

RESEARCH PAPER

Therapeutic response analysis in dogs with naturally occurring osteoarthritis

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Abstract

Objective Reporting the rate of positive (+) and negative (–) responders based on an objective outcome measure of pain-related functional disability/lameness in dogs with naturally occurring osteoarthritis (OA), and the relationship between initial lameness severity and the odds of being a (+) responder.

Study design Retrospective analysis of published peer-reviewed clinical trials in dogs with naturally occurring OA.

Animals Dogs ($n = 213$) with hip and/or stifle afflicted-joints.

Methods A responder analysis was undertaken using a previously determined cut-off value of $\pm 2.0\%$ of body weight using the peak of the vertically-oriented ground reaction force (PVF). Among the trials, PVF was acquired under similar conditions. Therapeutic approaches were therapeutic diets, natural health products and non-steroidal anti-inflammatory drugs.

Results Among dogs administered one of these therapeutic approaches ($n = 121$), 62.8% (95% confidence interval, 53.9–70.9) were defined as (+) responders, whereas 11.6% (7.0–18.5%) were (–) responders, accounting for a net (+) response rate of 51.2% (42.0–60.4%). The net (+) response rate of negative (placebo) control dogs ($n = 92$) was 1.1% (0.0–5.9%). The number needed to treat was four, and the effect size 0.7 (0.4–1.0). The odds ratio of being a (+) responder to the therapeutic approaches was 2.85 (1.57–5.17) ($p < 0.001$). For less severe lameness manifested with an increment

in PVF by 1% body weight, the chance of being a (+) responder following treatment decreased by 9% [odds ratio 0.91 (0.86–0.97), $p = 0.006$].

Conclusions and clinical relevance The rate of (+) responder optimizes decision making for the management of pain-related clinical signs of OA. Evidence-based medicine was further supported by clinical metrics from an objective outcome measure of pain-related functional disability/lameness. Furthermore, dogs with a mild lameness were less prone to be improved, emphasizing the need to carefully manage even OA dogs with a more subtle affliction.

Keywords canine gait analysis, chronic pain, natural health product, non-steroidal anti-inflammatory drug, therapeutic diet.

Introduction

Osteoarthritis (OA) involves progressive and interrelated structural changes to the whole joint. It is characterized by cartilage loss, abnormal subchondral bone remodeling and osteophytosis that are commonly seen upon imaging techniques (Blum et al. 2015). In parallel to those damages, severe joint pain evolves, which has the potential to alter normal function, particularly locomotion. This phenomenon is referred to as functional disability or lameness, and represents a major clinical sign in OA afflicted dogs (Renberg 2005).

Several quantitative outcome measures exist to evaluate the functional disability observed in OA dogs including proxy scoring systems and questionnaires (Rialland et al. 2012a,b; Walton et al. 2013),

locomotor activity recording (Brown et al. 2010) and gait analysis using ground reaction forces (GRF) (Aragon et al. 2007). Out of all the GRF, peak of the vertical GRF (PVF) is the parameter frequently used to document the function of a specific limb under normal or pathological conditions, as well as following surgical interventions (Aragon et al. 2007). When used as an outcome measure, the abnormally low PVF value observed in OA dogs is increased by the purported effects of the therapeutic modalities, which suggests an alleviation of the pain-related functional impairment. Therefore, several clinical trials have shown promising findings based upon this gait analysis of dogs administered therapeutic diets (Roush et al. 2010), natural health products (NHPs) (Hielm-Bjorkman et al. 2009a,b; Gupta et al. 2012) and non-steroidal anti-inflammatory drugs (NSAIDs) (Budsberg et al. 1999; Lipscomb et al. 2002).

There is a growing interest to qualify the therapeutic response in terms of positive (+) response to facilitate interpretation of chronic pain trials (Pham et al. 2004; Bombardier et al. 2011; Cooper et al. 2013). Application to clinical metrics can determine responder rate, odds ratio and number needed to treat. Use of the minimal detectable change at the 95% confidence interval (MDC_{95}) was previously proposed as a cut-off value to distinguish responder from the PVF measurement error recorded in privately-owned dogs with OA (Moreau et al. 2013a). Therefore, the purpose of the present study was to provide clinical metrics from a response analysis of published peer-reviewed clinical trials using PVF as a primary outcome measure of therapeutic efficacy in dogs with naturally occurring OA.

Based on an outcome measure of pain-related functional disability/lameness, our objectives were to report: 1) the rate of (+) and (-) responders, the number needed to treat and the effect size; and 2) the relationship between initial lameness severity and the odds of being a (+) responder.

We hypothesized that over 50% of (+) response would occur following the selected OA treatments comparatively to a rate close to null in dogs receiving a negative control (later referred to as control or placebo). We also hypothesized that dogs having more severe disability would show a better response than those with less severe lameness.

Materials and methods

Data from seven peer-reviewed published clinical trials in dogs with naturally occurring OA (Moreau

et al. 2003, 2004, 2007, 2012, 2013b, 2014b; Riialand et al. 2013) were included in this retrospective analysis. All the data were owned by the present authors. Several OA treatments were considered and later regrouped into the categories of therapeutic diets, NHPs and NSAIDs. The corresponding controls are also detailed (Table 1).

Force platform gait analysis

The PVF was measured during force platform gait analysis under similar speed and acceleration ranges and by using the same device and personnel. For every trial, measurements were performed at the beginning (baseline) and at the end of the study under the same trotting speed (1.9–2.2 meter second⁻¹, acceleration \pm 0.5 meter second⁻²). Normalized PVF in percentage of body weight from the first five valid trials in each time point of assessment, for each dog, were used for statistical purposes.

Selection criteria

To include a dataset in the present analysis, the following criteria had to be met: dogs weighing >20 kg with radiographic evidence of OA exclusively at the hip and/or stifle joints. Only the datasets from dogs having an initial PVF below 66.6% body weight were considered, otherwise dogs would have been too close to the normal values expected to be around 72% body weight (Madore et al. 2007; Nordquist et al. 2011). In the presence of bilateral lameness, the pelvic limb with the lowest PVF was used for analysis. Dogs that underwent orthopedic surgery within the past year and dogs with cranial cruciate ligament rupture having gross instability (positive drawer motion) were not eligible to the initial trials. When necessary, specific washout periods were respected for oral NSAIDs (2–4 weeks), NHPs (4–6 weeks), therapeutic diets (4–6 weeks) and injectable glycosaminoglycans (12–24 weeks). Among the 250 datasets, 213 were selected from which 121 dogs received either a therapeutic diet, NHP or an NSAID, as the three category subgroup. There were 92 dogs that received a control across these three categories, as described below.

Trials 1 and 2: Therapeutic diets

A total of 62 datasets met the inclusion criteria (Table 1). In trial 1, for the purpose of a negative (placebo) control, dogs were fed a commercial diet (Dog Chow; Nestlé Purina, MO, USA) for 30 days and

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