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A non-inferiority trial comparing paracetamol / codeine and meloxicam for post-operative analgesia in dogs

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Abstract

Background: There are limited published data on the analgesic efficacy of paracetamol/codeine in dogs.

Methods: Prospective, randomized, blinded, positive-controlled clinical trial with 70 dogs (paracetamol/codeine, n = 46; meloxicam, n = 24) undergoing surgery. Drugs were administered orally two hours before and for 48 hours after surgery at the licensed dose. Anaesthesia was standardised. Dogs received buprenorphine 6- hourly for the first 24 hours after surgery. Outcome assessments were made pre-trial and at regular intervals up to 48 hours after extubation and comprised the Glasgow Composite Measure Pain Score (GCMPS-SF), visual analogue scale for sedation and inflammation and mechanical nociceptive threshold (MNT). Non-inferiority of paracetamol/codeine compared with meloxicam was defined using a non-inferiority margin (Δ) against the 95% confidence interval of the difference between the treatment means.

Results: Pain scores were low in both treatment groups. With the exception of MNT all upper 95% confidence intervals for the differences between outcome variable treatment means were within + Delta for each variable, establishing non-inferiority for each outcome variable.

Conclusions: Paracetamol/codeine is a useful peri-operative analgesic that within the context of the peri-operative analgesia regimen studied (methadone premedication, buprenorphine for the 1st 24 hours after surgery) shows non-inferiority to the NSAID meloxicam.

Keywords: Paracetamol/codeine, dogs, peri-operative pain, analgesia, meloxicam

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are used extensively in human and veterinary medicine due to their antipyretic, anti-inflammatory and analgesic properties [1]. Along with opioids, they are considered one of the best classes of analgesic drugs at preventing postoperative pain and have a clear role in multimodal analgesia. Meloxicam, available as both oral and injectable solutions, is approved for use in dogs and has proven efficacy [1,2]. Despite paracetamol's (acetaminophen's) wide use in human medicine [3] and its toxicity being well established, its mechanism of action is not totally understood. Similarly to other non-steroidal anti-inflammatory drugs, paracetamol is able to inhibit prostaglandin synthesis from arachidonic acid by inhibiting cyclo-oxygenase enzymes (COX). This inhibition is likely to happen both peripherally and centrally resulting in both an analgesic and antipyretic effect [4]. Paracetamol has also been suggested to be a centrally acting TRPV1 receptor agonist [5]. Pardale-V ® is the oral preparation of paracetamol licensed for use in dogs in the UK. The formulation also contains codeine, which is an opioid. However the dose of codeine in Pardale – V ® is very low with a ratio of 400 mg of paracetamol to 9 mg of codeine in a single tablet. Oral codeine is rapidly metabolized to produce codeine-6-glucuronide in dogs [6]. Codeine-6-glucuronide has been shown to have antinociceptive effects in rats [7] although the effects of codeine-6-glucuronide on antinociception in dogs are unknown.

Non-inferiority testing is designed to test whether a novel therapy has non-inferior efficacy to the ones already in use. In order to determine non-inferiority an equivalence margin, or Delta, must be determined, which defines a range of values for which efficacies are close enough to be considered non-inferior to each other. The margin is

the maximally acceptable clinical difference that is accepted in return for the secondary benefits of the new therapy.

In veterinary medicine, despite being licensed to control acute pain in dogs there are a paucity of data regarding paracetamol/codeine's analgesic efficacy and the incidence of adverse effects is unknown. The aim of this study was to investigate analgesic efficacy of oral paracetamol/codeine (Pardale-V ®), at the licensed dose, in dogs undergoing surgery by comparison with meloxicam, which is licensed for dogs and has proven efficacy for soft tissue and orthopaedic peri-operative pain relief.

In this non-inferiority trial we hypothesized that paracetamol/codeine, at the licensed dose, has analgesic efficacy that is not inferior to meloxicam in dogs undergoing surgery.

Materials and Methods

Animals

Client owned dogs presented for soft tissue and orthopaedic surgery were recruited. Inclusion criteria were dogs older than two months of age, of any breed or sex and suitable for treatment with a non-steroidal anti-inflammatory agent. Exclusion criteria were dogs receiving any NSAID within the 48 hours before induction of anaesthesia, opioids within 12 hours before induction of anaesthesia or any history of diarrhoea, vomiting, polyuria/polydipsia, a hepatic or haemostatic condition suggestive of reduced blood clotting efficacy.

Case recruitment

Cases were recruited at two centres; soft tissue cases were recruited at Langford Vets, University of Bristol and orthopaedic cases were recruited at St. Davids Veterinary Group, Exeter. One investigator, a registered veterinarian unaware of treatment allocation recruited cases and collected all data. Written informed owner consent was obtained from the owners of all dogs recruited to the study. The study was approved by the University of Bristol ethical review committee (VIN/13/042).

All dogs had a fasting period of 12 hours. Water was allowed until the premedication was administered. Baseline assessments were made before first drug administration given by a registered veterinary nurse; two to four hours later anaesthesia was induced by a veterinary surgeon.

Treatments

At the time of presentation the dogs were randomly allocated into two groups: paracetamol/codeine (P group) or meloxicam (M group). Randomisation was achieved using the website https://www.random.org/ to generate a series of integers, with even integers assigned to the P group and odd integers assigned to the M group. An adjustment was made where necessary to this allocation to ensure that the appropriate number of cases were assigned to each group (i.e. cases were allocated in a 2:1 ratio for the P and M group respectively). Allocation to a 2:1 ratio is a study design that has been used previously in studies evaluating the efficacy of robenacoxib for the management of acute and chronic pain [8, 9]. The rationale for this distribution of cases is that it assigns a higher number of cases to the “new” treatment under test so that any adverse effects associated with the new treatment are more likely to be detected.

Dogs allocated to group P received oral paracetamol/codeine (Pardale-V ®, Dechra) at the licensed dose (33 mg kg^{-1}) at least two hours before induction of anaesthesia. Administration of oral paracetamol/codeine was repeated every 8 hours for up to 48 hours after extubation time (T_0). Dogs allocated to group M received oral meloxicam (Metacam ®, Boehringer Ingelheim) at the licensed dose (loading dose: 0.2 mg kg^{-1}) at least two hours before induction of anaesthesia. Administration of meloxicam was repeated, at the maintenance dose (0.1 mg kg^{-1}) every 24 hours for up to 48 hours after T_0. At the end of the study, 48 hours after T_0 all dogs were treated with meloxicam. Dogs allocated to the group P received the first dose of meloxicam, at the maintenance dose, eight hours after the last dose of paracetamol/codeine. See CONSORT Flow Diagram MURRELL as Supplementary Figure 1 for a schematic outline of enrolment of dogs, treatment allocation and follow-up.

Outcome assessments

Study outcome assessments for pain, inflammation, sedation and tolerability were made by the single, blinded assessor. Requirement for rescue analgesia was also recorded.

The first outcome assessment was performed at baseline, before first test drug administration followed by ten time points. The second outcome assessment was carried out at T_2, (2 hours after extubation which was counted as T_0); T_4; T_6; T_8; T_{12}; T_{24}; T_{28}; T_{32}; T_{36}; T_{48}, respectively 2, 4, 6, 8, 12, 24, 28, 32, 36 and 48 hours after extubation time.

Outcome assessments included were the Glasgow Composite Pain Score – Short Form (GCMPS-SF) [10], as the primary efficacy endpoint, the mechanical nociceptive threshold (MNT), the visual analogue scale for inflammation (VASi) and the visual analogue scale for sedation (VASs). At each time point the first assessment performed was the GCMPS-SF, followed by the VASi, VASs and MNT.

Pain was assessed using the GCMPS-SF. The GCMPS-SF was carried out as described on the questionnaire and after completing the assessment, the pain score was considered as the sum of the rank scores.

Inflammation was assessed with the VASi, using a line between 0 and 100 mm, where 0mm was considered no inflammation and 100mm major inflammation. The surgical wound was observed, checked with light touch and evaluated for local heat, swelling and redness.

Sedation of each patient was assessed using the VASs; a line between 0 and 100 mm where 0 mm was a fully awake patient and 100 mm was an unconscious patient. Sedation assessment was based on the subjective evaluation of the dog's consciousness, behavior and attitude.

MNT was measured using a pressure algometer (PRoD Topcat Metrology Ltd) as a biomarker of secondary hyperalgesia, defined as increased pain from a stimulus that would normally be painful in the area of surrounding uninjured tissue. The PRoD, fitted with a 2 mm tip, was applied perpendicular to the skin 2 cm around the surgical wound, which is an expected area of secondary hyperalgesia adjacent to the surgical site.

Increasing force (at 2 N sec^{-1}) was applied until the animal demonstrated any behaviour indicating conscious perception of pain, such as flinching, growling or trying to escape from the stimulus with a cut off of 18.5 Newtons. Each assessment was performed with the dog lying down and each reading was considered the average of three measurements made at two-minute intervals. Dogs received training and familiarization with the MNT procedure, assessors and the environment prior to the start of the study to minimize the potential effect of the researcher presence and the testing procedure on thresholds [11].

Tolerability was also assessed. Any adverse effects attributable to test drug administration were recorded any time during the study period to compare the incidence between groups. If adverse effects were detected in any animal (e.g. vomiting, diarrhoea, regurgitation), administration of the test drug was stopped, analgesia was continued with buprenorphine, and the dog was withdrawn from the study. Data up until the dog was withdrawn from the study were included in the analysis.

In orthopaedic patients, when it was not possible to assess for inflammation or perform MNT at any time point, due to a cast or bandage covering the surgical site, the assessments were carried out excluding only these two methods until the bandage was removed and it was possible to perform them again.

At relevant time points the assessments were made before drug administration. Adverse events and requirement for rescue analgesia were recorded any time during study period.

198

199 Anaesthesia

200 The anaesthetic protocol was standardized. All dogs received premedication with
201 methadone 0.3 mg kg^{-1} IM or IV alone or in combination with acepromazine 0.010 to
202 0.060 mg kg^{-1} (ACP, Novartis Animal Health) or midazolam 0.10 to 0.20 mg kg^{-1}
203 (Hypnovel, Roche Products Limited). Anaesthesia was induced using propofol to effect
204 1 to 4 mg kg^{-1} injected intravenously (Propofol-®Lipuro Vet, Virbac). Isoflurane (IsoFlo,
205 Abbott Animal Health) vaporized in oxygen was used for maintenance of anaesthesia.
206 Intra-operatively, if any cardiovascular response to surgery occurred, a fentanyl bolus
207 (1-5 µg kg^{-1}) was administered and the total dose was recorded. Adequate depth of
208 anaesthesia was monitored based on the presence or absence of a palpebral reflex,
209 the degree of jaw tone and position of the eye. A registered veterinary nurse or
210 veterinary surgeon monitored anaesthesia continuously in every patient, recording
211 every 5 minutes HR, RR, temperature, the flow rate of oxygen, the vaporiser setting
212 of isoflurane, SpO_2 and $ETCO_2$. Extubation was performed when the dog had regained
213 a swallowing reflex.

214

215 Analgesia

216 In addition to the test drug all dogs were treated with buprenorphine (Vetergesic,
217 Alstoe Animal Health) at a dose of 20 µg kg^{-1} IV for the first 24 hours after surgery.
218 The first dose was administered at T_0 and repeated every 6 hours up to, and excluding
219 T_{24}. At T_{24} buprenorphine administration was stopped until end of the study (T_{48}).

Rescue analgesia

Methadone 0.3 mg kg^{-1} IV was selected to provide rescue analgesia when required. It was administered when the assessor defined the GCMPS-SF equal to, or more than, 5/20 or 6/24 in a patient, for non-ambulatory or ambulatory patients respectively [10]. A repeated pain assessment, using GCPS-SF was performed 15-30 minutes after rescue administration. When GCPS-SF was below the defined range the dog returned to the predefined buprenorphine scheme. If a first dose of methadone was inadequate, administration was repeated as necessary based on the defined criteria (until the GCPS-SF was below 5/20 or 6/24). The subsequent analgesic protocol for each patient, with methadone or buprenorphine, was at discretion of the investigator in collaboration with the clinician and adapted to the individual need of the patient.

Statistical analysis

For the dogs that needed rescue analgesia the last observation carried forward (LOCF) was applied. Non-inferiority of paracetamol/codeine compared with meloxicam was defined using a non-inferiority margin (Δ) against the 95% confidence interval of the difference between the treatment means. The non-inferiority margin defines how much the control treatment may exceed the new treatment with the new treatment still being considered non-inferior to the control. The non-inferiority margin for the primary efficacy endpoint, the GCMPS-SF, was defined as 3; for the MNT all values were converted to a percentage of the baseline value for an individual dog and Delta was defined as a change of 10% from baseline; for the VASs and VASi it was 20 mm. A useful guide to non-inferiority testing can be found in [12]. An important aspect of this non-inferiority study is the determination of

Delta. In this study Delta values were selected that the authors thought were clinically relevant i.e. a difference of this value would represent a clinically relevant difference between the two drugs. This approach was selected because there are no established values for Delta for the outcome measures used in this study. Therefore 3 was chosen as a clinically relevant difference in the GCMP-SF. This difference was considered likely to “push” a non painful dog above the intervention threshold for the GCMP-SF so that rescue analgesia was required. 20 mm was chosen as a clinically relevant difference in the VASs and VASi because if the 100 mm line of the VAS is divided into 5 categories of sedation or inflammation (none, mild, moderate, severe and very severe) a difference of 20 mm is enough to cause a transition from one category to another and therefore was deemed to be clinically relevant. For the MNT, a clinically relevant difference was decided as 10%. This was decided because small differences in MNT are likely to reflect differences in the occurrence of secondary hyperalgesia between groups.

As the data were in the form of repeated measurements, the area under the curve (AUC) was calculated for each outcome measure. Only the area from T_2 to T_{48} was considered, and dogs with any missing values for a variable were dropped from the analysis of that variable. Only T_2 to T_{24} were considered for VASs as all values after 24 hours were 0. The AUC was then divided by the number of hours monitored to give an average score for any one hour, thus rescaling the AUC to the original measurement scale, and this value was used as the outcome measure. It is of interest to follow the time course of each treatment and so graphs of each outcome measure over time are presented below.

A two-sample t-test was used to check whether a difference in age and weight had arisen between the treatment groups despite randomisation. A Chi-square test was used to verify if there was any association between breed, sex and type of surgery and treatment group.

Summary statistics and statistical analyses were performed using SPSS statistics 25 (IBM, New York). Individual statistical independent two-sided t-tests were performed at significance level alpha = 0.05 and 95% confidence intervals for the differences between treatments were also produced. Inspection of histograms showed that data were approximately normally distributed, with the exception of VASs scores which required a log normal transformation, following the addition of 0.1 to avoid scores of zero, thus a standard approach to non-inferiority testing based on the normal probability distribution was justified. A Levene's test was used to test for the t-test's assumption of equality of variances treatment groups. The results from the non-inferiority analyses are presented graphically and show the mean difference between the average score in any one hour together with a 95% confidence interval for the difference. Broken, vertical lines on the graphs show ± Delta. The difference was calculated as Paracetamol/codeine treatment minus Meloxicam treatment. Thus, with the exception of MNT, as superior treatments have lower values, negative values for the difference indicate greater efficacy with Paracetamol/codeine and positive values greater efficacy with Meloxicam. For non-inferiority to be shown, the upper 95% confidence limit for the difference should be below + Delta, whilst for MNT the lower confidence interval would need to be greater than - Delta.

There were no prior data on which to base a power analysis for this study. The study size was limited by the duration of the student's (MP) appointment and the number of suitable dogs presenting at the clinics. It was anticipated that between 50 to 100 dogs could be recruited within the time available.

Results

Animals

Seventy client owned dogs were recruited from clinical cases undergoing soft tissue or orthopaedic surgery. Fifty nine orthopaedic cases were recruited from St David's Veterinary Group, Exeter and 11 soft tissue cases from Langford Vets, University of Bristol. No cases were excluded from recruitment based on the exclusion criteria. Soft tissue procedures were performed by an ECVS or RCVS specialist as primary surgeon or by a surgery resident under direct supervision of the specialist. All orthopaedic procedures were performed by a single experienced surgeon, an RCVS advanced practitioner. Twenty four dogs were allocated to group M and 46 dogs to group P. Due to missing data points within the repeated measurements 70, 70, 41 and 41 dogs were available for the analysis of GPCS, VASs, VASi and MNT, respectively. For VASi there were 14 dogs in the meloxicam group and 27 dogs in the paracetamol group for which data were available. For MNT there were 11 dogs in the meloxicam group and 30 dogs in the paracetamol group.

Demographic data

The mean ± SD age of the dogs enrolled onto the study was 51 ± 38 months, with a mean age of 51 ± 44 months in group M and 51 ± 35 months in group P. There was no significant difference in age between groups (p=0.96). The mean ± SD body weight

of all dogs enrolled onto the study was 26.0 ± 14.7 kg, with a mean of 28.6 ± 14.3 kg in group M and 24.7 ± 14.9 kg in group P, with no significant difference in bodyweight between groups (p=0.29). There was no significant difference in the gender distribution between groups (p=0.78). A variety of breeds were represented (38), the most represented breed was Labradors (6 in each group), and there was no significant difference in the distribution of breeds between groups. Twenty-two different surgical procedures were included (Table 1), with tibial tuberosity advancement (TTA) being the most frequent, in 19 cases (8 (33%) in group M and 11 (24%) in group P), followed by total hip replacement (THR), in 16 cases (3 (12.5%) in group M and 13 (28%) in group P). There was no significant difference in the type and number of surgical procedures between groups. In total three dogs received midazolam for premedication (one in the meloxicam group and 2 in the paracetamol group), the rest of the dogs were premedicated with acepromazine.

Table 1: A list of the different surgical procedures carried out in the meloxicam and paracetamol/codeine groups.

Procedure	Meloxicam Group	Paracetamol/codeine Group
Tibial Tuberosity Advancement	8	11
Open stifle lavage	1	
MPL	1	3
ED	3	2
Ulnar osteotomy	1	4
Total hip replacement	3	14

Achilles Tendon Repair	1	1
Femoral Head and Neck Excision	1	1
Dermoid sinus exploration	1	
Brachycephalic obstructive airway syndrome surgery (staphylectomy & alarplasty)	1	2
Hindlimb soft tissue sarcoma removal	1	
Partial maxillectomy	1	
Laparoscopic ovariohysterectomy	1	
Fracture repair		1
Stabilisation of a shoulder luxation		1
Anal sacculectomy		1
Castration		1
Total ear canal ablation		1
Facial biopsy		1
Placement of a urethral hydraulic occluder		1
Laryngeal tieback		1

334

Test treatments

There were no significant differences between groups in the baseline measurements of GCMPS-SF (p=0.9), MNT (p=0.70), VASs and VASi (p=0.78).

The primary efficacy endpoint was the GCMPS-SF score. From the 2 hour time point post extubation all dogs were ambulatory, therefore the GCMPS-SF was scored out of 24. Pain was well controlled in most cases in the post-operative period (Figure 1). For MNT, the pattern after surgery was as expected, with a decrease of the MNT after surgery and an increase over time for both drugs (Figure 2). Changes in sedation and inflammation over time in both groups are shown in Figures 3 and 4.

The results of the non-inferiority analysis for all the outcome variables are summarised in Table 2 and shown graphically in Figure 5. From the Levene's test we concluded no meaningful differences in variances between groups (see Table 2 for p values). A 2-sided t-test showed no significant difference between treatment means for any of the outcome variables. The upper 95% confidence intervals for the differences between outcome variable treatment means were less than + Delta for GCMPS, VASi and VASs, thus establishing non-inferiority for each of these outcome variables. As can be seen from Table 2 and in Figure 5 the lower 95% confidence interval for the difference in MNT is below - Delta, indicating that non-inferiority was not demonstrated, however, the very large standard error of the difference indicates that with only 11 dogs remaining in the meloxicam group and 30 in the paracetamol group due to missing values the study had little power remaining to identify non-inferiority, or otherwise, given the variability in MNT scores within treatments.

Table 2. The results of the non-inferiority analysis of all outcome measures, showing no difference in variance between treatments (Levene's test) and no significant difference between treatments (2-tailed t-test). The treatment means and their difference are shown together with the 95% confidence interval for the difference between the means. Note that the VAS sedation scores are natural log transformed (ln(x + 0.1)) to satisfy the assumption of a normal distribution. For each outcome variable, the LCI and UCI of the difference sit within ± Delta, demonstrating non-inferiority, at each of the given Deltas with the exception of MNT. The delta for VASs of 20.0 becomes 3.0 on the natural log scale.

	Levene's	***Test***		***t-test***				***Diff.***	***between***	***means***		
	F	**p**	**t**	**df**	**p (2-tail)**	**Paracet. (SE)**	**Melox. (SE)**	**Mean diff.**	**SE diff.**	**LCI**	**UCI**	**Delta**
GCPS	0.041	0.840	0.691	68	**0.492**	1.2542 (0.12)	1.1081 (0.18)	0.1462	0.21162	-0.2761	0.5684	**3**
MNT	0.465	0.499	-1.323	39	**0.193**	80.461 (5.42)	94.835 (10.20)	-14.374	10.8622	-36.345	7.5968	**10**
VAS infl.	1.428	0.239	-0.123	39	**0.903**	13.431 (0.63)	13.574 (1.11)	-0.1430	1.16722	-2.5039	2.2179	**20**
LnVAS sed.	0.000	0.995	-0.570	68	**0.570**	-0.3419 (0.16)	-0.1873 (0.22)	-0.1582	0.27738	-0.7117	0.3953	**3**

366 Rescue analgesia and concomitant treatments

367 Six dogs (three in group M (12.5%) and three in group P (6.5%) had scores equal to
368 or higher than 6/24 and therefore received one dose of methadone as a rescue
369 analgesic.

370 In group P one dog received acepromazine (0.01mg kg^{-1}) after recovery to treat
371 nervous temperament and excessive barking. One bolus of fentanyl at 1 to 5 µg kg^{-1}
372 IV was administered during the surgery in two dogs, one in the group M (4%) (with
373 TTA procedure) and one in the group P (2%) (undergoing surgery to correct
374 Brachycephalic Obstructive Airway Syndrome). In group M one dog required
375 additional analgesia during the surgery and mistakenly received methadone (0.1mg
376 kg^{-1}) IV instead of fentanyl.

377

378 Tolerability

379 Two dogs (8%) in group M had adverse effects that could potentially be attributable to
380 the test drug. These dogs were removed from the study, but data were collected until
381 the adverse event and included in the analysis. After the adverse event pain
382 assessments were performed to ensure post-operative comfort of the patient. One of
383 the dogs, undergoing a hind limb nodulectomy had diarrhoea at T_{12} and another having
384 a TTA procedure regurgitated at T_{12}. A dog in group P (2%), undergoing a TECA, had
385 one episode of regurgitation at T_4. As this dog had a history of regurgitation prior to
386 anaesthesia, the clinician did not consider this related to the treatment drug and this
387 dog was kept in the study. However, this episode cannot be excluded as a possible
388 adverse effect of paracetamol/codeine. No other adverse effects attributable to test
389 drug administration were found in group P and there were no significant differences
390 between groups.

Discussion

The key finding from this study was that paracetamol/codeine provides non-inferior analgesia to meloxicam in dogs undergoing surgery when combined with buprenorphine given for the first 24 hours after surgery and methadone for premedication. Pain scores were low over the period of assessment and requirement for rescue analgesia was low in both groups of dogs. In veterinary medicine NSAIDs are commonly used for post-operative analgesia in dogs. There is supporting evidence for meloxicam efficacy in controlling pain and inflammation in dogs undergoing surgery and therefore sufficient evidence for it to be used as a positive control for this study [1,2].

Methadone was given as premedication to provide an adequate and rapid onset of analgesia for surgery. Methadone was combined with a non-analgesic sedative (acepromazine or midazolam) to avoid confounding factors on the postoperative pain assessments.

The GCMPS-SF has been validated for the quantification of surgical pain in dogs [13], however, it is not entirely specific to pain and may be biased by concurrent sedation in the postoperative period [14]. To minimize the confounding factor of sedation, a VASs was also used to score sedation. The sedation scores in both groups decreased postoperatively but the difference between them was not significantly different and sedation scores were low during the time period over which pain was quantified.

Mechanical nociceptive threshold was also measured frequently. Post operative MNTs were numerically slightly lower in the paracetamol group, although the differences did not reach statistical significance because MNT was too variable within treatments to give sufficient power to detect non-inferiority. These variations were likely to be due primarily to the lower anti-inflammatory effect of paracetamol or lower analgesic efficacy compared to meloxicam [3], but also may be due to differences between individual dogs, as individual skin thickness, blood flow or distribution of the nociceptors, may affect the peripheral perception of stimuli [15] and are not easily controlled [11]. Mechanical hyperalgesia has been reported in dogs post-surgery using unimodal [16] and multimodal [17] analgesic strategies, as was utilised in this study.

The range of surgical procedures, and inclusion of different surgeons with variable experience between them are likely to add confounding factors influencing post-operative recovery and pain. However, an advantage of this study was that the orthopaedic surgeries were all performed by the same experienced surgeon. Further studies restricting recruitment to a single type of surgery and a single surgeon in all cases would be expected to have increased the power of a study.

Although paracetamol/codeine was found to be non-inferior to meloxicam in this study, it should be considered that the licenced formulation of oral paracetamol/codeine in the UK is recommended to be given three times daily, as opposed to meloxicam which is administered once daily. This may be associated with poor compliance with paracetamol/codeine treatment and therefore inadequate post-operative pain management.

This study had several limitations. No power calculation was performed because there were no prior data on which to base a sample size calculation, which was not ideal. However, a non-inferiority trial is a ‘through the looking glass’ reversal of the more familiar superiority trial, and a lack of power would lead to non-inferiority not being established; for example, because the mean difference was not estimated accurately enough, this leads to a wide confidence interval which would be more likely to overlap a chosen Delta. The chosen Delta values were non validated and it could be argued were somewhat arbitrary although they were selected based on what was considered to be clinically relevant differences between groups. Therefore the selection of Delta and the fact that it was non validated could also be considered a limitation of the study.

The primary objective of the study was to assess and compare perioperative efficacy of oral paracetamol/codeine and meloxicam. Initially, it was planned to assess dogs for a 72 hours study period; however, it was considerably more difficult to obtain owner consent for prolonged hospitalization rather than for 48 hours. Another limitation to a prolonged hospitalization was obtaining good compliance from the surgeons involved in the study, a problem common within large institutions with a heavy workload. At the end of the 48 hour assessment period dogs in the paracetamol/codeine group were switched to treatment with meloxicam. The time period that should be allowed when switching between NSAIDs is debatable with no clear consensus on an adequate “wash-out” period. Paracetamol is anecdotally believed to have less side effects than traditional NSAIDs and has been recommended as a “bridging treatment” during the wash out period between two traditional NSAIDs. Therefore it was considered

acceptable to switch from paracetamol/codeine to meloxicam without a “wash-out” period for continued analgesia after the end of the study.

Buprenorphine was used in addition to the test drug. The small number of dogs that required rescue analgesia may reflect that a premedication with methadone, pre-surgical administration of oral paracetamol/codeine or meloxicam and buprenorphine at extubation was sufficient to control post-operative pain and inflammation in most dogs. However, it is also recognised that the use of buprenorphine in the first 24 hours may be a confounding factor for the post-operative assessments because the use of paracetamol/codeine and meloxicam alone were only compared between 24 and 48 hours after surgery. However, this protocol mimics the reality of practice as the majority of surgeons use buprenorphine as part of a multimodal analgesia protocol for the postoperative recovery of patients [18,19].

Data were collected at two study centres, Langford Vets, University of Bristol and St. David’s Veterinary Group, Exeter. Collecting data from two centres increased the case recruitment, as St. David’s Veterinary Group is a very busy practice with a high daily case load. In addition, a loco-regional anaesthesia / analgesia protocol is common practice for orthopaedic procedures at Langford Vets, which would have confounded the concurrent assessment of analgesic efficacy of the test drugs, whereas it was not standard practice at St. David’s Veterinary Group at the time that the study was carried out. To minimize the effects of an inevitable increase in the number of people dealing with cases from two centres, anaesthesia was standardized and outcome scoring measures were always performed by the same assessor who was blinded to treatment group.

Data were missing from some assessments, mainly due to the impossibility of measuring MNT and VASi in patients that required bandages or casts post-surgically, however, all other assessments were performed with the same frequency.

In group M one dog required additional analgesia during the surgery and mistakenly received methadone (0.1mg kg $^{-1}$) IV instead of fentanyl. This treatment in a single dog is unlikely to have impacted upon the overall findings of the study.

It should be considered that averaging across time simplifies the analysis at the expense of losing the longitudinal information. It might be the case that the treatments differ in how they relieve pain, e.g. one having a more immediate effect than the other. However, this does not seem to be the case in the present study given the change in pain score over time represented graphically.

The order of the assessments could have been improved so that sedation was assessed first, followed by the GCMPS-SF. This would have allowed us to assess whether a dog was too sedated to meaningfully administer the GCMPS-SF scoring system. However, all dogs were fully recovered from anaesthesia by the 2 hour time point post extubation when pain assessments commenced. Using visual analogue scales for sedation and inflammation has a number of disadvantages; they are unvalidated and can be subject to significant intra-observer variability. Since the study was carried out a composite sedation scale has been published which has undergone a degree of validation [20], however, this was not available at the time that the study

was carried out. There are no validated scales to assess inflammation in dogs post-operatively.

The lack of significant difference between paracetamol/codeine and meloxicam in our study could be because both test drugs are similarly effective or ineffective. The distinction is difficult to make without the inclusion of a placebo group. However, the inclusion of a group receiving placebo and undergoing surgery cannot be considered ethical and therefore was not included as part of the study design.

This study suggests that meloxicam and paracetamol/codeine can be used in dogs to provide similar effects in the post-operative period. Although paracetamol has been used for many years to control pain in dogs, there was paucity of data to prove its efficacy on the post-operative period. We have demonstrated that paracetamol/codeine is non inferior to meloxicam in the postoperative period within the context of the peri-operative analgesia regimen (methadone premedication, buprenorphine for the first 24 hours after surgery) carried out for this study.

Competing interests

The authors have no competing interests to declare

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599

600 Figure legends

601

602 Figure 1: Mean Glasgow Composite Pain Scores throughout the study duration in dogs
603 administered paracetamol and meloxicam. Error bars indicate SEM. N= 24 in the
604 meloxicam group and 46 in the paracetamol group.

605

606 Figure 2: Mean percentage change (normalised to the baseline value) in mechanical
607 nociceptive threshold throughout the study duration in dogs administered paracetamol
608 and meloxicam. Error bars indicate SEM. N= 13 in the meloxicam group and 28 in the
609 paracetamol group.

610

611 Figure 3: Mean Visual Analogue Scale for sedation (VASs) scores throughout the
612 study duration in dogs administered paracetamol and meloxicam. Error bars indicate
613 SEM. N= 24 in the meloxicam group and 46 in the paracetamol group.

614

615 Figure 4: Mean Visual Analogue Scale for inflammation (VASi) scores throughout the
616 study duration in dogs administered paracetamol and meloxicam. Error bars indicate
617 SEM. N= 13 in the meloxicam group and 28 in the paracetamol group.

618

619 Figure 5. Graphs showing for each of the outcome variables the mean difference
620 between the hourly averaged outcome score, together with a 95% confidence interval
621 for the difference. Broken, vertical lines on the graphs show ± Delta. The difference
622 was calculated as Paracetamol treatment minus Meloxicam treatment. Thus, with the
623 exception of MNT, as superior treatments have lower values, negative values for the

difference indicate greater efficacy with Paracetamol and positive values greater efficacy with Meloxicam, and vice versa for MNT. For non-inferiority to be shown, the upper 95% confidence limit for the difference should be below + Delta, and for MNT the lower 95% confidence limit would have needed to have been greater than - Delta.