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RESEARCH ARTICLE

Long-Term Valuation of Oral Mavacoxib in Osteoarthrosic Dogs Using Force Platform Analysis

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ABSTRACT

The aim of this study was to assess the efficacy of mavacoxib, a cox-2 inhibitor, to improve the peak vertical force (PVF) and vertical impulse (VI) of lame client-owned dogs with severe coxofemoral osteoarthrosis (OA) by using a force platform. A group of ten canarian presa dogs with lameness and pain for a severe osteoarthrosis due to hip dysplasia were used for this study. Five additional sound dogs of the same breed were used as control groups. A single force platform used to register vertical forces was mounted in a 7 m runway. Mean (± SD) values for speed of dogs were 1.6±0.5 m/s. Data corresponding with 5 valid trials were recorded at walk at day 0, 7, 60 and 180 after starting treatment procedure. The dosing regimen consisted of a loading oral dose of 2 mg/kg to be repeated after 14 days, thereafter the dosing interval was 1 month. OA dogs showed a significant improvement of PVF after two months of about 7% bm in the force exerted by diseased limbs and a significant VI improvement after two months of about 1.6% bm in the VI exerted by diseased limbs. This study clearly showed that dogs treated with mavacoxib increased PVF over time, as soon as seven days after medical therapy, demonstrating a high potential for clinical use in the treatment of lameness associated with OA of hip joint.

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INTRODUCTION

Objective evaluation of gradual recovery of lameness during or after treatment is a discussed topic (Mölsä *et al.,* 2010). Veterinary clinicians assess pain severity in their patients based on vocalization, activity level, degree of lameness, and reaction to manipulation; however, all these methods are subjective and may be influenced by external factors. Moreover, pain scoring systems also do not provide a fully objective evaluation (Horstam *et al.,* 2004).

Biomechanical measurement of ground reaction forces (GRF) in dogs is a well-established method used to describe both normal canine gait and the type/severity of lameness. Force platform gait analysis is an objective, quantitative, non-invasive and reliable method to characterize the ground reaction forces during locomotion both in humans and dogs (Anderson and Mann, 1994; Ragetly *et al.,* 2012). Force platform gait analysis has been consistently used in dogs after cranial cruciate ligament surgery (Jevens *et al*., 1993), total hip replacement (Budsberg *et al*., 1996; Dueland *et al.,* 2001), triple pelvic osteotomy (Tano *et al*., 1998) and dorsal laminectomy (Van Klaveren e*t al*., 2005; Suwankong *et al*., 2007), as well as to verify the efficacy of different therapeutical strategies for the treatment of osteoarthrosis (OA) in dogs (Hielm-Björkman *et al.,* 2012; Eskelinen *et al.,* 2012)

Some authors demonstrated that about 20% of all dogs are presented at some time during their life with clinical signs of OA at veterinary practices. Aim of OA treatment in dogs is to neutralize the irreversible structural changes and it often involves medical therapy, including administration of non-steroidal anti-inflammatory drugs (NSAIDs), which have been shown to produce clinical benefits (Sanderson *et al.,* 2009; Moreau *et al.,* 2010). Therefore, it is assumed that control of pain and inflammation will increase the functionality of the OA affected joints (Pelletier *et al.,* 2000).

Mavacoxib (Trocoxil™, Pfizer, MY, USA) is a NSAID cyclooxygenase-2 (COX-2) inhibitor, structurally

related to celecoxib (Penning *et al.*, 1997). The metabolically labile aromatic methyl substituent of celecoxib has been replaced in mavacoxib with a metabolically stable fluoro-substituent (Paulson *et al*, 2000). This change resulted in a compound with low clearance and a prolonged t½ (Cox *et al.*, 2010). These pharmacokinetic characteristics make Mavacoxib unique among other NSAIDs (e.g. carprofen, celecoxib, deracoxib), that have clearance values at analgesic or therapeutic osteoarthritic doses in laboratory dogs more than six times greater than mavacoxib (Paulson *et al*., 2001).

In previous studies, the efficacy of NSAIDS was verified using a single force plate mounted in a walkway, and the dogs were walked or trotted over the plate (Bockstahler *et al*., 2007). The aim of this study is to assess the efficacy of mavacoxib to improve the weight-bearing capacity of lame client-owned dogs with OA secondary to hip dysplasia, by using a force platform to measure PVF and VI.

MATERIALS AND METHODS

Animals: 10 adult canarian presa dogs (5 males, 5 females) with lameness and pain attributed to osteoarthrosis by hip dysplasia were eligible for inclusion in the study. None of the dogs was forced to develop physical activity. A x-ray examination was required to confirm the presence of osteoarthrosis as evidenced by subchondral bone sclerosis, bone remodelling, osteophytes or enthesophytes in the affected joint (degrees D and E of hip dysplasia for the International Cinologic Federation).

Additional radiographs of knee and elbow joints, physical and orthopedic examinations were performed to ensure that hip osteoarthrosis was the main reason for the observed clinical signs and general health was otherwise normal. Moreover, dogs included in this study needed to be affected by chronic OA and not have received, for at least 2 months, any kind of medications (e.g. non-steroidal anti-inflammatory drugs, analgesics), nutraceuticals (e.g. glucosamine or chondroitin, vitamin E, omega 3 fish oil), or adjunctive therapies (e.g. acupuncture). The control group consisted of five sound and healthy dogs of the same breed.

The dosing regimen for OA group consisted of a loading dose of 2 mg⁄ kg bw to be repeated after 14 days, thereafter the dosing interval was 1 month.

Measurements: A single, dynamometric and permanently mounted force platform (Pasco®, California, USA) was used to acquire PVF and VI. The device platform was mounted in the center of, and level with, a 7 m runway covered by a rubber carpet. In order to avoid interferences, the carpet covering the force platform was independent of the surrounding. All dogs were always guided at walk over the force plate by the same handler. Velocity was measured by use of a motion sensor (Pasco®, California, USA) positioned 1m apart.

Five valid trials at a sampling frequency of 250 Hz were obtained of each animal. A trial was considered valid when the limb fully contacted the force platform, and with the dog walking next to the handler without pulling on the leash. The trial was discarded if the dog was distracted during the measurement, or if the limb struck the edge of the force plate or any portion of the contra-lateral paw hit the force plate. One member of the research team evaluated the trial to confirm which limb touched the center of the force platform.

The platform was interfaced with a dedicated computer using *datastudio* (Pasco®, California, USA), a software specially designed for the acquisition, numerical conversion and storage of data. Acquisition of data was performed before starting treatment (D0) and at day (D): D7, D60 and D180. The obtained PVF (N) and VI (N.s) were normalized relative to body weight (% BW) to characterize the possible improvement of the lameness during the treatment with mavacoxib (Bertram *et al*., 2000; Horstam *et al*., 2004). Although each dog had a bilateral lameness, only the more severely affected hind limb (lesser PVF) was chosen for study to limit a possible bias caused by inconsistent weight redistribution to the less affected contra-lateral hind limb.

Statistical analysis: Data were analyzed by a different (blind) researcher to whose performed acquisition of data. For the analysis of these data a linear mixed effects model was considered: the experimental factor (time) was a fixed effects factor, while the blocking factor (dog) was a random effects factor. Parameters in this model were estimated by using the package nlme in the R statistical software (Sun and Li., 2011). Signification of the differences in supporting force or vertical impulse between periods of observation was tested by means of the analysis of variance. Following this analysis, post-hoc comparisons between fixed effects had been performed by using Tukey procedure. For assessing the validity of the model, Shapiro-Wilk test was applied for testing normality of the residuals, and Levene test for testing homoscedasticity. The significance level was set at $P<0.05$ in all tests.

RESULTS

The body weight of enrolled dogs ranged from 39 to 54 kg (48.3±4.6 kg) and was 2-8 years of age (3.7±1.5 years). Mean values for velocity of dogs were 1.6±0.5 m/s. No significant difference existed between dogs in average walking velocity ($P=0.055$). PVF and VI mean values are shown (Table 1).

Table 1: Mean and standard deviation of PVF and VI (in % of the dog weight) applied on the diseased leg. Data are shown for each day of observation. PVF L: peak vertical force in the lame group. PVF S: peak vertical force in the control group. VI L: vertical impulse in the lame group. VI S:vertical impulse in the control group

PVF L	Day	Mean	sd	VI L	day	Mean	sd
	0	37.25	5.93		0	13.32	0.73
	7	40.20	4.84		7	13.70	0.32
	60	43.32	1.34		60	14.78	0.64
	180	43.93	3.02		180	15.30	0.85
PVF S	0	47.40	3.39	VI S	0	13.75	0.21

Analysis of variance showed that the differences in PVF between periods of observation were significant ($P<0.0001$, $F=60.975$ with 4 and 27 degrees of freedom). Particularly, we emphasized the increasing in supporting force after six months of treatment: the difference after

two months (about almost a 7% of increase) was already significant (P=0.0003). From the second month onwards there was no substantial improvement in supporting force (P=0.98). Finally we compared the mean supporting force after six months of treatment with that of the healthy group of dogs: the estimation of percentage (%) of supporting force in dogs after 6 months of treatment was of 43.9%. whilst for healthy dogs the mean percent of supporting force was estimated as 47.4%, but this difference didn't result significant (P=0.4170) (Fig. 1).

The validity of the model fit was assessed by testing normality and homoscedasticity of the residuals. Both assumptions could be accepted: Shapiro-Wilk test for normality gave P=0.1218 and Levene test for homoscedasticity gave P=0.5227.

Analysis of VI showed significant changes after two months (P≤0.001). From the second month there was no substantial improvement in VI (P=0.32). Moreover, comparing the VI after six months with that of the healthy group, in diseased dogs it was of 15.3%, while for healthy group was 13.7%. This difference was again non-significant (P=0.3289) (Fig. 2). The validity of the model fit was assessed by testing normality and homoscedasticity of the residuals. Both assumptions could be accepted because Shapiro-Wilk test for normality had a P=0.1505 and Levene test for homoscedasticity had a P=0.4285.

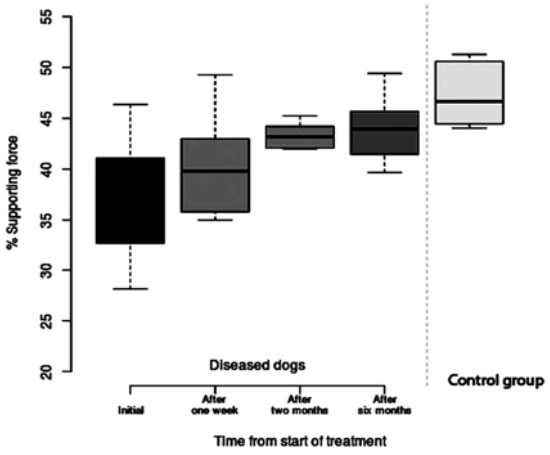

Fig. 1: Evolution of PVF in lame group dogs after treatment during the six months follow up period.

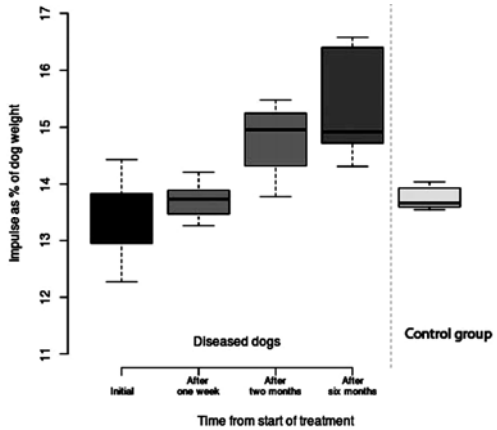

Fig. 2: Evolution of VI in lame group dogs after treatment during the six months follow up period.

DISCUSSION

The primary intent of using force platform analysis in our study was to investigate this technique as an objective method to evaluate the NSAID efficacy in the locomotor system. In this trial, efficacy of mavacoxib in lame osteoarthritic dogs was investigated observing the PVF and VI; because other scoring measurement systems to evaluate the severity of pain in the dog should be partially influenced by a variety of human and/or animal behaviors and physiologic conditions as tested by other authors (Horstam *et al*., 2004). Horstam *et al.,* (2004) suggested that platform analysis determined how much load patients place on the limb and it avoided observer and inter-observer variations that were encountered with pain scoring systems.

The relationship between radiographic signs of OA and limb function has been described to be poor in previous reports (Roy *et al*., 1992). In a recent study with force platform analysis (Gordon *et al*, 2003), no correlation was found with the radiographic OA score of osteoarthritic dogs, and other authors (Bockstahler *et al*., 2007) advise against the use of this technique to assess osteoarthrosis. However, in our study we performed a X-ray examination in order to select only dogs with the most severe degrees of hip dysplasia (D - E), which ensured the presence of OA.

The objective improvement in both parameters (PVF and VI) of the support phase, after treatment, indicated that dogs were able to execute a walking gait more comfortably, with less reticence and more weight support (Fig. 3). This effect was observed after one week of treatment, more rapidly than in a similar study administrating carprofen® and meloxicam®, where objective improvement was detectable after 60 days of treatment increasing PVF GRF in a median value of 2.4% bw (Moreau *et al*., 2003). In our study, diseased dogs improved in almost 8% bw. Although evolution of lameness was expressed as a mean of all dogs, the behavior of results could be very different depending on the degree of lameness: dogs with worse weight bearing developed a faster and greater improvement during the treatment period.

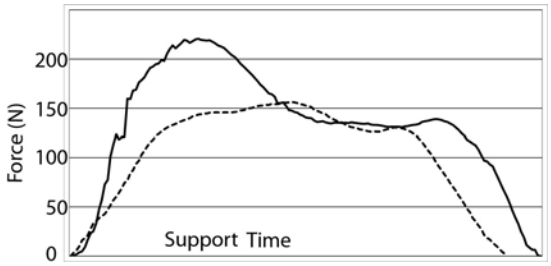

Fig. 3: Graph showing loading range at day 0 (dotted) and day 180 (solid). Note that not only PVF ant support time increased, even the shape clearly changed to a more typical two-peaks curve.

In our study, force platform analysis resulted sensible to detect changes in the forces applied by lame limbs through a treatment period, as reported by other authors in previous experiments (Budsberg *et al*., 1996; Tano *et al*., 1998; Moreau *et al*., 2003; Holstam *et al.,* 2004). Hence, this method allowed a full documentation of the kinetic

benefits provided by pharmaceutical and physical therapies for orthopedic conditions observing forces that generate movement.

Patient velocity had a significant effect on force platform values and it must be limited to a narrow range when data were obtained (Paulson *et al*., 2001); for this reason, the enrolment of dogs with the same conformation (same breed) ensured a narrow range of velocities that they could develop. Force platforms inserted in treadmills allow avoiding factors that could produce variability in results, such as speed; however, studies with this device were limited by the size of the dog, since in larger animals, stride length exceed the limits of the platform and parameters as VI could not be measured (Bockstahler *et al*., 2007).

Focusing on gait, some authors proposed trot as a better gait to perform gait analysis because low grade pelvic limb lameness was more easily detected at trot than during walking (Voss *et al*., 2007; Colborne, 2008). In our case, lameness of the OA dogs group was so evident by direct observation, even at walk.

Body weight and conformational variables (e.g. femoral length) were also main factors influencing force platform values. Consequently, these variables needed a statistical normalization of peak forces and other parameters with a linear scaling, in order to be used as a standard to minimize the effect of body weight on ground reaction data and to allow comparison of animals with differing body weights or anatomic conformation (Bertram *et al.,* 2000). In our study, statistical normalization was not used because the efficacy of the treatment on dogs with OA was assessed comparing the gait improvement of each dog with its D0 value, gaining force exerted by the lame limb, expressed in % bw.

Bockstahler *et al.* (2007) demonstrated the negative impact of body weight gain on GRF values, and conversely, the improvement in weight support when body weight decreased, considering that joint loading is a painful action when OA is present. In accordance with their observation, we paid special attention to explaining to owners that they should not change feeding of their dogs during the study period. However, if the weight was changed, because of the resultant forces were expressed in % bw, results could not be significantly modified.

Asymmetry should be a factor to take into account, since significant differences were found in peak vertical forces between right and left thoracic limbs. According to the results found by Molsa *et al.* (2010) in Labrador Retrievers, dogs put significantly more weight on the right thoracic limb than on the left one. However, the author did not explain this asymmetry. This factor could interfere with the interpretation of results comparing limbs of both sides; however, in our study, we performed measurements in individual limbs, compared with them during the study period.

Literature reported that conventional NSAIDs, by inhibiting COX-1, can disturb gastric tissue homeostasis, leading to serious gastroduodenal damage (Reimer *et al*., 1999). Selective COX-2 inhibitors minimize this effect, although some authors reported that a therapy administered to dogs for eight weeks produced and increased lesions in the gastroduodenal mucosa (Moreau *et al.,* 2005). In our study, NSAID treatment was well tolerated, as demonstrated by the dogs' owners' failure to notice any clinically relevant disturbances or adverse effects. Moreover, the prolonged mavacoxib t½ associated with constant and progressive improvement of lameness supported our protocol that required doses separated by 2–4 weeks, rather than a once-daily NSAID administration (Cox *et al*., 2010).

Conclusion: This study clearly showed that dogs treated with mavacoxib increased PVF over time, as soon as seven days after medical therapy, demonstrating a high potential for clinical use in the treatment of lameness associated with OA of hip joint.

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