properties mediated through prostaglandin synthesis (Lotz-Winter, 1990). Finally, curcumin, which is the main biologically active phytochemical compound of *Curcuma longa*, showed inhibitory actions against major inflammatory mediators (Aggarwal et al., 2013; Henrotin et al., 2013; Mathy-Hartert et al., 2009; Mobasheri et al., 2012) while being effective in reducing pain in OA knee patients (Kuptniratsaikul et al., 2009; Madhu et al., 2013). In agreement with those findings, a recent Cochrane systematic review concluded to potential benefits of oral herbal medicines, being more effective than placebo (Cameron and Chrubasik, 2014). However, as also highlighted, further high quality, fully powered studies are required to gain insight in the therapeutic potential of medicinal plants as well for other NHPs (Vandeweerd et al., 2012).

These studies suggest that NHP formulations containing the aforementioned medicinal herbs as principal ingredients might be useful in the management of OA. Whether or not such formulations are effective against the functional impairment that prevails in a model of natural OA needs to be scrutinized rigorously. With the scope of providing strong evidence-based findings, the aim of this RCT was to assess NHP formulations in the canine natural OA model when compared with dogs receiving a placebo over an 8-week duration.

2. Materials and methods

2.1. Design and subject selection

This study was a randomized, double-blind, parallel-group, placebo-controlled trial. Dogs were evaluated over either 56 or 61 days depending on the balanced attribution of locomotor activity recording (see Section 2.3). The trial was conducted under the approbation of the Institutional Animal Care and Use Committee (#Rech-1437) in accordance with the guidelines of the Canadian Council on Animal Care. All owners provided written informed consent.

Adult dogs weighed more than 20 kg and had radiographic evidence of OA exclusively at the hip or stifle joints. Radiographs (hips, stifles, and elbows) were obtained under sedation as previously described (Moreau et al., 2010). Hind limb lameness in association with the presence of OA was confirmed by veterinary surgeons. At the time of screening, all dogs were free of any compound purported to relieve the clinical signs of OA according to washout periods ranging between 4 and 12 weeks. Hence, a 4-week washout period was respected for oral NSAIDs and a 6-week period for NHPs including fatty acid supplements, OA therapeutic diets or treats. Dogs having received injectable pentosan polysulfate sodium or corticosteroid 1 year before the screening visit were not eligible. A 12-week washout period was requested for injectable polysulfated glycosaminoglycan and hyaluronan, and for oral or topical corticosteroid. During the study, dogs were exempted from the administration of any type of medication except those prescribed for exo- and endoparasite control. Additional exclusion criteria were as follows: dogs with surgical repair of the cranial cruciate ligament within 1 year prior to study initiation, dogs suffering from neurologic or other musculoskeletal lesions, dogs that underwent orthopedic surgery within the past year and dogs with CCL disease having gross instability (positive drawer motion upon orthopedic examination).

2.2. Complete blood count and biochemistry panel

To ensure that some parameters were within normal limits during the study, each dog underwent routine blood hematological and biochemical analyses in order to evaluate health status at study initiation (baseline, day 0) as well as at week 4 (day 28) and week 8 (day 56). A veterinary clinical pathologist examined all blood counts and biochemistry panels.

Many herbs can increase the risk of bleeding through antiplatelet properties (Samuels, 2005). The buccal mucosal bleeding time is a simple test commonly used in the clinical setting to detect platelet dysfunction in dogs (Callan and Giger, 2001). Each dog underwent a buccal mucosal bleeding time procedure at baseline and at week 8. Mucosal punctures were performed on the upper labial mucosa, using a disposable, fully automated incision device (Surgicutt® Bleeding Time device, International Technidyne Corporation, USA). This device provided a controlled incision of 1.0 mm (depth) per 3.5 mm (length). The time of incision was noted, and circular filter paper (Whatman®, USA) was held 1–2 mm away from the incision to blot the blood, taking care not to disrupt the clot, or to allow blood to drip into the dog's mouth. The end point was when the incision stopped bleeding. Normal buccal mucosal bleeding time is defined to be less than 3 minutes.

2.3. Randomization, blinding and therapy regimen

Thirty-two privately-owned dogs were randomly allocated in two equal groups (placebo or NHP) according to a permuted-block randomization procedure, which included six blocks of four treatment possibilities (A or B) distributed in a 1-to-1 ratio (i.e. AABB, ABAB, ABBA, BBAA, BABA and BAAB). Among those blocks, eight were randomly selected using random integers to define the treatment allocation sequence. Also, seven blocks were randomly selected using random integers to allocate seven motor activity recordings to treatment A and seven others to treatment B. The 32 treatment allocations (with or without locomotor activity recording) were transcribed on individual cards in sequentially numbered, sealed, opaque envelopes to ensure concealment. A third party was responsible for the randomization process and for the treatment preparation. At the trial site, both treatments were labeled exclusively as treatment A or treatment B and were encapsulated identically. The trialists, the animal health technicians and all dog owners were blinded to which treatment (A or B) was given to each dog. The key code revealing what referred to treatments A and B remained confidential with the third party and was revealed only after study completion and preliminary analyses.