Advance Access Publication 25 October 2007

eCAM 2009;6(4)465–471
doi:10.1093/ecam/nem143

Original Article

Evaluating Complementary Therapies for Canine Osteoarthritis—Part II: A Homeopathic Combination Preparation (Zeel®)

Anna Hielm-Björkman[1], Riitta-Mari Tulamo[1], Hanna Salonen[2] and Marja Raekallio[1]

[1]Faculty of Veterinary Medicine, Department of Equine and Small Animal Medicine, PO Box 57, FI-00014 University of Helsinki, Finland and [2]Soukka Small Animal Clinic, Merivalkama, 1 02320, Espoo, Finland

A homeopathic combination preparation (HCP) for canine osteoarthritic pain was evaluated in a randomized, double-controlled and double-blinded clinical trial. Forty-four dogs with osteoarthritis (OA) that were randomly allocated into one of three groups completed the study. All dogs were fed test products or placebo for 8 weeks. The dogs were evaluated at the clinic four times, with 4-week intervals. Six different variables were assessed: veterinary-assessed mobility, two force plate variables, an owner-evaluated chronic pain index and pain and locomotion visual analogue scales (VASs). Intake of extra non-steroidal anti-inflammatory drugs was also evaluated. A Chi-squared test and a Mann–Whitney test were used to determine significant improvement between groups. When changed into dichotomous responses of 'improved' or 'not improved' three out of the six variables showed a significant difference ($P = 0.016$, $P = 0.008$, $P = 0.039$) in improved dogs per group, between the HCP group and the placebo group. The odds ratios were over one for the same variables. As extent of improvement in the variables from start to end of treatment, the HCP product was significantly more improved in four ($P = 0.015$, $P = 0.028$, $P = 0.049$, $P = 0.020$) of the six variables, compared with the placebo. Our results indicated that the HCP Zeel® was beneficial in alleviating chronic orthopedic pain in dogs although it was not as effective as carprofen.

Keywords: alternative medicine – complementary medicine – dog – homotoxicology – placebo

Introduction

We analyzed the use of a low-dilution complex formulation, the homeopathic combination preparation (HCP) Zeel® (1) for the treatment of osteoarthritis (OA) in dogs. OA is today the most common joint disease affecting dogs (2), with canine hip dysplasia (CHD) and elbow dysplasia (ED) being two common variants. In spite of the prevalence and seriousness of canine OA, to date, no research has been published on the effects of homeopathy on OA in dogs (3). In contrast, there is a growing body of research in human medicine on the utilization of homeopathy in general and for OA in particular [for an excellent lecture series on homeopathy and inflammatory diseases, see (4–9) and their references]. Comprehensive meta-analyses of the use of homeopathy on humans have indicated that homeopathy indeed has a positive input on a range of diseases (10,11), whereas others have shown the opposite (12). Two double-blind studies have been conducted specifically on HCP Zeel® in human patients suffering from OA. A therapeutic equivalence was found between Zeel® and the non-steroidal anti-inflammatory drug (NSAID) Diclofenac (13). In another comparative trial on human OA, Zeel comp.® was found to be as good as hyaluronic acid (14). Neither of these trials included placebo groups. It has been recommended for

For reprints and all correspondence: Anna Hielm-Björkman, DVM, CVA, Faculty of Veterinary Medicine, Department of Equine and Small Animal Medicine, PO Box 57, FI-00014 University of Helsinki, Finland. Tel: +358-400885255; Fax: +358-9-19157298;
E-mail: anna.hielm-bjorkman@helsinki.fi

human use (15) and also used on rabbits (16) and horses (17).

Our aim was to evaluate the Zeel® HCP as a therapy for canine OA, using a randomized, double-controlled and double-blinded clinical trial (18–22). Based on previous research, we hypothesized a positive effect of HCP. In addition to a placebo group as a negative control, we included an established canine analgesic as a positive control so as to further explore the impact of the treatment. It should be stressed that this is not a classical homeopathic treatment either in the sense of using one drug at a time or in that it is extremely diluted; the product used here was a complex combination and only diluted until molar concentrations of 10^{-5}–10^{-12} mol/l.

Subjects and Methods

Dogs

Inclusion criteria were that dogs have clinical signs and a radiographic diagnosis of OA in either a hip joint or an elbow joint (23). The owner had to have described at least two of the following signs as being chronic or frequent: difficulty in lying down and/or in getting up from a lying position, difficulty in jumping or refusing to jump, difficulty in walking up or down stairs, or definite lameness. Dogs were excluded from the study if they had had prior surgery on the evaluated joint, inadequate clinical symptoms, systemic or infectious disease, neurological deficits, lameness from articular infection, or recent trauma. In this study, 51 dogs were included and 44 concluded the study. Baseline data in Table 1.

Table 1. Baseline data for all three groups

Possible confounding factors at baseline	Carprofen	HCP	Placebo
n	15	14	15
hip OA/elbow OA (n)	12/3	12/2	12/3
Sex: male/female	7/8	8/7	10/5
Median age (years),	5	7,5	6
Min–Max	1–9	1–11	1–11
Median duration of signs (years)	>2	1–2	1–2
Median weight (kg),	38	27,5	34
Min–Max	31–56	22–54	18–54
Mean ± SD of continuous variables at start of trial			
Veterinary-assessed mobility index[a]	5.00 ± 4.61	6.79 ± 6.46	5.20 ± 4.26
Force plate–PVF[b]	75.92 ± 23.48	70.96 ± 22.58	78.46 ± 22.23
Force plate–impulse[b]	10.92 ± 4.02	8.64 ± 3.06	9.72 ± 3.43
Chronic pain index[a]	16.47 ± 6.21	15.86 ± 6.20	14.87 ± 4.79
Pain VAS (cm)[a]	3.55 ± 2.17	4.24 ± 2.16	3.70 ± 1.77
Locomotion VAS (cm)[a]	4.57 ± 2.03	4.87 ± 2.26	4.61 ± 2.12
Median, Min–Max of variable at 4 weeks prior to trial (W_{-4})			
NSAID doses per month	none, none to 3–5/week	none, none to daily/almost daily	none, none to about 1/week

Distribution of possible confounding factors between groups at time W_0 (for extra NSAIDs at W_{-4}). HCP, homeopathic combination preparation; NSAID, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; PVF, peak vertical force; VAS, visual analogue scale.
[a]A higher value means more pain.
[b]A lower value means more pain.

Test Products and Treatment Regime

The groups of dogs were medicated as follows: the active treatment group was given the HCP (Zeel® ad us. vet. 5 ml, Biologishce Heilmittel Heel GmbH, Baden-Baden, Germany, see Table 2) at a dose of ½–1 ampoule/day [<25 kg or >25 kg body weight (BW)] given once daily. The positive control was given a canine NSAID, carprofen (Rimadyl® 50 mg, Pfizer, Helsinki, Finland), at a dose of 2 mg/kg twice daily. The products differed from each other in form; the carprofen and its placebo (lactose) came as a white pill, the HCP and its placebo (an isotonic sodium chloride solution) as an ampoule of clear liquid. Further, all dogs received a slightly green (lactose) capsule, that acted placebo for a parallel study (24). All dogs in the treatment groups were administered three products; one real and two placebos. In the negative control (placebo) group, all products administered were placebos. The products were coded and assembled by a research assistant who was not involved in the rest of the study. For ethical reasons, all owners were given a supplementary package of the same NSAID carprofen (Rimadyl®) in normal packaging at the start of the trial. This could be used as additional pain relief (dose of 1 tablet for a dog of 20–30 kg, 2 tablets for a dog of 31–40 kg and 3 tablets for a dog of 41–60 kg) if the dog was in considerable pain, but this had to be recorded in the questionnaires.

Study Protocol

Prior to the study, candidates were screened through telephone interviews. Owners were asked not to give the dogs NSAIDs or corticosteroids for at least 30 days and no Na-pentosan polysulfate (Carthrophen®, Biopharm Australia Pty. Ltd., Australia) for at least 90 days prior to the initiation of the study.

The first questionnaire was answered at home 4 weeks before the trial started (W_{-4}). The following four questionnaires where answered at the follow ups, at 4-week intervals (W_0, W_4, W_8 and W_{12}). An assistant made the first appointments for the dogs, which were then allocated, in order of arrival, into the groups using a computer-generated random list. Only the location of

Table 2. Content of Zeel® ad us. vet.

Zeel® ad us. vet.	Dil	mg
Cartilago suis	D6	5.0
Funiculus umbilicalis suis	D6	5.0
Embryon totalis suis	D6	5.0
Placenta totalis suis	D6	5.0
Solanum dulcamara	D3	25.0
Symphytum officinale e radice	D6	25.0
Nadidum	D8	5.0
Coenzyme A	D8	5.0
Sanguinaria canadensis	D4	7.5
Arnica montana	D3	50.0
Sulfur	D6	9.0
Natrium diethyloxalaceticum	D8	5.0
Acidum alpha-liponicum	D8	5.0
Toxicodendron quercifolium e summitatibus rec	D2	25.0

The content of one 5.0 ml ampoule of the low-dilution homeopathic combination preparation (HCP): Zeel®–injection solution. Mg of the different dilutions in the ampoule (Dil = D2–D8 (often also marked as 2×–8×) = diluted 1:10 two to eight times). From the Heel company veterinary guide, Baden-Baden, Germany 1997.

diagnosed OA (hip or elbow) was stratified in the randomization. At W_0 initial clinical, orthopedic and neurological examinations were performed and diagnostic criteria included decreased range of motion and pain on stretching the hip or flexing the elbow. The hip and elbow, as well as all other limb joints, were evaluated for pain, swelling and/or crepitus. Radiographs of the dogs' hips and/or elbows, and other joints if needed, were taken only at time W_0. The W_0 evaluation and W_0 questionnaire was set as baseline, except for extra carprofen where W_{-4} was used as baseline. The dogs were then given the products orally from W_0 to W_8. At W_{12}, the dogs had been washed off from all medication for 4 weeks and were evaluated to determine possible long-term effects of the different treatments. All evaluators (veterinarians and owners) and trial personnel were blinded. Owners of the dogs were required to sign informed consent forms. The study protocol was approved by the Ethics Committee of the University of Helsinki.

Veterinary Evaluation

Two veterinarians subjectively assessed locomotion, jumping and walking stairs at W_0, W_4, W_8 and W_{12}, using 5-point scales where 0 = normal and 4 = dog is totally lame/does not jump at all/does not walk stairs at all (24). The evaluations of the two veterinarians correlated well ($R = 0.853$, $P < 0.01$). The three scores assigned by the two veterinarians were summed to form a veterinary-assessed mobility index [$2 \times 3 \times (0$ to $4)$].

Owner Evaluation

The questionnaire consisted of three parts. First, the owners responded to 18 questions about attitude, behavior and locomotion using a descriptive scale from 0 to 4. Of these, 11 questions were combined to form a validated owner-assessed chronic pain index (25). The second part contained two 10-cm visual analogue scales (VASs): one for pain and the other for locomotion. The end of the lines to the left (0 cm) represented no pain or difficulties in locomotion and to the right (10 cm), the worst possible pain or the most severe difficulties in locomotion. The third part consisted of five questions about possible adverse reactions to treatment, including change in appetite, vomiting, diarrhoea, atopic skin reactions and the need for extra carprofen. The question about extra analgesics used the following scale: during the last 4 weeks, additional carprofen was given; 1 = not at all, 2 = 1–2 times, 3 = about once a week, 4 = about 3–5 times a week and 5 = daily/almost daily.

Objective Evaluation of Gait

Gait was analyzed by force plate gait analysis (Kistler force plate Type 9286, Kistler Instrumente AG Winterhur, CH-8408, Switzerland), which objectively assesses weight bearing of limbs. The signal from the plate was processed and stored using a computer-based software program, and velocities and acceleration were determined by three photoelectric cells placed 1 m apart and a start-interrupt timer system (Aquire 6.0, Sharon Software Inc., DeWitt, USA). The dogs were trotted from left to right by their owners. The speed had to be in the same range (±0.5 m/s) for the dog each time the test was performed (at W_0, W_4, W_8 and W_{12}). The acceleration was < 0.5 m/s/s and there had to be contact with the plate first by the forelimb and shortly after with the hind limb of the same side for the evaluation to be valid. The test was repeated until sufficient valid results were obtained for both left and right limbs. Three valid measurements for each side and for each visit were then chosen by a blinded assistant, who was not otherwise participating in the study, according to speed, acceleration and no interferences, such as gait abnormalities or extra body movements. The mean of these three measurements was used for analysis. The ground reaction forces were normalized for each dog's BW and mean peak vertical force (PVF) and mean vertical impulse were used as variables. Only measurements from the more severely affected limb at time W_0 were used in the analysis.

Blood Samples

Blood samples were collected from the dogs at each visit. Kidney, liver and protein values [blood urea nitrogen (BUN), creatinine, serum alanine aminotransferase (ALAT), alkaline phosphatase (AFOS), total proteins and albumin] were analyzed.

Statistical Analysis

The number of dogs needed in each group was calculated with a two-tailed test. The sample size was sufficiently large to detect a 47% difference in treatment outcome (effective versus non-effective) with a statistical power of 0.8 and allowing for a 5% alpha error.

For the dogs that had used extra carprofen more than three times per week at W_8, we changed all their variables values at evaluation W_8 into the most negative value measured at that time, separately for each variable. This was done to counteract the effect of the taken NSAID and enabled us to use the whole data in the first statistical analyses.

For calculating the percentage of dogs per group that improved between baseline and W_8 and the odds ratio, the results of each variable were converted into dichotomous responses of 'improved' and 'not improved'. Dogs that deteriorated and dogs with no change in the evaluated variable were considered 'not improved'. The difference between the treatment groups and the placebo where calculated using a Chi-Squared test. The odds ratio was calculated using the common Mantel Haenszel odds ratio estimate and the confidence interval (CI) was set to 95%. An odds ratio over 1.0 indicated a beneficial effect of the test treatments.

The change from baseline to W_8 was also calculated for each variable. The difference between the GLM and placebo group was analyzed using the Mann–Whitney test. The change from W_0 to W_8 in the force plate variables was similar for the front and hind legs, although the values were different. Therefore, force plate data of all four legs were analyzed together. Dogs that did not manage to get force plate results due to major lameness were considered 'not improved' in the dichotomous analyses and were excluded from the median change data. A correlation test was used to evaluate the association between the assessments of the two veterinarians. Statistical significance was set at $P < 0.05$. Statistical tests were preformed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline

Seven of these 51 dogs were excluded from the material at some time during the study because they did not meet the medical inclusion criteria (operation on the affected hip joint, a transverse vertebra ($n = 2$), a cruciate ligament injury, degenerative myelopathy, polyarthritis of the phalanges and castration just prior to the third visit). The baseline differences between groups were not statistically significant (Table 1).

Dichotomous Responses

All major data are presented in Table 3. Four dogs (all in the placebo group) used extra carprofen more than three times per week at W_8 and two dogs were not able to trot over the force plate. When the data of all variables were changed into dichotomous responses of either 'improved' or 'not improved', three of the variables [veterinary-assessed mobility index ($P = 0.018$), force plate PVF ($P = 0.006$) and pain VAS ($P = 0.043$)] indicated significantly more improved dogs in the HCP group compared with the placebo group. The odds ratio for the veterinary-assessed mobility index was 6.88 (95% CI

Table 3. Percentage of improved dogs and median (+range) of improvement from W_0 to W_8, for evaluated variables, per group

	carprofen ($n = 15$)		HCP ($n = 14$)		Placebo ($n = 15$)	
	Improved $P=$	Improvement Median (range), $P=$	Improved $P=$	Improvement Median (range), $P=$	Improved (%)	Improvement Median (range)
Veterinary mobility index	66.7% 0.031	3 (0 to –8) 0.001	71.4% 0.018	1.5 (−5 to 7) 0.015	26.7	−3 (−14 to 3)
Force plate PVF	66.7% 0.031	3.2 (−8.2 to 1.8) 0.079	78.6% 0.006	2.3 (−3.4 to 10.2) 0.028	26.7	−0.9 (−33.6 to 10)
Force plate Impulse	80.0% 0.011	0.4 (−0.5 to 1.3) 0.009	64.3% 0.101	0.2 (−1.3 to 1.3) 0.093	33.3	−0.0 (−3.3 to 0.8)
Chronic pain index	80.0% 0.028	9 (−9 to 19) <0.001	57.1% 0.364	2 (−6 to 9) 0.049	40.0	−3 (−25 to 8)
Pain VAS	85.7% 0.001	1.4 (−6 to 8.4) <0.001	57.1% 0.043	0.2 (−3.5 to 4.9) 0.020	20.0	−1.7 (−7 to 3.2)
Locomotion VAS	85.7% 0.002	3.1 (−1.9 to 6.2) 0.001	57.1% 0.102	0.7 (−5 to 4.8) 0.205	26.7	−1 (−6.6 to 5)

For each treatment group: First column: Percentage of dogs in the group that improved. Second column: Median (with range) of change from W_0 to W_8 ((+) = improvement, (−) = deterioration) in evaluated variables for the carprofen-, HCP- and placebo groups. P = Difference in improvement between treatment groups and placebo (the force plate values here do not include two dogs for whom no results were obtained). (n, number of patients per group; HCP, homeopathic combination product; Improved, percentage of dogs that improved per group; PVF, peak vertical force; VAS, visual analogue scale).

1.35–35.06) indicating that a dog that had received the HCP was 6.88 times more likely to have a positive response than a dog that had received the placebo. The odds ratio for the force plate PVF was 9.17 (95% CI 1.63–51.43), for the force plate impulse 3.24 (95% CI 0.69–15.20), for the owner-assessed chronic pain index 2.00 (95% CI 0.46–8.78), for the pain VAS 5.33 (95% CI 1.02–27.76) and for the locomotion VAS 3.67 (95% CI 0.77–17.43).

Medians (+ Range) of the Change from W_0 to W_8

The medians and ranges of the changes from W_0 to W_8 in each variable are shown in Table 3. Two dogs from the placebo group are excluded from the two force plate evaluations. All variables showed a similar trend of improvement, with carprofen being most efficient, placebo least, and HCP being between these two. In the negative control group (placebo), all change medians were on or below the 'no change' line, indicating deterioration. There was a significant difference in four of six variables in the extent of improvement between the HCP and the placebo group; the veterinary-assessed mobility index ($P = 0.015$), the PVF ($P = 0.028$), the chronic pain index ($P = 0.049$) and the pain VAS ($P = 0.020$). Data from W_4 are not shown, as all values were between the values of W_0 and W_8. Statistical analyses were not performed on the results from W_{12}, as so many dogs were using extra carprofen at this time.

Extra Carprofen

The use of the additional NSAIDs varied as follows: at W_{-4}, 14% of the carprofen group, 28% of the HCP group and 8% of the placebo group used extra NSAIDs once a week or more often. At W_8, the respective values were 0, 14 and 27%, and at the follow up at W_{12}, 33, 21 and 29%. Only the difference between the carprofen group and the placebo group was significant ($P = 0.012$) at W_8.

Complications and Side-Effects

All of the altered blood values and the clinical side-effects were considered mild or within normal range. No difference between groups was seen. One dog in the placebo group was euthanized due to severe pain during the follow-up period.

Discussion

We examined the effect of the HCP Zeel® on OA in dogs. Compared with the placebo group, the HCP treatment gave significantly better results both as number of cases that improved per group and as efficacy or extent of improvement. Thus, the results of what apparently is the first randomized, controlled, double-blinded study on the use of a HCP on OA in dogs indicate that the treatment indeed tends to have significant positive impact. The results add to previous positive results on the use of this HCP on OA in studies on humans (13,14), rabbits (16) and horses (17), suggesting that the treatment may be beneficial also for other species. To be noted is that, compared with the placebo group, the group of dogs being treated with carprofen improved even more. This is in accordance with previous studies that have demonstrated a treatment effect of 56–81% for carprofen and only 23–38% for placebo (26,27). But, as carprofen and other NSAIDs can potentially have severe side-effects such as hepatic disease, renal toxicosis and irritation of the gastrointestinal tract, ultimately leading to hemorrhagic ulcers and even death (28,29), it is of utmost importance that we continue doing clinical research on all alternative treatments for OA.

Other data also support our results: it is generally accepted that seasonal differences influence OA, with patients being worse in cold, damp and unstable weather (in our study = $W_{4–8}$) and better in dry (W_0) and warm (W_{12}) weather (30,31). In the placebo group, a trend was detectable; in the change of means between W_0 and W_8, we could see deterioration in nearly all variables (negative values in Table 3) and use of more extra NSAID; and improving at follow up (W_{12}) as the weather warmed up. In the two treatment groups an opposite pattern was detected. They demonstrated a positive effect during the test period ($W_{0–8}$) but worsened at the follow up (W_{12}), which can be speculated to indicate the positive effect of the drugs and a worsening after discontinuation at W_8. The increase in the intake of extra NSAIDs at W_{12} in the carprofen group further supports this.

However, although significant differences between groups were found in this study, it suffers from some limitations that at the same time point to possibilities for future research. Future studies should ideally ascertain that the treatment group, as well as the positive and negative control groups, is large enough to detect difference even when data are lost. Having two dogs in the placebo group that were not able to perform the runs over the force plate and were therefore excluded from the data, slightly ameliorated the median values for this group, perhaps resulting in less significance in the treated groups. Second, the location (hip or elbow), the multitude (uni or bilateral) and severity of OA varied across the dogs, leading to assessment problems e.g. using the force plate due to transferring the weight to other legs. Heterogeneity also leads to high variance; a problem in a small study like ours, with a relatively moderate sample size, and subsequently results in lower significance. Third, the dose and mode of application of HCP in our study was ½–1 ampoule/day (depending on BW) in one oral dose. However, the dosing and presentation of the Zeel®

product has since changed; it is now given as a tablet and at 300% of the dose used in this study. Furthermore, for optimal results, Zeel® is often combined with other homeopathic products (such as Traumeel®) in clinical practice (1), but combining products was not suitable for our protocol. Future research might want to assess effect using different doses, methods of application or combinations. Finally, as very little research on chronic pain assessment for dogs still is available, it will make future research easier when we have more validated scales to use. Measuring ground reaction forces using a force plate (32–35) were the most objective measurement used, but they are not so reliable to use on a very variable cohort. Validated owner-based scales are now also becoming available and will maybe be used more in the future (25,36–38).

Thus we must conclude that the results are intriguing, as all positive results in homeopathic medicine. As the study was rigorously carried out as a randomized, double-controlled, double-blind trial and as the placebo effect anyway should be smaller when evaluating dogs and not humans, we can elaborate on a possible working mechanism for this product. It seems plausible that the treatment effects reported previously could have been seen in this trial as well: in a randomized, sham-controlled placebo study on rabbits with experimentally induced knee OA, a significant difference in gross morphology and in histopathological score was found between the joints treated with HCP Zeel comp.® and those untreated (16). Also, cartilage slices incubated for 6 days in a medium containing Zeel® showed better preservation of structures than controls in an *in vitro* study using methods of interference polarization microscopy and x-ray difractometry for analysis (39).

An *in vitr*o study (40) demonstrated that two of the ingredients in our test product were able to inhibit leucocyte elastase activity; *Arnica montana* D4 up to 70% and *Rhus toxicodendron* (same as *Toxicodendron quercifolium* in Table 2.) D3 up to 77% (elastase is an enzyme that is released during inflammatory reactions and attacks the articular cartilage which is rich in proteoglycans). In a second study (41), *Rhus toxicodendron* at D1 and D2 potencies, as well as 10 other plant extracts, was shown to inhibit cell growth of human cutaneous F54 fibroblasts.

Recently, a reconstituted Zeel comp. N® combination (as well as its constituent mother tinctures) were reported to show distinct inhibitory effects on the production of Leukotriene B_4 by 5-lipoxygenase (5-LOX) and on the synthesis of prostaglandin PGE_2 by COX-1 and 2 enzymes. Together with the other inhibiting activities, this dual inhibition of both LOX- and COX-metabolic pathways may offer an explanation for the reported clinical efficacy and favorable gastrointestinal tolerability of the original Zeel comp. N® remedy (42) and of the veterinarian product we used in this study, that was very similar.

In conclusion, the results of this relatively small study of dogs with moderate to severe OA showed that dogs receiving the HCP Zeel® for 8 weeks had significantly less pain than their placebo peers. Homeopathy as a treatment is often seen as controversial, so this positive treatment result for dogs for this low-dilution HCP should be of major interest for human OA researchers and clinicians, alike. As chronic pain due to OA is a major reason for decreased quality of life nowadays, both for humans and dogs, we should proceed with more studies in this direction.

Funding

The Finnish Foundation of Veterinary Research, Helvi Knuuttila Foundation.

Acknowledgements

The authors are grateful for grants received from the Finnish Kennel Club, Pfizer Finland, Boeringer Ingelheim Germany, Vetcare Finland and Heel Germany, which financed the acquisition of a force plate that made objective analyses possible. Further, we would like to thank Pfizer Finland and Heel Germany for contributing the products and their placebos used in the different treatment groups in this study, without cost. We also wish to thank our two anonymous reviewers and Mrs Willis, for their valuable comments.

References

1. *Biotherapeutic Index – Ordinatio Antihomotoxica et Materia Medica*. 5th revised English edn. Baden-Baden, Germany: Biologische Heilmittel Heel GmbH, 2000, 9–23, 90–93, 434–6.
2. Bennet D, May C. Joint diseases of dogs and cats. In: Saunders WB (ed). *Textbook of Veterinary Internal Medicine*, 4th edn, 1995, 2053–8.
3. Hektoen L. Review of the current involvement of homeopathy in veterinary practice and research. *Vet Rec* 2005;157:224–9.
4. Bellavite P, Conforti A, Pontarollo F, Ortolani R. Immunology and homeopathy. 1. Historical background. *Evid Based Complement Alternat Med* 2005;2:441–52.
5. Bellavite P, Conforti A, Pontarollo F, Ortolani R. Immunology and homeopathy. 2. Cells of the immune system and inflammation. *Evid Based Complement Alternat Med* 2006;3:13–24.
6. Bellavite P, Conforti A, Ortolani R. Immunology and homeopathy. 3. Experimental studies on animal models. *Evid Based Complement Alternat Med* 2006;3:171–86.
7. Bellavite P, Ortolani R, Pontarollo F, Piasere V, Benato G, Conforti A. Immunology and homeopathy. 4. Clinical studies-Part 1. *Evid Based Complement Alternat Med* 2006;3:293–301.
8. Bellavite P, Ortolani R, Pontarollo F, Piasere V, Benato G, Conforti A. Immunology and homeopathy. 4. Clinical studies-Part 2. *Evid Based Complement Alternat Med* 2006;3:397–409.
9. Bellavite P, Ortolani R, Pontarollo F, Pitari G, Conforti A. Immunology and homeopathy. 5. The rationale of the 'Simile'. *Evid Based Complement Alternat Med* 2007;4:149–63.
10. Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997;350:834–43.

11. Kleijnen J, Knipschild P, Ter Riet G. Clinical trials of homeopathy. *Br Med J* 1991;302:316–23.
12. Ernst E. A systematic review of systematic reviews of homeopathy. *Br J Clin Pharmacol* 2002;54:577–82.
13. Maronna U, Weiser M, Klein P. Orale Behandlung der Gonoarthrose mit Zeel comp/Comparison of the efficacy and tolerance of Zeel comp. and Diclofenac for the treatment of gonoarthrosis: results of a doubleblind equivalence study. *Orthopädische Praxis* 2000;36:285–91.
14. Nahler G, Metelmann H, Sperber H. Behandlung der Gonoarthrose mit Zeel comp. – Ergebnisse einer randomisierten, kontrollierten klinischen Pröfung im Vergleich zu Hyaluronsäure [in German]. *Orthopädische Praxis* 1996;5:354–9.
15. von Frase W. Anwendungsmöglichkeiten von Zeel comp. N (Ampullen) [in German]. *Biol Med* 1999;28:149–51.
16. Stancikova M, Bfly M, Svik K, Metelmann HW, Schmolz MW, Istok R, et al. Effects of ZEEL Comp. on experimental osteoarthritis in rabbit knee. *Rheumatology* 1999a;13:101–8.
17. Boyeux M. Die anwendung von Zeel® in der behandlung der artropatien des renn-und sportpferdes [in German]. *Biologische Tiermedizin* 1984;3:50–5.
18. Altman RD. Design and conduct of clinical trials in osteoarthritis. *Scand J Rheum* 1990;Suppl. 81:24–7.
19. Shott S. Study design. *J Am Vet Med Assoc* 1990;197:1142–4.
20. Budsberg ST. The randomized clinical trial. *Vet Surg* 1991;20:326–8.
21. Kapatkin AS, Mayhew PH, Smith GK. Canine hip dysplasia: evidence-based treatment. *Comp Cont Educ Pract Vet* 2002;24:590–9.
22. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Lancet* 2001;357:1191–4.
23. FCI (Federation Canine International). Hip Dysplasia and Elbow Classification, workshop in Dortmund 14.6, 1991 (brochure).
24. Hielm-Björkman A, Tulamo R-M, Salonen H, Raekallio M. Evaluating a complementary therapy for moderate to severe canine osteoarthritis. Part I: green lipped mussel (*Perna canaliculus*). *Evid Based Complement Alternat Med* 2007, doi:10-1093/ecam/nem136.
25. Hielm-Bjorkman AK, Kuusela E, Liman A, Markkola A, Saarto E, Huttunen P, et al. Evaluation of methods for assessment of pain associated with chronic osteoarthritis in dogs. *J Am Vet Med Assoc* 2003;222:1552–8.
26. Vasseur PB, Johnson AL, Budsberg SC, Lincoln JD, Toombs JP, Whitehair JG, et al. Randomized, controlled trial of the efficacy of carprofen, a non-steroidal anti-inflammatory drug, in the treatment of osteoarthritis in dogs. *J Am Vet Med Assoc* 1995;206:807–11.
27. Holtsinger RH, Parker RB, Beale BS, Friedman RL. The therapeutic efficacy of carprofen (Rimadyl-V™) in 209 clinical cases of canone degenerative joint disease. *Vet Comp Orthop Traumatol* 1992;5:140–4.
28. FDA (Food and drug administration) US ADE (United States Adverse Drug Experience) reports summary 1998. *Animal Pharm* 1998;435:9.
29. MacPhail CM, Lappin MR, Meyer DJ, Smith SG, Webster CRL, Armstrong PJ. Hepatocellular toxicosis associated with administration of carprofen in 21 dogs. *J Am Vet Med Assoc* 1998;212:1895–901.
30. Aikman H. The association between arthritis and the weather. *Int J Biometeorol* 1997;40:192–9.
31. Strusberg I, Mendelberg RC, Serra HA, Strusberg AM. Influence of weather conditions on rheumatic pain. *J Rheumatol* 2002;29:335–8.
32. Budsberg SC, Chambers JN, Van Lue SL, Foutz TL, Reece L. Prospective evaluation of ground reaction forces in dogs undergoing unilateral total hip replacement. *Am J Vet Res* 1996;57:1781–5.
33. Budsberg SC, Johnston SA, Schwarz PD, De Camp CE, Claxton R. Efficacy of etdolac for the treatment of osteoarthritis of the hip joints in dogs. *J Am Vet Med Assoc* 1999;214:206–10.
34. Moreau M, Dupuis J, Bonneau M, Desnoyers M. Clinical evaluation of a neutraceutical, carprofen and meloxicam for the treatment of dogs with osteoarthritis. *Vet Rec* 2003;152:323–9.
35. Theyse LFH, Hazewinkel HA, Van Den Brom WE. Force plate analyses before and after surgical treatment of unilateral fragmented coronoid process. *Vet Comp Orthop Traumatol* 2000;13:135–40.
36. Holton LL, Scott EM, Nolan AM, Reid J, Welsh E, Flaherty D. Comparison of three methods used for assessment of pain in dogs. *J Am Vet Med Assoc* 1998;1:61–6.
37. Hudson JT, Slater MR, Taylor L, Scott HM, Kerwin SC. Assessing repeatability and validity of a visual analogue scale questionnaire for the use in assessing pain and lameness in dogs. *Am J Vet Res* 2004;65:1634–43.
38. Wiseman-Orr ML, Nolan AM, Reid J, Scott EM. Development of a questionnaire to measure the effects of chronic pain on health-related quality of life. *Am J Vet Res* 2004;65:1077–84.
39. Orlandini A, Rossi M, Setti M. Die Wirksamkeit von Zeel und neue Forschungsmethoden in der Rheumatologie. *Biologische Medizin* 1997;26:164–5.
40. Stancikova M. Hemmung der Leukozytenelastase-Aktivität in vitro mit Zeel® T, Zeel® comp. und ihren verschiedenen potenzierten Bestandteilen [in German]. *Biologische Medizin* 1999;2:83–4.
41. Valentiner U, Weiser M, Moll I, Schumacher U. The effect of homeopathic plant extract solutions on the cell proliferation of human cutaneous fibroblasts in vitro. *Forschende Komplementärmedizin und Klassische Naturheilkunde* 2003;10:122–7.
42. Jäggi R, Wurgler U, Grandjean F, Weiser M. Dual inhibition of 5-lipoxygenase/cyclooxygenase by a reconstituted homeopathic remedy; possible explanation for the clinical efficacy and favourable gastrointestinal tolerability. *Inflamm Res* 2004;53:150–7.

Received July 6, 2006; accepted July 12, 2007