N2016-0012: Improving quality-of-life in dogs with osteoarthritis

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Popular scientific summary

Approximately 20% of all adult dogs have osteoarthritis. The incidence varies with both breed and body condition, with overweight Labrador retrievers having an incidence of hip osteoarthritis of 50% by 6 years of age, and a median lifespan 2 years shorter than that of dogs with an optimum weight. Osteoarthritis is a progressive condition that diminishes life quality, and may lead to consideration of euthanasia to prevent unnecessary suffering. Osteoarthritis cannot be cured, although total joint replacement or joint fusion surgery is possible for some affected joints. Effective medical treatment protocols are therefore of great interest to clinicians and owners. In general practice, evaluation of these protocols, and of lameness in general, is highly dependent on subjective and potentially biased assessments made by the owners and veterinarians.

We wanted to examine ways in which lameness assessments could be made more reliably between clinic visits and between veterinarians, but also to assess the effect of commonly used supplemental medicines on the lameness experienced by osteoarthritic dogs, as well as identifying possible blood tests that could help early diagnosis or monitor treatment progress.

We found that use of a pressure-sensitive mat was a reliable and relatively rapid method for measuring canine gait in both healthy and osteoarthritic dogs. In dogs with multiple affected limbs and low grades of lameness, the system struggled to differentiate between healthy and osteoarthritic dogs – especially when the overall severity of the lameness was mild. Our experience with measurements based on video-recordings was similar.

Use of four weeks of supplemental treatment with either gabapentin or tramadol, in addition to the standard anti-inflammatory treatment the patient was already receiving, improved limb use in osteoarthritic dogs. Neither medicine appeared to cause problems with the liver or kidneys in our study, but there was a high incidence of other side effects such as nausea, tiredness and disorientation similar to those reported in humans. Careful counselling before use of these medicines is recommended, and further studies into compounds that might be better tolerated are needed.

We investigated five blood biomarkers to explore the possibility of early diagnosis of osteoarthritis before radiographic or clinical signs, and work on this is ongoing.

Introduction, background, purpose and issue

Approximately 20% of all adult dogs have osteoarthritis, a progressive condition that diminishes life quality, and which may lead to consideration of euthanasia to prevent unnecessary suffering. Osteoarthritis cannot be cured, although total joint replacement or joint fusion surgery is possible for some affected joints. Effective medical treatment protocols are therefore of great interest to clinicians and owners. However, evaluation of these protocols, and of lameness in general, is highly dependent on subjective and potentially biased assessments made by the owners and veterinarians.

Lameness evaluations in the clinic are typically based on visual assessment of gait at walk or trot. Evaluations can be heavily influenced by the walking surface, distractions to the patient or walker, experience and expectation. Evaluators generally do not agree with each other, since each uses an individual, subjective scale. Little or no agreement has been shown between subjective evaluations of lameness and force-plate analysis of limb loading, and significant placebo effects (up to 33-39%) on both veterinarian and owner assessments have been reported in treatment studies. Force-plate analysis, which objectively measures peak and total limb loading, is considered the gold standard for lameness assessment, but costly and technically demanding. A newer development is the pressure-sensitive walkway, which enables analysis of several sequential steps to be made very rapidly with no inconvenience to the patient, since the measurement tool resembles a normal floor covering and is not unpleasant or unusual to walk over. Recent advances in camera phone technology which mean that high quality recordings can be played back at much slower speeds, has the potential to increase the reliability of lameness assessments for veterinarians in general practice. Standardizing the recording and viewing of walking patients, may reduce subjectivity, enhance identification of changes in gait, and establish a visual record of patient progress.

Conventional treatment of osteoarthritis in dogs consists of weight control, exercise control and the use of non-steroidal anti-inflammatory medicines (NSAIDs). Veterinary licensed NSAIDs remain the mainstay of treatment for these animals. Residual lameness is commonly seen, probably indicating persistent pain developing into chronic pain and reduced quality of life. Adjunctive medical therapies are often indicated in patients with chronic pain, including the use of medicines that affect transmission of pain signals in the spinal cord, e.g. tramadol and gabapentin. Although awareness and use of adjunctive medicines for veterinary patients has increased in recent years, very limited data are available on their efficacy or safety. Despite this, clinical experience suggests that these compounds can be effective in alleviating pain. Both tramadol and gabapentin are utilized as add-on analgesia in our hospital for patients responding inadequately to NSAIDs but lack of information regarding their relative efficacies or risk profiles limits their recommendation.

Certain parameters in the blood that reflect inflammation or turnover of cartilage or bone may have value as objective markers of osteoarthritis in the dog. If a predictable response to effective treatment could be demonstrated in the circulating levels of these biomarkers, a simple blood test might provide veterinarians with an objective tool to measure improvements or deteriorations in osteoarthritis status.

The aims of this project were: to determine the reliability of a commercial pressure-sensitive walkway in healthy and osteoarthritic dogs; to determine if low-grade lameness due to osteoarthritis could be reliably identified; to determine if simple video analysis could be used to measure lameness; to test the effect of tramadol and gabapentin in addition to non-steroidal anti-inflammatory treatment; and to identify potential biomarkers for discriminating between healthy dogs and osteoarthritis patients for studies of treatment response.

Materials and methods

Institutional approval was obtained for this study (2017-1), and advice sought from the Animal Experiments Inspectorate. Written owner consent was obtained for all studies.

A gait laboratory equipped with 4 Tekscan Medical #3140 sensors incorporated in to a 1.95 m long by 0.45 m wide pressure-sensitive walkway (PSW) and covered by a 3 m x 0.6 m mat along with a high definition (1920 x 1080) video camera was used throughout the study. Pressure data from the walkway was converted using software (Walkway 7.66) to vertical forces, enabling calculation of kinetic and temporal characteristics for each limb before and after normalization to body mass. The system was equilibrated to 75 Hz on a daily basis and the 4 sensors were calibrated using a phantom mass weighing 21.6 kg on a weekly basis. Following acclimatization, 6 successive valid recordings were obtained for each dog while they walked the PSW, with 3 recordings in each direction of travel. A recording was considered valid when all four limbs fully contacted the PSW and the dog walked straight forward without stopping, hesitating, or having overt head movements, and when walking velocity was controlled at 0.9-1.1 m/s.

Assessment in healthy dogs

Client-owned dogs (n=41) with no history of osteoarthritis or joint disorders were recruited via hospital staff and social media appeals in 2018. Dogs were screened using owner-reported history, clinical and orthopaedic examinations and visual gait analysis. Inclusion criteria included an age of 2-7 years, body mass of 15-40 kg and body condition score of 4-6. Exclusion criteria included abnormal findings on examination, previous joint or fracture surgery or suspicion of orthopaedic disease. Using the recording protocol outlined above, we obtained temporal and kinetic characteristics for all 41 dogs, and repeated measurements for 10 dogs to assess between-day repeatability. Symmetry indices between left and right limbs, fore and hind limbs, and diagonally were calculated to determine reference intervals and for comparison with osteoarthritic dogs.

Comparison with osteoarthritic dogs

Client-owned dogs (n=24) with previously diagnosed osteoarthritis were recruited via social media appeals in 2019. Dogs were screened using owner-reported history, clinical and orthopaedic examinations and visual gait analysis. Inclusion criteria included an age over 1 year (1.5 years for giant breeds), body mass over 25 kg, and radiographic evidence of osteoarthritis either at our institution or at the client's usual clinic. Exclusion criteria included clinical suspicion of other local or systemic disease besides OA on thorough clinical examinations, owner histories and routine biochemistry, haematology and urinalysis. The recording protocol described above was used. Data were handled similarly to part 1. Precision was assessed by calculating an intra-analytical CV based on data from all dogs included in this substudy.

Effect of supplemental medication (tramadol and gabapentin) on limb use

The same patient population as in (2) above was included in this part of the study. In addition to the criteria listed in (2), patients had ongoing lameness confirmed on clinical and orthopaedic examination despite treatment with a veterinary licensed NSAID given at an appropriate dose for at least six weeks prior to trial start. The recording protocol above was used on 4 occasions (before and after each 4-week treatment period with tramadol or gabapentin). Haematology, biochemistry and urinalysis were performed at each visit. Patients were randomized into a crossover design with a one-week washout, and the study was single-blinded. Either tramadol (3-5 mg/kg three times daily PO) or gabapentin (8-12 mg/kg three times daily PO) were dispensed by independent personnel according to the randomization

scheme. Information on physical adverse events were collected using open questions. Weather data were retrieved from the local weather station reports. An intent-to-treat analysis was performed looking at the effect of medicine, order of treatment, initial measurement values and weather on the response to treatment. Haematology and biochemistry were compared pre- and post-treatment for each medicine.

Simple spatiotemporal video analysis of healthy and osteoarthritic dogs

Dogs from the patient populations in (1) and (2) were used for this substudy. Video recordings using a video camera placed on a tripod set to half the withers height of each dog and 2.2 m from the walkway. Recordings were obtained in both directions of travel. Following export to a computer, one recording in each direction was selected for analysis. Subjective gait analysis was performed by two observers using the video recordings to assign a lameness grade using a numerical scale from 0-5, using the worst score for each dog. Dogs were characterized as forelimb or hind limb lame. Frame-by-frame analysis was performed to identify durations of the stance and swing phases for each limb using timestamps from the software, and values averaged across directions of travel. Symmetry indices comparing left:right, fore:hind and diagonal limb pairs were calculated using previously described formulae. Mid-stance still images were identified for each limb and exported from recordings for each direction of travel. Vertical distances in pixels were obtained for the following anatomic landmarks: base of paw, dorsal aspect of head (excluding ears), dorsal aspect of shoulders, and highest point in the pelvic region. Head height, shoulder height and pelvic height were calculated along with symmetry indices between left and right limb pairs. Indices for the healthy and osteoarthritis cohorts (and for forelimb and hind limb lame dogs separately) were compared statistically. Discriminant ability was tested using receiver-operating curves.

Biomarker assays

Blood samples from 10 dogs from part (1) and 6 additional dogs recruited using a similar protocol and assessed as healthy using the same criteria were compared with blood samples from the first visit for the osteoarthritis cohort (24 dogs). Serum was stored at -80°C until analysis. Five biomarkers were selected for screening based on previous published work and clinical suspicion of relevance to osteoarthritis: hyaluronic acid (HA), matrix metalloproteinase 13 (MMP-13), procollagen type IIa (PIIANP), cartilage oligomeric matrix protein (COMP) and collagen type-2 cleavage (C2C). Blood concentrations between healthy and osteoarthritic dogs were compared.

Results

Assessment in healthy dogs

Sixteen male and 25 female dogs of medium and large breeds with mean age of 4 years and body mass of 27.2 kg were studied. Values for thoracic and pelvic limbs were similar to those previously reported for dogs. Direction of travel had no impact on measurements. High precision was observed with coefficients of variation for within-day of 1.0-6.5% and between-day of 2.4-7.7%.

Comparison with osteoarthritic dogs

Twelve male and 9 female dogs of large breeds with mean age of 9.3 years and body mass of 36.3 kg were studied. Twelve dogs were primarily forelimb lame, and 9 dogs hind limb lame. Visual lameness grading scores were 1-3 out of 5. Within-day coefficients of variation were generally higher for this population and were seen for all limbs not just the worst affected. Symmetry indices for this population

showed considerable overlap with the healthy population, with only higher grade lamenesses being clearly distinguished from normal. Left:right symmetry indices showed the best performance.

Discussion, conclusions and practical benefit

We were able to demonstrate good precision for the Tekscan pressure-sensitive walkway system in healthy dogs, with within-day and between-day precisions as good as or better than previously reported data. Precision was lower in the osteoarthritic population, but this is not unexpected, as joint-related pain is unlikely to be constant but instead will vary with repeated activity such as gait analysis. Our osteoarthritic population was representative of many older dogs seen in clinical practice, with generalized joint-related pain but one limb more severely affected than the others. These typically present with complex gait abnormalities due to compensation for multiple affected joints, and despite clearly abnormal gait patterns often have relatively low scores on visual gait analysis, due to a masking effect. While objective gait analysis using force plates or similar systems to that used here have shown utility in diagnosis and monitoring of single limb lameness, for example with cruciate ligament rupture, these patients rarely present a clinical diagnostic challenge and at least in the early stages of treatment, visual analysis is sufficient to assess the presence or absence of improvement. In contrast, determining the worst affected limb or measuring changes in severity can be challenging in multi-joint disease. We were therefore interested to see if the walkway system could detect and characterize these patients. Unfortunately, it appears that this is quite difficult, at least until the lameness grade becomes moderately severe, and the results of the second part of the study showed that discriminant ability was poor for our osteoarthritic population.

Reliable diagnosis of mild lameness in osteoarthritic dogs remains challenging, even with modern diagnostic tools, and the search for a useful blood biomarker of early osteoarthritis to enable timely intervention (and perhaps slowing of the development of the disease) continues.

Publications

In addition to four final-year student projects (specialer) so far, this project has yielded one published peer-reviewed article in an international journal, with three manuscripts in preparation, as well as 4 conference abstracts/posters with an additional abstract submitted for consideration.

Peer-reviewed papers

Kinetic gait analysis in healthy dogs and dogs with osteoarthritis: An evaluation of precision and overlap performance of a pressure-sensitive walkway and the use of symmetry indices. Nielsen MBM, Pedersen T, Mouritzen A, Vitger AD, Nielsen LN, Poulsen HH, Miles JE. PLoS One. 2020 Dec 15;15(12):e0243819. https://doi.org/10.1371/journal.pone.0243819

Papers submitted or in preparation

Gabapentin and tramadol increase peak vertical force in osteoarthritic dogs receiving non-steroidal anti-inflammatory drugs: a single-blinded, randomised, cross-over clinical trial.

Simple video-based spatiotemporal gait analysis is not better than subjective visual assessment of lameness.

Blood biomarkers for osteoarthritis: comparison with healthy dogs and longitudinal tracking in response to treatment.

Peer-reviewed abstracts at international conferences

Miles JE, Vitger AD, Poulsen HH, Nielsen LN. Direction of travel can influence canine gait characteristics. 2018. *Proceedings of the 2018 British Small Animal Veterinary Congress. Birmingham, UK. pp. 474-5*

Objectives: To describe the effect of direction of travel on measurements of peak vertical force (PVF) and vertical impulse (VI) obtained using a Tekscan walkway system. **Methods:** Following acclimatisation, recordings were obtained for six healthy dogs walking twice in in each direction along the walkway. PVF and VI measurements were normalised and used to calculate left:right symmetry ratios for forelimb and hindlimb loading in each travel direction and for all recordings. **Results:** Mean walking speed was 1.2 ± 0.14 m/s. Mean body mass was 25 ± 5 kg. No gross evidence of pulling to left or right was observed. Mean symmetry ratios for PVF and VI varied consistently but insignificantly with direction of travel. However, individual variation in symmetry ratios ranged from ±0.4–14 % for PVF and ±0.4–11 % for VI. Forelimb to hindlimb ratios of both PVF and VI varied by ±3-4 % with direction of travel. **Statement:** Direction of travel may influence gait characteristics and thereby both determination of local reference intervals and discriminatory ability between normal and abnormal limbs. Consistent walkway room setup and use of multiple passes in both directions appear sensible in order to minimise error between measurements at different times, and to compensate for the effect of direction of travel on outcome measures.

Miles JE, Nielsen MBM, Mouritzen A, Pedersen T, Nielsen LN, Vitger AD, Poulsen, HH. Gait analysis of lameness-free dogs: experience with a Tekscan pressure-sensitive walkway system*. Proceedings of the 2019 British Small Animal Veterinary Congress. Birmingham, UK. 2019. p. 521*

Objectives: To define reference intervals and investigate repeatability for key gait parameters in a lameness-free canine population using a pressure-sensitive walkway (PSW) system. **Methods:** Following institutional ethical approval, 40 healthy client-owned dogs of various breeds weighing 15-40 kg and between 2-6 years old were recruited. Orthopaedic pathology was ruled out by clinical examination and validated owner questionnaires. Six valid trials (3 in each direction) were obtained using a 2m by 0.46m PSW (Tekscan 5101E-VH4), equilibrated daily and calibrated weekly. For a valid trial, all paws had to contact the PSW for two or more consecutive strides, with a constant velocity of 0.9-1.1 m/s, while walking with a loose leash without overt head movements. Measurements were repeated for 10 dogs on a different day. Symmetry indices for key gait parameters were derived and reference intervals for these created from bootstrapped 2.5% and 97.5% percentiles. **Results:** Stance time, stride length and peak vertical force reference intervals were typically under ±10%, and narrower for forelimbs than hindlimbs. Coefficient of variation for repeated measurements was typically under 10%. Direction of travel had statistically significant, but clinically unimportant effects, on several gait parameters. **Clinical significance:** PSW gait parameters show relatively little variation, such that deviations beyond reference intervals may permit identification and monitoring of lameness in clinical patients. A PSW may be useful in assessing clinical gait profiles and monitoring response to treatments such as surgery or physiotherapy. **Statement:** PSW data are repeatable and valid for determination of reference intervals for gait parameters in lameness-free dogs weighing 15-40kg.

Miles JE, Vitger AD, Poulsen HH, Møller JH. Simple spatio-temporal gait analysis is not better than the human eye. 2020. *Poster session presented at 2020 British Small Animal Veterinary Congress, Birmingham, UK.* **https://curis.ku.dk/admin/files/239391366/JamesMilesPosterSimpleSpatiotemporalGait.pdf**

Objectives: Visual gait analysis suffers from subjectivity, and it is difficult to compare lameness grades between clinic visits and between veterinarians, but objective spatio-temporal analysis is generally restricted to the laboratory setting. Could simple video analysis offer a more objective and repeatable method of evaluation for mild grades of lameness in clinics? **Methods:** Video recordings obtained prospectively from 58 dogs using a standardised protocol were analysed using freely available software to determine ratios of stance and swing times. Captured still images were used to calculate symmetry ratios of head, shoulder and pelvic height between left and right limbs. Analysis time was recorded to assess practicability. **Results:** On clinical evaluation, 37 dogs were sound and 21 dogs were lame (9 forelimb, 12 hindlimb). The majority of lame dogs were graded as 1/5 or 2/5: none exceeded 3/5. On average, video recording took 7 minutes, stance/swing time analysis took 10 minutes, and

height-ratio calculation took 19 minutes per dog. Measurement repeatability was good. Only the symmetry ratio for head height was significantly different between sound and forelimb lame dogs (p=0.001), but graphical assessment indicated this was skewed by the most lame dogs. **Impact/clinical significance:** While the described methods are simple and cheap, the simple spatio-temporal measures tested here could not discriminate between sound and mildly lame dogs (for which the need for such measures may be considered greatest), and busy clinicians may find the time requirements impractical. The veterinarian's eye, aided by video playback, remains the most sensitive lameness detection tool in clinical practice.

Miles, JE, Vitger, AD, Poulsen, HH, Nielsen, LN, Andersen-Ranberg, E, Bøjesen, J & Christensen, P. Tramadol and gabapentin improve peak vertical force in osteoarthritic dogs already receiving non-steroidal anti-inflammatory drugs. *Poster session presented at 2020 British Small Animal Veterinary Congress, Birmingham, UK.* https://curis.ku.dk/admin/files/239391254/JamesMilesPosterTramadolAndGabapentin.pdf

Objectives: Osteoarthritis is a common, disabling condition of older dogs. The response to non-steroidal anti-inflammatories may be insufficient to maintain a good quality of life. Limited data exist regarding the effect of adjunctive analgesics in these patients despite widespread usage. **Methods:** Twenty-four osteoarthritic dogs were prospectively recruited to a randomised, observer-blinded, crossover study. In addition to non-steroidal anti-inflammatory treatment, patients received either tramadol (3-5 mg/kg) or gabapentin (8-12 mg/kg) thrice daily for 4 weeks, with a one-week washout between treatments. Using a Tekscan pressure-sensitive walkway, peak vertical force for the worst-affected limb was used as the outcome measure. Haematology, biochemistry and urinalysis were performed before and after each treatment period. **Results:** Eighteen dogs completed the trial. Both tramadol and gabapentin significantly ($p<0.01$) increased peak vertical force (mean 6.7% and 6.4%, respectively). No carryover or period effects of treatment were seen ($p>0.05$). No statistically significant difference was found between treatments, but more dogs achieved an increase of >5% in peak vertical force with gabapentin than with tramadol (61% vs 50%). No significant changes to selected paraclinical parameters were observed. One or more side effects (typically transient and dose-dependent) occurred in up to 70% of dogs with both treatments. **Impact/clinical significance:** Both tramadol and gabapentin can improve weight bearing in osteoarthritic dogs, and both appear safe for short-term use in older patients, but the incidence of side effects appears high compared to previous reports, and may outweigh the benefits in some patients. Owner counselling is recommended before and during use of these medications.

Miles JE, Nielsen MBM, Nielsen LN, Ólafsdóttir A, Aðalsteinsdóttir K. Clinical potential of five serum biomarkers in the diagnostic work-up of dogs with osteoarthritis*, Submitted for 2021 British Small Animal Veterinary Congress, Online.*

Objectives: To identify serum biomarkers differentiating dogs with and without osteoarthritis (OA). **Methods:** Following institutional ethical approval, 24 dogs (27.2-48.5 kg, 3.6-13.6 years) previously diagnosed with OA affecting different joints with varying severity were included in the study. Sixteen dogs (16.2-36 kg, 2.0-6.7 years) without detectable orthopaedic pathology were included as clinically healthy controls. Other disorders were ruled out by thorough clinical examinations and standard hematological and biochemical analyses. Serum was stored at -80^{o}C until analysis of five biomarkers using commercially available enzyme-linked immunosorbent assays: Hyaloronic acid (HA), Matrix Metalloproteinase 13 (MMP-13), Procollagen Type IIA (PIIANP), Cartilage oligomeric matrix protein (COMP), and Collagen Type-2 Cleavage (C2C). Medians and range of concentrations were calculated and differences between groups were tested for significance using Mann Whitney tests ($p<0.05$). **Results:** Higher concentrations of C2C and MMP-13 were observed in dogs with OA (median, [95% CIs] C2C: 23.7 ng/ml [18.2; 45.2 ng/ml], MMP-13: 0.70 ng/ml [0.51;1.09 ng/ml]) compared to clinically healthy dogs (C2C: 12.3 ng/ml [10.1; 35.3 ng/ml], MMP 13: 0.34 ng/ml [0.27; 0.88 ng/ml]), whereas lower concentrations of PIIANP were observed in dogs with OA (11.6 ng/ml [10.7; 18.02 ng/ml] compared to clinically healthy dogs (15.8 ng/ml [11.7; 31.7 ng/ml]). Observed differences were not significant. **Statement:** None of the 5 biomarkers measured in the present study were useful in differentiating heterologous groups of dogs with and without OA. Further studies are, however, recommended in order to investigate possible diagnostic potentials of C2C, MMP-13 or PIIANP in some particular group of dogs with OA.