Efficacy of an oral nutraceutical for the treatment of canine osteoarthritis

A double-blind, randomized, placebo-controlled prospective clinical trial

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Keywords

Dogs, osteoarthritis, glucosamine, activity monitor, chondroitin

Summary

Objectives: To assess the safety and efficacy of an orally administered nutraceutical (Glu/CS+; + for additional ingredient) for the treatment of clinical osteoarthritis (OA) in dogs.

Methods: In this double-blind, randomized, placebo-controlled clinical trial, client-owned dogs with clinical signs of OA in one or more joints were assigned to a Glu/CS+ (n = 30) or placebo (n = 30) group. Dogs were administered Glu/CS+ or placebo orally and wore an activity monitor (AM) continuously throughout a 97 day study period. Prior to the initiation of the treatment, seven days of baseline activity was collected. On days –7, 30, 60 and 90 of the study, owners completed a patient assessment form (Canine Brief Pain Inventory). Data between groups were compared.

Results: No serious adverse events were reported. No difference was found between groups when evaluating daily activity counts during the seven-day pre-treatment period and the 90-day treatment period. Owner assessment (pain interference and pain severity scores) improved over the 90-day treatment period for both groups, however no difference was found between treatment groups.

Conclusions: Treatment with oral Glu/CS+ for a 90 day treatment period when compared to placebo treatment did not result in a significant increase in activity counts in dogs with clinical OA. However, owner assessment scores similarly improved throughout the study period for dogs in both groups, suggesting a caregiver placebo effect in this outcome measure.

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Vet Comp Orthop Traumatol 2017; 30: 318–323
https://doi.org/10.3415/VCOT-17-02-0020
Received: February 5, 2017
Accepted: April 19, 2017
Epub ahead of print: August 1, 2017

Supplementary material for this article is available at https://doi.org/10.3415/VCOT-17-02-0020

Introduction

Osteoarthritis is a slowly progressive degenerative condition that most frequently involves the tissues of the synovial joints and is characterized by pain and lameness associated with pathological changes within the joints and loss of articular cartilage (1–3). A primary goal for the treatment of the clinical signs observed in dogs with osteoarthritis is to provide relief of inflammatory pain, and therefore improve quality of life (4). Conventional therapies such as non-steroidal anti-inflammatory drugs (NSAID) are commonly used in dogs with osteoarthritis, and the clinical benefits derived from this treatment are well recognized (4–5). However, NSAID can be associated with undesirable side effects such as kidney and liver toxicity as well as gastrointestinal ulceration or perforations (5–6). In an attempt to explore the use of alternative therapies, nutritional supplements, such as glucosamine hydrochloride (Glu) and sodium chondroitin sulfate (CS) are often integrated into multimodal treatment plans for dogs with osteoarthritis (7-9). Clinical trials in dogs using subjective or objective outcome measures evaluating combinations of Glu/CS are limited and reveal variable clinical efficacy (10–13). In addition, systematic reviews examining the use of nutraceuticals in dogs with osteoarthritis reached the conclusion that the evidence of the efficacy of nutraceuticals is poor, with the exception of diets supplemented with omega-3 fatty acids, and further studies with more objective measurements of outcome are needed (14, 15).

One study using only subjective assessments of outcome compared a Glu/CS combination to a positive control, carprofen, in dogs with chronic lameness, stiffness, joint pain and radiographic evidence of hip and elbow osteoarthritis for a 70 day treatment period (10). Dogs within the carprofen arm of treatment showed significant improvements from the baseline in all five parameters during the treatment

period. Dogs receiving the Glu/CS showed statistically significant improvements from the baseline, specifically in regards to pain, weight-bearing and overall condition scores at 70 days. In contrast, a randomized, double-blind placebo-controlled study in client-owned dogs with chronic osteoarthritis in one or two elbows, stifles or hips assessed the efficacy of treatment with Glu/CS (with addition of manganese), carprofen, meloxicam or placebo (11). This study used ground reaction forces and subjective clinical assessments by an orthopaedic veterinary surgeon and owners. Statistically significant improvements in the ground reaction forces and subjective orthopaedic surgeon assessments were found in dogs receiving meloxicam and carprofen, but dogs receiving the placebo or the Glu/CS and manganese product showed no statistically significant improvements in any of the outcome measures. In addition, a more recent prospective, randomized, double-blinded trial in client-owned dogs with osteoarthritis evaluated the therapeutic efficacy, tolerability and safety of type-II collagen alone, in combination with Glu/CS or placebo using both subjective and objective outcome measurements (12). The Glu/CS treatment group had a significant reduction in pain on subjective assessments, however the ground reaction forces remained unchanged.

In human literature, clinical efficacy of these supplements is often drawn into question. A network meta-analysis reviewing the effects of Glu/CS or their combination or placebo in human patients with osteoarthritis of the hip or knee resulted in an assessment of 10 trials comparing the reduction of joint pain and radiographic evidence of joint space narrowing (16). The analysis concluded that Glu/CS did not reduce joint pain nor did it have an impact on joint space narrowing and suggested that health authorities and insurers not cover the costs of these treatments. Furthermore, a Cochrane database systemic review evaluated the benefits and safety of chondroitin for treating osteoarthritis compared with placebo or a comparator oral medication (not limited to NSAID, analgesics, opioids, and glucosamine) (17). Forty-three randomized controlled trials were evaluated and these trials, mostly of low quality, revealed chondroitin was better than placebo in improving pain associated with osteoarthritis. Although the benefit was small and some of the differences persisted, they recommended that more high-quality studies are needed to assess the benefits of chondroitin in osteoarthritis, and the popularity of chondroitin as an over-the-counter supplement could be related to its associated low risk. Efficacy of clinical interventions in the veterinary profession largely rely on the veterinarian and owner assessments for determination of outcomes (18, 19). While these assessments are important, measuring objective changes in the patient after an intervention would complement conclusions about the efficacy of the treatment. Interest has grown in the use of activity monitors (AM) as an objective outcome measurement in dogs with osteoarthritis to assess the efficacy of treatment interventions within a dog's day-to-day environment (20–22). Activity monitors have been shown to detect a treatment response in dogs with osteoarthritis in a randomized, placebo controlled trial evaluating an NSAID (20). The AM used in that study contained an accelerometer which continuously measured the occurrence and intensity of motion for set periods of time which are stored in the form of activity counts (AC); this allows for AC to be documented before and after an intervention.

Because of conflicting reports regarding the benefits of Glu/CS in veterinary patients and the variety of ingredients included in nutraceutical products, the objective of this study was to determine the safety and efficacy of a commercially available Glu/CS+[a] product compared to placebo treatment in dogs with clinical signs of osteoarthritis in one or more joints over a 90 day treatment period. Our null hypothesis was that treatment group would not influence daily owner questionnaire scores or patient activity counts.

Materials and methods

The Institutional Animal Care and Use Committee at the College of Veterinary Medicine at the University of Minnesota approved this study. All clients received a detailed description of the protocol and signed and informed consent form prior to the screening process. Inclusion criteria were as follows: dogs had to be nine months of age or older, weigh 5 kg or more, have a medical history and physical examination findings (performed by a single ACVS Diplomate or single ACVS surgical resident) consistent with chronic osteoarthritis (greater than three months duration) in one or multiple joints, and have confirmed radiographic evidence of osteoarthritis on orthogonal radiographs in the affected joint(s) (See also ▶Appendix Tables 1 and 2: Available online at www.vcot-online.com). Dogs had to be in good health (based on veterinary examination) and have no clinically significant abnormalities on a pre-enrolment complete blood count and serum biochemistry. Complete blood counts and serum biochemistry were repeated at the conclusion of the study period. Dogs had to be removed from glucocorticoids, opioids, nutraceuticals, joint specific diets, or any over-the-counter supplements for four weeks and NSAID administration for two weeks prior to enrolment. Dogs that had received intra-articular injections (e.g. hyaluronic acid, polysulfated glycosaminoglycan, corticosteroids, stem cells, platelet rich plasma or other) within three months preceding or had joint surgery performed within six months prior to enrolment were not included. In addition, clients with planned changes to their dog's routine/day-to-day activities, such as a vacation or moving, throughout the study period were excluded. An Excel based random group generator[b] was used prior to the study initiation for randomization of groups and was facilitated by a technician who was not involved in patient assessments. Dogs were enrolled in the study and placed in their group in order of the predetermined ran-

a Dasuquin: glucosamine hydrochloride, sodium chondroitin sulfate and avocado/soybean unsaponifiables power: Nutramax Laboratories, Inc., Edgewood, MD, USA

b Excel: Microsoft Corporation, Redmond, WA, USA

domization. Owners and all staff involved in any clinical observations, assessments, or data analysis were blinded to treatment group assignment. Medication was first dispensed to owners on day 0 after completion of baseline data collection. Two technical staff were designated for dispensing and instructing clients how to administer the treatments. All treatments were removed from their original packaging and concealed in bags with labelled instructions for administration. Dogs in the placebo group were dosed with a single soft chew, chicken flavoured dog treat[c] once daily for 90 days that did not contain any anti-inflammatory ingredients. Dogs in the Glu/CS+ group were dosed by weight per labelled instructions according to manufacturer, and because of this, some dogs received more than one soft chew treatment during the study, but all dogs in this group were still only dosed once daily.

Clients completed a Canine Brief Pain Inventory (CBPI; http://www.vet.upenn.edu/research/clinical-trials/vcic/penn-chart/cbpi-tool) questionnaire addressing the dog's osteoarthritis pain and function prior to enrolment (Day –7) and at each follow-up visit thereafter (days 30 ± 3, 60 ± 3 and 90 ± 3). Day –7 served as the baseline score for the CBPI (23). Questions 1–4 in the CBPI were summed to establish pain severity score (PSS) and questions 5–10 were summed to establish a pain inference score (PIS); only dogs with a PSS and PIS ≥2 were enrolled (23–24). Activity counts were measured with an AM[d] device attached to a collar[e] worn on the dog's neck (20–22, 25). Collars were individually fitted to each dog and a specific hole on the collar used was marked to allow consistency with tightness in placement throughout the study period. Owners were instructed not to place a leash or use any lead attachment to the device collar (26–27). The AM was placed on dogs at the end of the day –7 hospital visit and on follow-up visits (days 0 ± 1, 30 ± 3, 60 ± 3 and 90 ± 3) the battery in the collar was replaced and the AM data was downloaded, this process was minimized to less than 10 minutes. The days between day –7 to day 0 served to establish a baseline value for each patient so that changes in the patient's AC after the administration of an intervention could be assessed. The AM is waterproof and clients were instructed that the device should not be removed for bathing or swimming, a leash should not be attached to the AM collar and their dog should wear the collar continuously throughout the duration of the trial. The accelerometer-based AM continuously records the occurrence and intensity of motion. The AM stored the information in the form of AC and was set for one-minute epoch lengths. On day 0, data from the AM was downloaded and treatments were dispensed and clients were counselled on the administration of the test articles by a dispenser.

A physical examination was performed at each scheduled or unscheduled visit. A rescue protocol was in place if a dog's clinical signs or symptoms of osteoarthritis worsened and additional interventions (NSAID and/or analgesics) were medically indicated. Pet owners incurred no costs for participation and were compensated with a six-month supply of the test nutraceutical upon completion of the study.

Statistical analysis

All data until the dog completed the study or was rescued from the study were included in the analysis. The accelerometer data are continuous, repeated measures data with multiple pre-treatment (baseline) measurements and covariates. Total daily activity count reported by the AM was statistically evaluated. After the initial data analysis step of verifying distributions, calculating summary statistics and data checking, the change in the groups over time and individual daily differences were compared using a repeated-measures analysis of variance. Baseline days (days –7 to 0), group assignment (Glu/CS+ or placebo), CBPI scores, and the baseline day to group interaction were assessed as independent variables; post-intervention days (days 0 to 90) were assessed as the dependent variables. Time, group, and the time to group interaction were assessed. To test for a difference in rescue rates between the two treatments, a logistic regression on rescue with treatment as the predictor was used. A p-value of <0.05 was considered statistically significant.

Results

Study population

Sixty (n = 30/group) clinically healthy client-owned dogs were enrolled in the study from a single institution. No statistical difference was found between groups for sex distribution, mean body weight distribution (Glu/CS+ 26.3 ± 11.3 kg and placebo 27.7 ± 11.2 kg) and mean age of dogs (Glu/CS+ 8.5 ± 3.1 years and placebo 7.8 ± 2.8 years). A total of 13 dogs were withdrawn from the clinical study for treatment failure – six of 30 in the Glu/CS+ group and seven of 30 in the placebo group as no difference in treatment failure rate was identified.

Adverse events

No serious adverse events were found. Within the Glu/CS+ group, one dog had a single episode of vomiting, and within the placebo group one dog experienced a single episode of vomiting and two had an episode of diarrhoea. These adverse events resolved without the addition of veterinary care. One dog in the placebo group developed a urinary tract infection and was treated with antibiotic medication during the study period. All dogs enrolled in the trial (including treatment failure cases) had repeat complete blood count and serum biochemical analyses after completion of the study and no clinically significant changes were noted.

Treatments

According to client reports and monthly review of the treatments dispensed, all dogs received the prescribed treatment for days 0 through 90. The CBPI pain severity questions 1–4 and pain interference questions 5–10 significantly decreased over time

c Hill's Science Diet Canine Soft and Chewy Training Treats: Hill's Pet Nutrition, Inc., Topeka, KS, USA
d Actical Respironics Mini Mitter: Philips Respironics, Bend, OR, USA
e ¾ inch Collar Strap: SportDOG, Knoxville, TN, USA

from day –7 for both groups (▶Figure 1, ▶Figure 2). There was no difference between groups at any time point for either CBPI pain severity questions 1–4 or pain inference questions 5–10. There was no difference between groups at any time point.

Mean daily AC remained statistically similar over the baseline and treatment periods regardless of group (p = 0.91 for placebo treated group; p = 0.83 for Glu/CS+ treated group). When mean daily AC for each individual day after intervention were compared, a single statistical difference was identified. On day 3 after treatment, AC were significantly increased (p = 0.03) in dogs treated with Glu/CS+. No significant differences were found between groups in the remaining 89 of 90 treatment days and mean daily AC were greater numerically in the placebo group in 52 of the 90 (57.8%) treatment days (▶Figure 3).

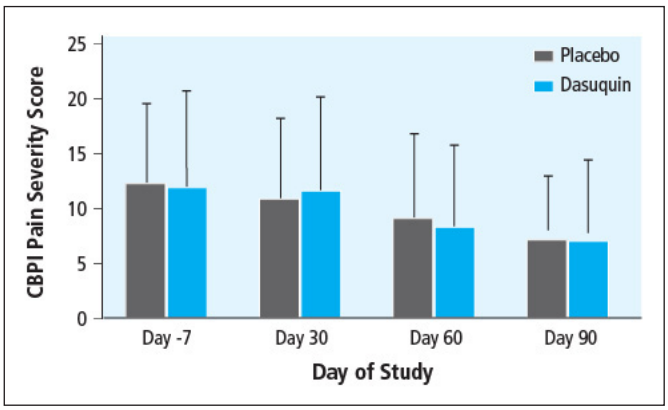

Figure 1
The sum ± SD of Canine Brief Pain Inventory (CBPI) questions 1–4 evaluating pain severity. A significant decrease over time was found in both the placebo treatment (black) and Glu/CS+ treatment (blue) groups. No difference between groups was found.

Discussion

In this randomized, placebo-controlled, clinical trial we found treatment group did not influence daily owner questionnaire scores, treatment failure rate, or patient activity counts; thus, we failed to reject our null hypothesis. There are conflicting reports regarding the potential therapeutic benefits of Glu/CS products in veterinary medicine (10–13). For example, there is evidence that various glucosamine/chondroitin products are bioavailable in the dog and provide a treatment benefit in induced canine models of osteoarthritis (28–31). Contributions to therapeutic variation include differences in study design and additives in Glu/CS product studied. These differences make it difficult to draw an all-encompassing conclusion regarding Glu/CS products safety and efficacy in dogs. Given these mixed findings, we elected to design a clinical trial that tested the safety and efficacy of a Glu/CS+ product as the sole treatment for osteoarthritis in dogs. The results of this study do not support a therapeutic effect from Glu/CS+ in dogs with spontaneous osteoarthritis, but we cannot comment on its overall efficacy given the limited number of dogs (n = 30) and duration of treatment (90 days). For comparison, a treatment response has been reported using this AM in dogs with osteoarthritis; one study (n = 35) reported an increase in total activity counts in dogs treated with carprofen and another study (n = 13) reported an increase in total activity counts in dogs treated with canine-specific anti-nerve growth factor antibody (20, 32).The potential benefits of Glu/CS in dogs with osteoarthritis has been questioned not only due to the limited scientific clinical evidence, but also the lack of information on variation in absorption, pharmacokinetics, and the mechanism of action remains largely unknown.

In this study, a similar proportion of dogs (6/30 Glu/CS+; 7/30 placebo) were withdrawn from the study because of treatment failure. This can serve as an alternative method to look at the efficacy of a treatment; again there was no difference between groups. The treatment failure rate was higher than reported in some studies where no dogs (treatment or placebo treated) were rescued (20, 32). A reasonable explanation for this is the duration of the study. The duration of this study was longer and all but three dogs were rescued in the first four weeks of treatment (▶Appendix Tables 1 and 2: Available online at www.vcot-online.com).

This study used both subjective and objective outcome measures. Recently it has been recommended that until a consensus has been reached regarding the outcome measures used to assess canine osteoarthritis, an inclusion of at least one existing, validated outcome measure in each future study is needed (18–19). Since this study investigated the systemic treatment effect of an oral intervention in dogs with osteoarthritis, often in multiple joints, we elected to focus on outcome measures that report on the patient in its natural environment. We also wanted to balance subjective evaluation of the patient with objective changes in the patient. We elected not to use force platform gait analysis as many of

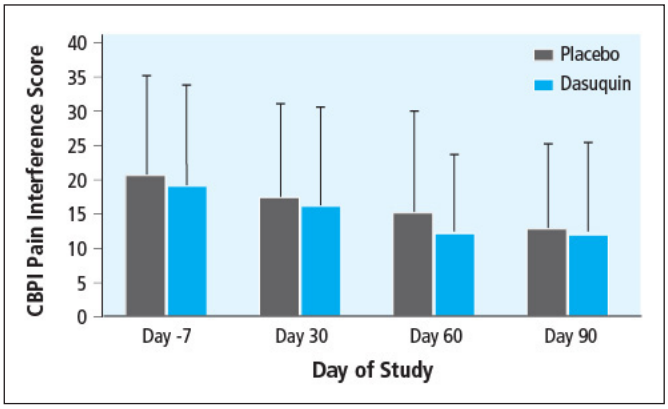

Figure 2
The sum ± SD of Canine Brief Pain Inventory (CBPI) questions 5–10 evaluating pain inference. A significant decrease over time was found in both the placebo treatment (black) and Glu/CS+ treatment (blue) groups. No difference between groups was found.

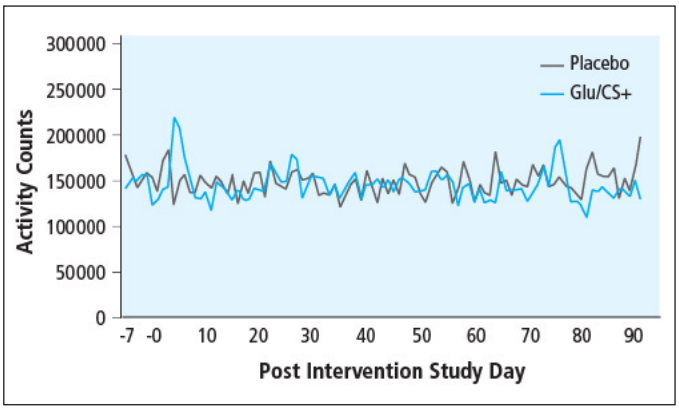

Figure 3
Mean daily activity counts over the treatment period in the placebo treatment (black line) and Glu/CS+ treatment (blue line) groups. Glu/CS+ was significantly greater on Day 3; no other differences were found.

the dogs enrolled in this study had multiple joints affected by osteoarthritis, thus limiting the utility of force platform gait analysis as an outcome measure. For efficacy, we used the CBPI and an AM that have been previously validated as outcome measures in patient populations with similar characteristics to those in this study (20–25). We used owner reporting of adverse events, veterinary physical exams and patient blood work to evaluate safety.

The owner subjective assessment used within this study (CBPI) has been previously validated in dogs with osteoarthritis and owner information is useful for the assessment of the dog outside of a hospital setting. The previously described caregiver placebo effect was found to be common in the evaluation of a patient response to treatment not only within the pet owners, but also veterinarians (33). In this study, placebo treated dogs had significantly improved CBPI pain severity and pain interference scores. At the same time, activity counts (objective outcome measure) for dogs in the placebo treated group remained unchanged over time. This supports a conclusion that there was a caregiver placebo effect associated with the owners of the dogs in this study population.

Ideal statistical analysis of activity monitor data remains open for debate. We compared total daily activity counts between groups on a daily basis, change over the entire study period between groups, and the frequency of which group had numerically greater activity counts. This is similar to previous studies looking for a treatment effect in dogs with osteoarthritis (20, 32). We did not report activity intensity even though it has been previously reported in dogs that the AM that was used in this study could be used to distinguish between sedentary, walking, and trotting activities (34). We elected to not investigate this outcome measure because activity intensity in a previous study was addressed in 15 second epochs over a three minute period, and in this study dogs were studied for three months (34). We are not suggesting that activity intensity is not important, only that it remains challenging to investigate it over an extended period of time. It is also important to note that while we used the term "validated" with respect to AM, we remain unsure how to translate the clinical relevance of these data with respect to the distance travelled by the pet wearing the AM.

To the authors' knowledge, the long-term safety of Glu/CS and related nutritional supplement products in dogs has not been reported. Adverse reactions reported in veterinary literature primarily involved gastrointestinal signs (10–11). In the present study, one adverse event was reported within the Glu/CS+ group (vomiting) and three within the placebo group (1 vomiting; 2 diarrhoea), all of which resolved without veterinary intervention. In addition, there were no significant changes in the pre-screening biochemical or haematological results as compared to the 90 day repeat in any of the dogs. Although Glu/CS+ proved to be safe in this study population, we cannot comment on its overall safety given the limited number of dogs (n = 30) and duration of treatment (90 days). There are several potential study biases that could have influenced the outcome of this study. We did not block randomize based on patient signalment (e.g. body weight, body condition score, age, gender, breed, duration of disease). Duration of disease certainly could be a study bias. In this study, overall mean patient age exceeded eight years and duration of disease had to be greater than three months for inclusion in the study. We found determining exact duration of disease difficult since most of our patients were older patients with osteoarthritis secondary to hip or elbow dysplasia, and with clinical signs that began when the patient was younger and had continued for several years. It is well known that patient size influences reporting from activity monitors. We elected to control these potential biases via randomization, blinding and including a placebo treatment group. Additionally, we evaluated these biases by statistically testing for the presence of group differences - none were found. We also did not randomize based on characterization of the osteoarthritis (e.g. location(s), aetiology, severity, duration). Intuitively, not all osteoarthritis is the same. For example, bilateral hip osteoarthritis secondary to hip dysplasia with a six year duration may respond differently to an intervention than unilateral elbow osteoarthritis secondary to osteochondrosis with a three month duration. We did not address these potential concerns in this study because, in practice, the product studied is used for nearly all types of osteoarthritis.

In this randomized, placebo-controlled, clinical trial we found Glu/CS+ did not have a beneficial treatment effect when compared to placebo treatment when evaluated by daily owner questionnaire scores and patient activity counts

Author Contributions

RS and MC were responsible for the conception and design of the study. All authors were all involved in the data acquisition, analysis and interpretation, and all authors were involved in the drafting or revising of the manuscript and approved of the submitted version.

Conflict of interest

There are no conflicts of interest to declare.

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