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ORIGINAL RESEARCH

Single-dose enflicoxib versus a 7-day course of firocoxib for postoperative pain control in dogs undergoing orthopaedic surgery: A multicentre, randomised, masked, non-inferiority study

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Abstract

Background: Perioperative analgesia is essential in dogs undergoing orthopaedic surgery, and enflicoxib's long duration makes single-dose administration attractive.

Methods: A prospective, multicentre, randomised, masked trial compared enflicoxib (8 mg/kg) given 24 hours before surgery with firocoxib (5 mg/kg) given daily for 7 days. Two hundred and sixteen dogs were enrolled. Pain was assessed using the short form of the Glasgow composite pain scale (SF-GCPS) at predefined timepoints from 2 hours to 7 days after surgery. Inflammation was scored using a visual analogue scale, and owners evaluated demeanour, mobility and perceived analgesic quality. The primary efficacy endpoint was the area under the curve of the SF-GCPS scores during the first 48 hours after surgery (SF-GCPS $AUC_{2–48\,h}$). Treatment success was also calculated.

Results: Enflicoxib was non-inferior to firocoxib for SF-GCPS $AUC_{2–48\,h}$. Early postoperative inflammation (2–8 hours) was significantly lower with enflicoxib. Pain scores at individual timepoints, treatment success and owner assessments were similar between groups.

Limitations: The non-inferiority margin was not formally validated.

Conclusions: A single preoperative dose of enflicoxib provided safe, effective control of postoperative pain and inflammation associated with orthopaedic surgery in dogs and represents a practical perioperative non-steroidal anti-inflammatory drug option.

KEYWORDS
dogs, enflicoxib, firocoxib, non-steroidal anti-inflammatory drugs, orthopaedic surgery, postoperative pain

INTRODUCTION

Perioperative pain is a major concern because of its impact on welfare, recovery and long-term functional outcomes. Inadequately controlled pain can delay mobilisation, hinder participation in rehabilitation and diminish overall quality of life.[1–3] Modern international guidelines emphasise that perioperative analgesia is a core component of anaesthetic care and should follow a proactive, multimodal approach.[2,4] Within this framework, non-steroidal anti-inflammatory drugs (NSAIDs) are considered first-line agents because their effects complement opioids, local anaesthetics and other adjunctive analgesics.[2,4]

Beyond their analgesic role, perioperative use of NSAIDs is associated with a reduced risk of anaesthetic-related death in dogs.[5] This suggests that effective pain management may improve physiological stability and overall anaesthetic safety. In canine orthopaedic surgery, NSAIDs are routinely prescribed once or twice daily for several days to manage

postoperative pain and inflammation.[6,7] However, real-world adherence to these regimens is often suboptimal, with missed or delayed doses reported even during short treatment courses.[8] Inconsistent dosing can lead to inadequate analgesic coverage and may increase reliance on opioids, with their associated adverse effects.

Enflicoxib is a selective Cyclooxigenase-2 (COX-2) inhibitor with a sustained pharmacological activity. Pharmacokinetic and pharmacodynamic studies have shown that a weekly dosing regimen maintains plasma concentrations of its active metabolite within the therapeutic range for control of pain and inflammation.[9,10] Recent studies in dogs undergoing orthopaedic[11] or soft tissue surgery[12] reported that a single dose of enflicoxib was non-inferior to a standard NSAID regimen for postoperative pain management over 7 days. Enflicoxib, requiring only one preoperative dose, could therefore remove the need for owner-administered NSAIDs during the critical early postoperative period. Reduced dosing frequency improves adherence to NSAID therapy and may enhance overall treatment compliance.[8,13]

Firocoxib is a COX-2-selective NSAID with proven efficacy in the management of perioperative pain in dogs when administered once daily.[7,14] It is therefore an appropriate comparator when evaluating new NSAIDs for orthopaedic surgeries.

The aim of this field trial was to evaluate whether a single dose of enflicoxib administered 24 hours before surgery is non-inferior to a standard regimen of daily firocoxib for the control of postoperative pain and inflammation in dogs undergoing orthopaedic procedures.

MATERIALS AND METHODS

This was a prospective, multicentre, randomised, masked, controlled, parallel group, non-inferiority field study conducted in accordance with Good Clinical Practice guidelines.[15] Thirteen practices participated (Spain, $n = 9$; France, $n = 4$). The protocol was authorised by the Spanish Agency of Medicines and Medical Devices (476/ECV) and the French Agency for Food, Environmental and Occupational Health and Safety (EC-21-409) and complied with national regulatory and animal welfare requirements. Written informed consent was obtained from all owners before enrolment. Dogs remained under their owners' care at home. Recruitment took place between May 2022 and July 2024.

Animal selection

Client-owned dogs presented for orthopaedic surgery were prospectively screened. Dogs of any breed or crossbreed, of either sex, weighing more than 3 kg and older than 10 weeks were eligible. To be enrolled, dogs had to be clinically healthy, except for the condition requiring surgery. Suitability was confirmed by a complete physical examination, and by preoperative haematology, biochemistry and urinalysis.

Dogs could not have received NSAIDs, amantadine, anaesthetics or tranquillisers within 48 hours before surgery. Short-acting local or systemic corticosteroids were not permitted within 30 days, and long-acting corticosteroids, mavacoxib or monoclonal anti-NGF antibodies within 60 days. Sedatives, opioids or gabapentin were not allowed within 24 hours. Dogs with known hypersensitivity to sulphonamides, to either study drug or to any excipient, were excluded. Other exclusion criteria included a history of haemorrhagic or gastrointestinal disorders, evidence of cardiac, renal or hepatic disease and pregnant, lactating, breeding, dehydrated, hypotensive or hypovolaemic animals. Dogs that had undergone surgery within 60 days, had concurrent painful conditions or had undergone procedures that might confound pain scoring were also excluded. Animals that were aggressive, fearful or challenging to handle were not enrolled.

Concomitant treatment with other analgesic or anti-inflammatory drugs or with potentially nephrotoxic drugs was not permitted during the postoperative period, except as rescue analgesia. Dogs with well-controlled, mild concurrent conditions were allowed to participate, and their existing medication could be continued if it was not expected to influence study outcomes.

Dogs could be withdrawn at any time if an adverse event (AE) required discontinuation of treatment or interfered with the assessment of the study medication, if forbidden concomitant medication was administered, if a major protocol deviation occurred or if the owner withdrew consent.

Treatments and masking

Dogs meeting all criteria were randomised in a 1:1 ratio to receive enflicoxib or firocoxib using pre-prepared computer-generated randomisation lists stratified by site.

To preserve masking, the veterinarian responsible for efficacy and safety assessments remained unaware of treatment allocation throughout the study and had no access to treatment-related documentation. A second person at each site (the dispenser) was responsible for all treatment-related interventions and had no role in efficacy or safety assessments. Owners were not masked but were instructed to discuss any treatment-related issues exclusively with the dispenser in order to maintain investigator masking.

Dogs allocated to enflicoxib received a single oral dose of 8 mg/kg enflicoxib (Daxocox tablets for dogs, Ecuphar/Animalcare Group) 24 hours before surgery (day −1). Dogs allocated to firocoxib received an oral dose of 5 mg/kg firocoxib (Previcox chewable tablets; Boehringer Ingelheim) on day 0 (within 2 hours before surgery) and once daily from day 1 to day 7.

Surgery and anaesthesia

Day 0 was the day of surgery. At each practice, surgeries were always performed by the same surgeon, and the anaesthetic protocol was standardised across sites to minimise variability. Premedication consisted of methadone hydrochloride and dexmedetomidine intramuscularly. Anaesthesia was induced with propofol and maintained with isoflurane or sevoflurane. Lactated Ringer's solution was administered intravenously throughout anaesthesia. Intraoperative monitoring included electrocardiography, pulse oximetry, capnography, non-invasive arterial blood pressure and oesophageal temperature. If additional intraoperative analgesia was required, a continuous rate infusion of dexmedetomidine could be administered. Rescue intraoperative analgesia with fentanyl and local anaesthesia with lidocaine was permitted. Extubation was performed once the swallowing reflex had returned. Surgery time was recorded from skin incision to extubation.

Efficacy assessments

At each site, a single veterinarian was responsible for all assessments, which took place at 2, 5 and 8 hours (day 0), 24 hours (day 1), 48 hours (day 2), 72 hours (day 3), 120 hours (day 5) and 168 hours (day 7) after surgery. Time zero (t0) was the end of surgery (extubation).

Pain was scored using the short form of the Glasgow composite pain scale (SF-GCPS) described by Reid et al. yielding a range of 0–24 or 0–20 when mobility could not be assessed.[16] For consistency, definitions to differentiate behavioural categories were provided to all investigators.[17]

Because sedated or anxious dogs can obtain high SF-GCPS scores unrelated to pain,[18,19] the level of sedation was assessed at the same timepoints as pain on day 0 before SF-GCPS scoring. A sedation scale ranging from 0 'no sedation' to 12 'deep sedation' was used.[20] If the sedation score at a given timepoint was eight or higher, the SF-GCPS was not recorded. The relationship between SF-GCPS and sedation and/or anxiety was also evaluated with an ad hoc four-point scale (from 0 'not related' to 3 'probably related').

Inflammation at the surgical wound was assessed at the same timepoints using a visual analogue scale (VAS) ranging from 0 'no inflammation' to 10 'severe inflammation'. The wound region was observed without palpation or manipulation, and the presence of local heat and redness of the affected area was considered.

Owner-reported dog wellbeing was daily evaluated using numerical rating scales. Owners scored demeanour and mobility on a scale from 0 'normal' to 4 'severely modified or impaired'. Perceived quality of analgesia was scored from 1 'very satisfactory' to 4 'not at all satisfactory'.

Postoperative rescue analgesia

Rescue analgesia was indicated if the SF-GCPS score reached or exceeded 6 of 24 (or 5/20 when mobility could not be assessed).[16] Within the first 8 hours after surgery, methadone was used, and from 8 hours after surgery, buprenorphine was applied. On day 0, rescue analgesia was administered only if the relationship between SF-GCPS and sedation or anxiety was scored 0 or 1 to ensure that intervention was triggered by pain rather than sedation or anxiety. Any dog that received rescue analgesia was classified as a non-responder at that timepoint but remained in the study, and subsequent scheduled assessments were performed as planned.

Safety assessments

Follow-up haematology, biochemistry and urinalysis were performed on day 7 to evaluate any potential treatment-related changes. Safety was further assessed by recording all AEs, regardless of nature, severity or suspected relationship to treatment. For each AE, clinical signs, severity (mild, moderate, severe or life-threatening), outcome and any concomitant treatment used to manage the event were recorded. A masked causality assessment was performed using the ABON system recommended by the European Medicines Agency,[21] classifying AEs as probable, possible, unlikely or unknown in relation to study treatment. The number and percentage of dogs experiencing at least one AE and the total number of AEs in each treatment group were used to calculate incidence.

Statistical analysis

Sample size calculations were based on the primary efficacy endpoint (the calculated area under the curve [AUC] of the SF-GCPS total scores from 2 to 48 hours after surgery [SF-GCPS $AUC_{2–48\,h}$]) derived from previous literature. In the Freedom of Information Summary for Firocoxib,[22] the SF-GCPS $AUC_{2–48\,h}$ in untreated dogs was approximately 250 points. Another study of enflicoxib versus meloxicam[11] showed that the average SF-GCPS $AUC_{2–48\,h}$ for each treated group would be approximately 160 points, with a standard deviation of 72. Therefore, a non-inferiority margin of 25 points was considered clinically relevant. According to this criterion, a sample size of 104 animals per group was required for 80% power when applying a *t*-test for non-inferiority with a one-sided significance level of 5%. Considering a 5% of potential withdrawals, the final sample size was set to 110 animals per group.

Baseline demographic and clinical characteristics were compared between groups in the intention-to-treat (ITT) population. Qualitative variables were compared using chi-square tests when assumptions were met; otherwise, Fisher's exact test or likelihood ratio tests were used. Quantitative variables

were compared using Student's *t*-test when normality and homoscedasticity assumptions were satisfied and Mann–Whitney *U*-tests otherwise. Homogeneity of variances was assessed with Levene's test and normality with Kolmogorov–Smirnov test.

Non-inferiority for the primary efficacy endpoint was tested using one-sided and two-sided *t*-test. Treatment effect was expressed as the difference in SF-GCPS $AUC_{2–48\,h}$ between groups (enflicoxib minus firocoxib). Because lower SF-GCPS scores indicate better analgesia, non-inferiority of enflicoxib was concluded if the upper limit of the 95% confidence interval (CI) for the mean difference was below the non-inferiority margin. For dogs in which the SF-GCPS was calculated out of 20 (mobility not assessable), scores were rescaled to a 0–24 range.

Missing SF-GCPS values were imputed with the mean of the relevant treatment group at the corresponding timepoint. Sensitivity analyses were conducted to assess the robustness of the primary analysis: excluding the 2-hour timepoint, at which most imputations were required, and also without any imputation.

Secondary efficacy endpoints included SF-GCPS and inflammation scores at each timepoint as well as owner-reported dog wellbeing scores and the percentage of SF-GCPS responders. SF-GCPS and inflammation scores over time were analysed using linear mixed models, with treatment group, time and their interaction as fixed effects and animal as a random factor. The percentage of responders and the dog wellbeing scores were analysed as described for the baseline qualitative variables.

All efficacy endpoints were analysed on two populations. The ITT population comprised all dogs that received at least one dose of medication and had at least one efficacy assessment. The per-protocol (PP) population comprised all ITT dogs that were fully compliant with the protocol, excluding those with major deviations likely to affect the efficacy evaluation. Safety analyses were performed in all dogs that received at least one dose of medication. Statistical analyses were conducted using SAS System (version 9.4, SAS Institute Inc.). A nominal significance level of 5% ($p < 0.05$) was applied for all statistical tests.

An additional post hoc exploratory analysis was performed to assess whether early non-response within the first 8 hours after surgery was associated with the type of surgical procedure. Procedure distribution between treatment groups was compared descriptively, and exploratory analyses of early non-response according to grouped procedure category were performed by means of a logistic regression model including treatment group, procedure category and their interaction.

RESULTS

Animals

A total of 216 dogs were enrolled (108 dogs randomised to each group). Four dogs (two per group) had no efficacy data and were not included in the efficacy analyses. Therefore, 212 dogs with at least one efficacy assessment (106 in each treatment group) comprised the ITT population. Twenty-eight dogs in the ITT population had major protocol deviations and were excluded from the PP analysis, which included 184 dogs (90 in the enflicoxib group and 94 in the firocoxib group). Patient disposition is summarised in Figure 1.

Average age was 5.8 years (0.3–15.0 years), and mean bodyweight was 21.27 kg (3.0–69.10 kg). Baseline demographic characteristics (ITT population) were broadly similar between groups (Table 1). A significant difference in bodyweight was observed ($p = 0.035$) but this difference was small (≈2%) and not considered clinically relevant.

Fifty-three breeds were represented, including 84 crossbred dogs. Seventeen different orthopaedic procedures were performed. The most frequent were tibial tuberosity advancement, tibial plateau levelling osteotomy (TPLO), fracture repair or osteosynthesis, amputations and arthroplasties. The distribution of orthopaedic procedures was broadly comparable between treatment groups (Table S1), and no significant differences were detected between groups in surgical type or duration. Concomitant antibiotic therapy was administered to 89 dogs (84.0%) in the enflicoxib group and 83 dogs (78.3%) in the firocoxib group, primarily as preemptive prophylaxis.

Efficacy evaluation

In the ITT population, the mean SF-GCPS $AUC_{2–48\,h}$ was 119.17 (SD 75.25) in the enflicoxib group and 124.83 (SD 78.21) in the firocoxib group, with a mean difference (enflicoxib minus firocoxib) of −5.661 (SD 76.74). The upper limit of the 95% CI for the difference was 11.75, which was below the predefined non-inferiority margin of 25 points (non-inferiority, $p = 0.002$). In the two-sided analysis, the upper 95% CI limit was 15.12 (non-inferiority, $p = 0.004$; Figure 2), also below the predefined non-inferiority margin. Sensitivity analyses showed consistent results when analysing the AUC without the 2-hour timepoint and without imputing missing data. In the PP population, the non-inferiority criterion was also met.

At individual timepoints, SF-GCPS total scores decreased over time in both groups (Figure 3), with no significant differences detected at any timepoint (Table 2).

Inflammation at the surgical wound decreased over time in both groups (Figure 4). Early mean inflammation scores were consistently lower in the enflicoxib group, with statistically significant differences at 2, 5 and 8 hours after surgery (Table 3).

Regarding rescue analgesia administration, overall, 74 of 106 dogs (69.8%) in the enflicoxib group and 76 of 106 dogs (71.7%) in the firocoxib group did not receive rescue analgesia at any timepoint and were classified as responders, with no significant difference between treatments ($p = 0.7627$). Non-response occurred predominantly during the early postoperative period. As shown in Table 4, responder rates increased rapidly

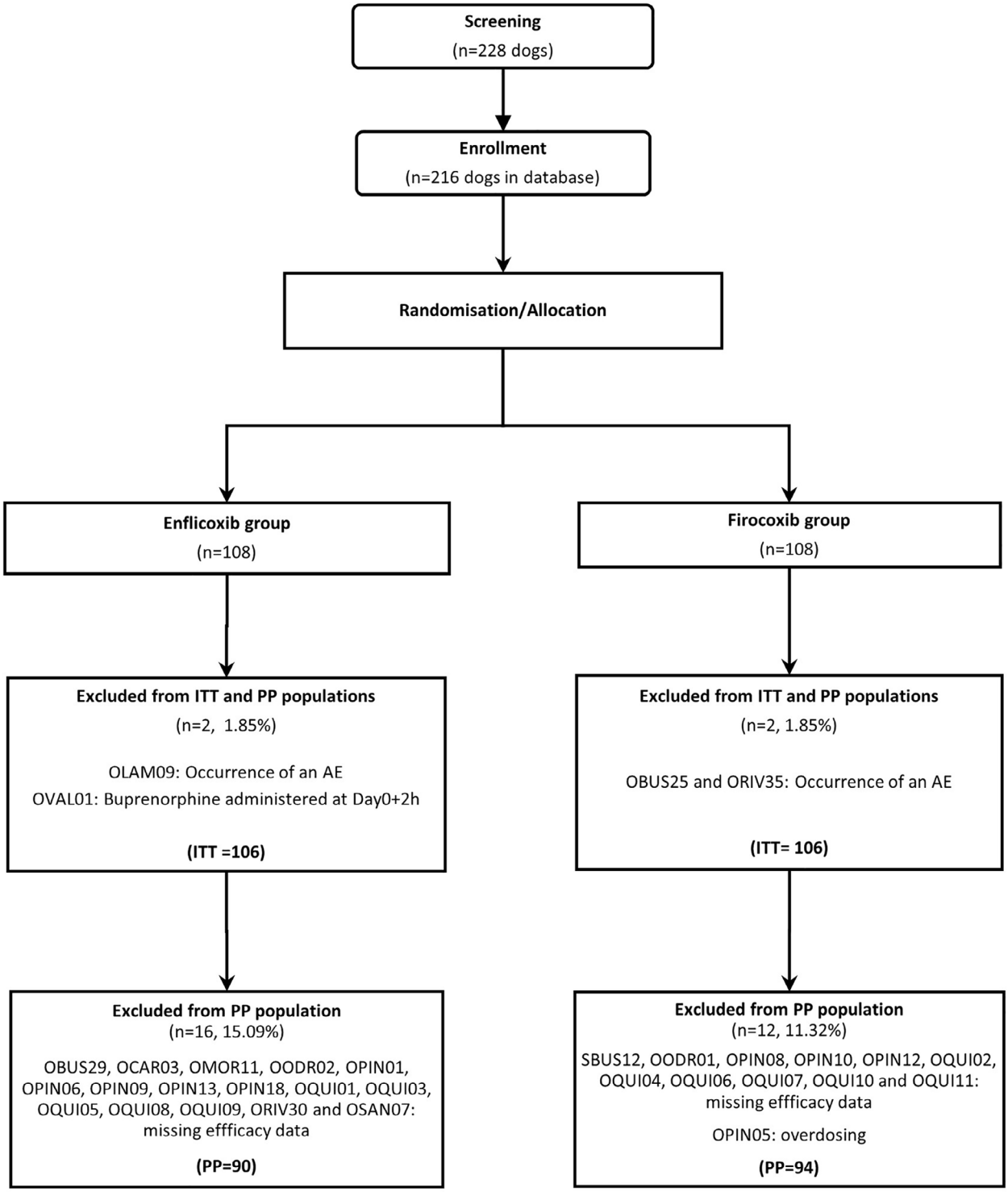

FIGURE 1 Flowchart of dog disposition throughout the study.

in both groups, approaching 90%–100% from 8 hours onwards and remaining consistently high until the end of the study, with no differences between groups at any timepoint.

Values represent the number and percentage of responders and non-responders at each postoperative assessment timepoint in the ITT population. Dogs were classified as non-responders if they reached the SF-GCPS intervention threshold (≥6/24 or ≥5/20 when mobility could not be assessed) at that timepoint.

Early non-response occurred in 39 of 108 dogs (36.1%) in the enflicoxib group and 37 of 108 dogs (34.3%) in the firocoxib group. In an exploratory logistic model including treatment, procedure category and their interaction, early non-response varied across grouped procedure categories ($p = 0.0089$), whereas no association with treatment group was identified. Particularly, TPLO interventions were associated with higher odds of early non-response compared to the other procedures.

TABLE 1 Baseline demographic characteristics in the intention-to-treat population.

	Enflicoxib, $n = 106$	Firocoxib, $n = 106$	p-Value*
Sex, *n* (%)			
Male	52 (49.1%)	51 (48.1%)	0.891
Female	54 (51.9%)	55 (51.9%)	
Age (years)			
Mean (SD)	5.65 (3.84)	5.98 (3.70)	0.223
Range	0.25–15.0	0.33–13.0	
Breed			
Purebred	61 (57.5%)	67 (63.2%)	0.340
Mixed	45 (42.5%)	39 (36,8%)	
Bodyweight (kg)			
Mean (SD)	21.56 (14.86)	20.98 (14.74)	0.035
Range	3.00–69.10	3.00–62.40	
Rectal temperature			
Mean (SD)	38.47 (0.36)	38.48 (0.33)	0.408
Range	37.40–39.50	37.80–39.40	
Surgery duration (minutes)			
Mean (SD)	72.84 (37.12)	71.30 (32.01)	0.474
Range	14–247	15–167	

*Significance level $p < 0.05$.

Owner assessments yielded similar scores between groups on most days (Figure 5). On day 7, a higher proportion of owners in the enflicoxib group rated analgesia quality as very satisfactory or satisfactory compared with firocoxib (81.9% vs. 66.0%, $p = 0.0293$). Similar patterns for all secondary efficacy endpoints were observed in the PP population, and the significant differences in early postoperative inflammation were maintained.

Safety evaluation

The safety analysis included 216 dogs that received at least one dose of study medication (108 in each group). A total of 41 AEs were reported. Following masked causality assessment, 27 AEs were considered unlikely to be related to enflicoxib or firocoxib administration. Among the remaining 14 AEs, two were classified as probably related to treatment (one in each group; both described as vomiting), eight as possibly related (four per treatment group; vomiting, anorexia and diarrhoea) and four as of unknown relationship. All AEs were considered mild and self-limiting and resolved with no medication by the end of the study. NSAID discontinuation was not needed. There were no significant differences between groups in AE severity ($p = 0.1843$) or in causality classification ($p = 0.6839$), and none of the animals had to be withdrawn from the study. At the end of the study, no clinically relevant alterations were detected in haematological, biochemical or urinalysis parameters in either group compared with baseline values. No intraoperative AEs attributable to hypotension were reported in either group, and no clinically relevant hypotension requiring specific intervention was recorded during anaesthesia.

DISCUSSION

This study showed that a single preoperative dose of enflicoxib was non-inferior to a standard daily regimen of firocoxib during 7 days for the control of postoperative pain and inflammation associated with orthopaedic surgery in dogs. The primary efficacy endpoint met the predefined non-inferiority margin, and SF-GCPS scores over time were comparable between groups. Taken together with the secondary efficacy endpoints, these findings support enflicoxib as an effective perioperative NSAID option for dogs undergoing orthopaedic procedures.

The results are consistent with current international analgesia guidelines, which emphasise proactive, multimodal perioperative pain management and the routine use of NSAIDs as a core component of anaesthetic care.[2,4] NSAIDs target inflammatory nociception and act synergistically with opioids and local anaesthetics,[2] and, within this framework, demonstrating that enflicoxib provides

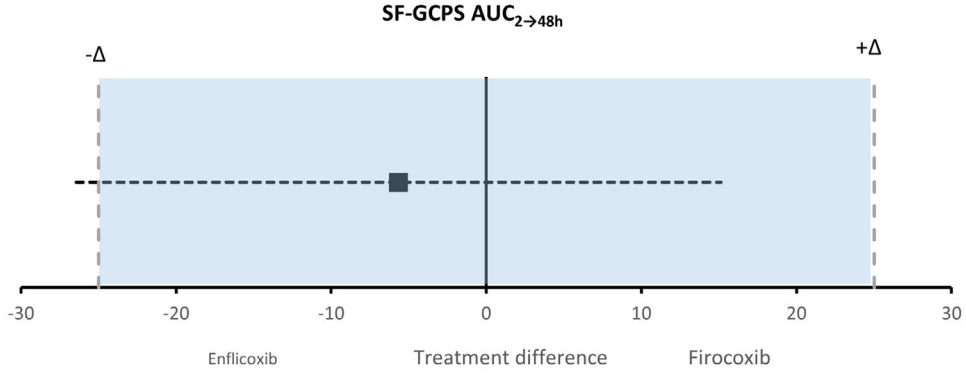

FIGURE 2 Mean difference and 95% confidence interval (CI) for the short form of the Glasgow composite pain scale (SF-GCPS) area under the curve (AUC) for the first 48 hours after surgery (two-sided non-inferiority *t*-test). The vertical dashed lines indicate the pre-specified non-inferiority margin of 25 points (±Δ). The shaded area represents the non-inferiority range. The difference was calculated as enflicoxib minus firocoxib; non-inferiority is demonstrated when the upper 95% CI limit lies below +Δ.

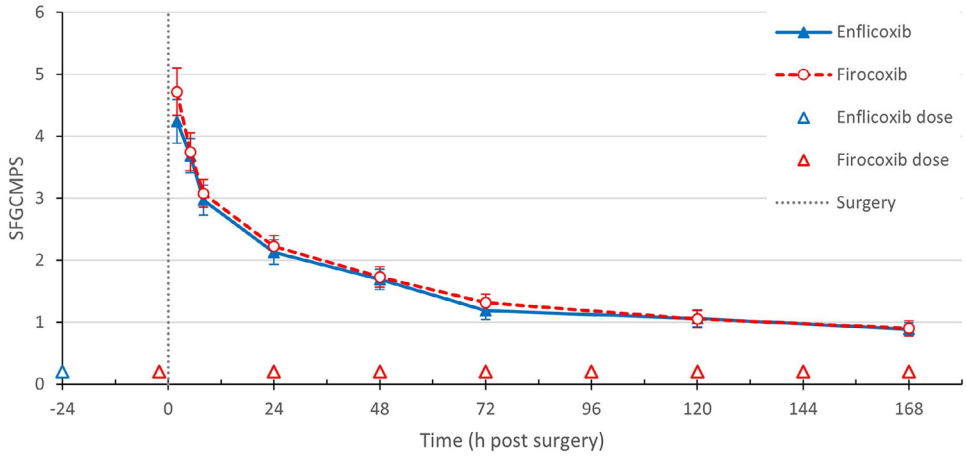

FIGURE 3 Evolution of the short form of the Glasgow composite pain scale (SF-GCPS) total scores (mean ± standard error) at each timepoint in each treatment group.

TABLE 2 Short form of the Glasgow composite pain scale (SF-GCPS) total scores at each timepoint in the intention-to-treat population.

GCPS-SF	Enflicoxib (mean ± SE)	Firocoxib (mean ± SE)	Difference			*p*-Value
			MD	LCI	UCI	
2 hours	4.24 ± 0.380	4.72 ± 0.353	−0.293	−0.919	0.333	0.3591
5 hours	3.69 ± 0.304	3.75 ± 0.273	−0.066	−0.642	0.509	0.8211
8 hours	2.97 ± 0.223	3.08 ± 0.239	−0.091	−0.666	0.484	0.7568
24 hours	2.13 ± 0.173	2.23 ± 0.199	−0.094	−0.668	0.480	0.7472
48 hours	1.69 ± 0.164	1.73 ± 0.165	−0.011	−0.586	0.563	0.9688
Day 3 (72 hours)	1.19 ± 0.129	1.32 ± 0.141	−0.216	−0.827	0.395	0.4882
Day 5 (120 hours)	1.06 ± 0.142	1.05 ± 0.136	0.155	−0.462	0.772	0.6223
Day 7 (168 hours)	0.89 ± 0.125	0.90 ± 0.106	−0.010	−0.586	0.566	0.9728

Note: Mean ± standard error (SE) by treatment group, mean difference (enflicoxib minus firocoxib) and 95% confidence interval (CI) of the difference.
Abbreviations: LCI, lower 95% CI; MD, mean difference; UCI, upper 95% CI.

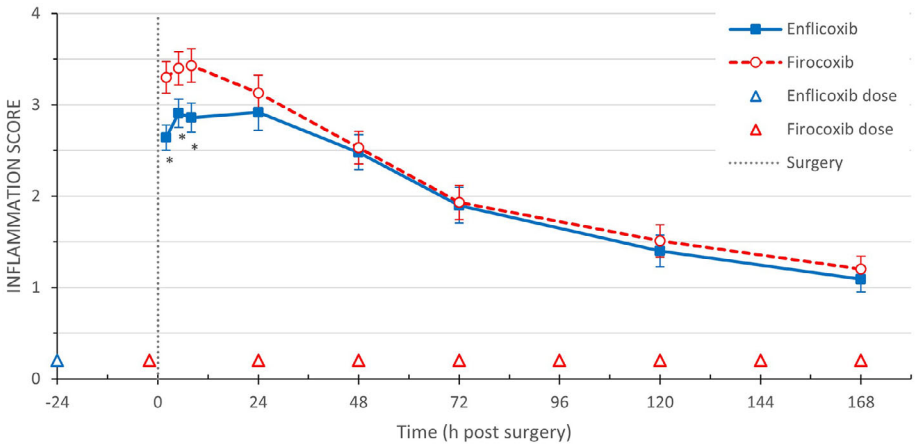

FIGURE 4 Level of inflammation at the surgical wound, assessed with a visual analogue scale (mean ± standard error) at each timepoint in each treatment group. * *p*-Value less than 0.05 for between-group differences.

adequate perioperative analgesia supporting its integration into standard multimodal protocols aimed at optimising both welfare and safety.

A key clinical advantage of enflicoxib is its prolonged duration of action. Most NSAIDs require once or twice daily postoperative administration,[6,23,24] and real-world compliance with such regimens can be poor, particularly after orthopaedic surgery when owners are simultaneously managing restricted activity, wound care and monitoring.[8,13] Enflicoxib active metabolite sustains COX-2 inhibition for 1 week,[9,10] and weekly dosing maintains clinical improvement in dogs with osteoarthritis.[13,25,26] This study extends this evidence to the perioperative setting, removing the need for owner-administered NSAIDs during this critical period and potentially improv-

TABLE 3 Inflammation scores (visual analogue scale, 0–10) at each timepoint.

Inflammation score	Enflicoxib (mean ± SE)	Firocoxib (mean ± SE)	Difference			*p*-Value
			MD	LCI	UCI	
2 hours	2.64 ± 0.139	3.30 ± 0.173	−0.660	−1.13	−0.188	0.0061*
5 hours	2.91 ± 0.154	3.40 ± 0.182	−0.491	−0.962	−0.019	0.0416*
8 hours	2.86 ± 0.160	3.43 ± 0.184	−0.575	−1.05	−0.104	0.0169*
24 hours	2.92 ± 0.199	3.13 ± 0.191	−0.208	−0.679	0.264	0.3884
48 hours	2.48 ± 0.192	2.53 ± 0.180	0.034	−0.506	0.438	0.8880
Day 3 (72 hours)	1.90 ± 0.194	1.93 ± 0.187	−0.089	−0.583	0.404	0.7227
Day 5 (120 hours)	1.40 ± 0.175	1.51 ± 0.178	−0.023	−0.519	0.474	0.9286
Day 7 (168 hours)	1.09 ± 0.140	1.20 ± 0.141	−0.108	−0.581	0.365	0.6547

Note: Mean ± standard error (SE) by treatment group, mean difference (enflicoxib minus firocoxib) and 95% confidence interval (CI) of the difference.
Abbreviations: LCI, lower 95% CI; MD, mean difference; UCI, upper 95% CI.
*$p < 0.05$ for between-group differences.

TABLE 4 Treatment response by postoperative timepoint (intention-to-treat population).

Study day	Enflicoxib, *n*[a] (%)	Firocoxib, *n* (%)	*p*-Value
Day 0 end of surgery + 2 hours[a]			
ResponderNon-responder	71 (88.8)9[b] (11.3)	75 (91.5)7[c] (8.5)	0.5628
Day 0 end of surgery + 5 hours[a]			
ResponderNon-responder	90 (85.7)15[d] (14.3)	89 (84.8)16[e] (15.2)	0.8458
Day 0 end of surgery + 8 hours[a]			
ResponderNon-responder	93 (88.6)12 (11.4)	93 (87.7)13 (12.3)	0.8510
Day 1 (24 hours)			
ResponderNon-responder	103 (97.2)3 (2.8)	100 (94.3)6 (5.7)	0.4983
Day 2 (48 hours)			
ResponderNon-responder	101 (96.2)4 (3.8)	102 (96.2)4 (3.8)	1.0000
Day 3 (72 hours)[f]			
ResponderNon-responder	86 (100.0)	87 (98.9)1 (1.1)	1.0000
Day 5 (120 hours)[f]			
ResponderNon-responder	83 (98.8)1 (1.2)	84 (98.8)1 (1.2)	1.0000
Day 7 (168 hours)			
ResponderNon-responder	104 (99.0)1 (1)	104 (98.1)1 (1)	1.0000

[a]Number of animals that were not sedated or anxious and were assessed with the short form of the Glasgow composite pain scale.
[b]One animal received methadone hydrochloride at the 5-hour timepoint.
[c]One animal received methadone hydrochloride at the 5-hour timepoint. One received buprenorphine at the 8-hour timepoint. One received methadone hydrochloride at the 5-hour timepoint and buprenorphine at the 8-hour timepoint.
[d]Three animals also received a dose of buprenorphine at the 8-hour timepoint.
[e]One animal also received a dose of buprenorphine at the 8-hour timepoint.
[f]Some animals attended either day 3 or day 5 visit.

ing overall adherence and consistency of analgesic cover.

The findings align with previous data in orthopaedic patients, where enflicoxib was non-inferior to meloxicam,[11] and a multicentre soft tissue surgery trial showing non-inferiority to carprofen.[12] In the present study, efficacy was comparable to firocoxib. This consistency across different comparators, surgical settings and study designs reinforces the relevance of enflicoxib as an alternative NSAID for a broad range of procedures.

A notable secondary observation was the significantly lower inflammation at the surgical site in the enflicoxib group during the first hours after surgery. This period corresponds to maximal tissue trauma and inflammatory activation. Although the longer-term clinical impact of this early anti-inflammatory difference cannot be fully determined, it may contribute to improved early comfort and smoother immediate recovery. It may also help to explain the higher proportion of owners who rated analgesia as satisfactory or very satisfactory on day 7 in dogs receiving enflicoxib. Owner assessments are inherently subjective,[27] but they remain essential for understanding how treatments perform in routine practice and for supporting adherence to prescribed regimens.

Importantly, beyond the primary endpoint, treatment response was evaluated, reflecting overall analgesic success. This approach is consistent with the design of many clinical trials and provide a robust and clinically interpretable assessment.[6,11,23,24] Reg-

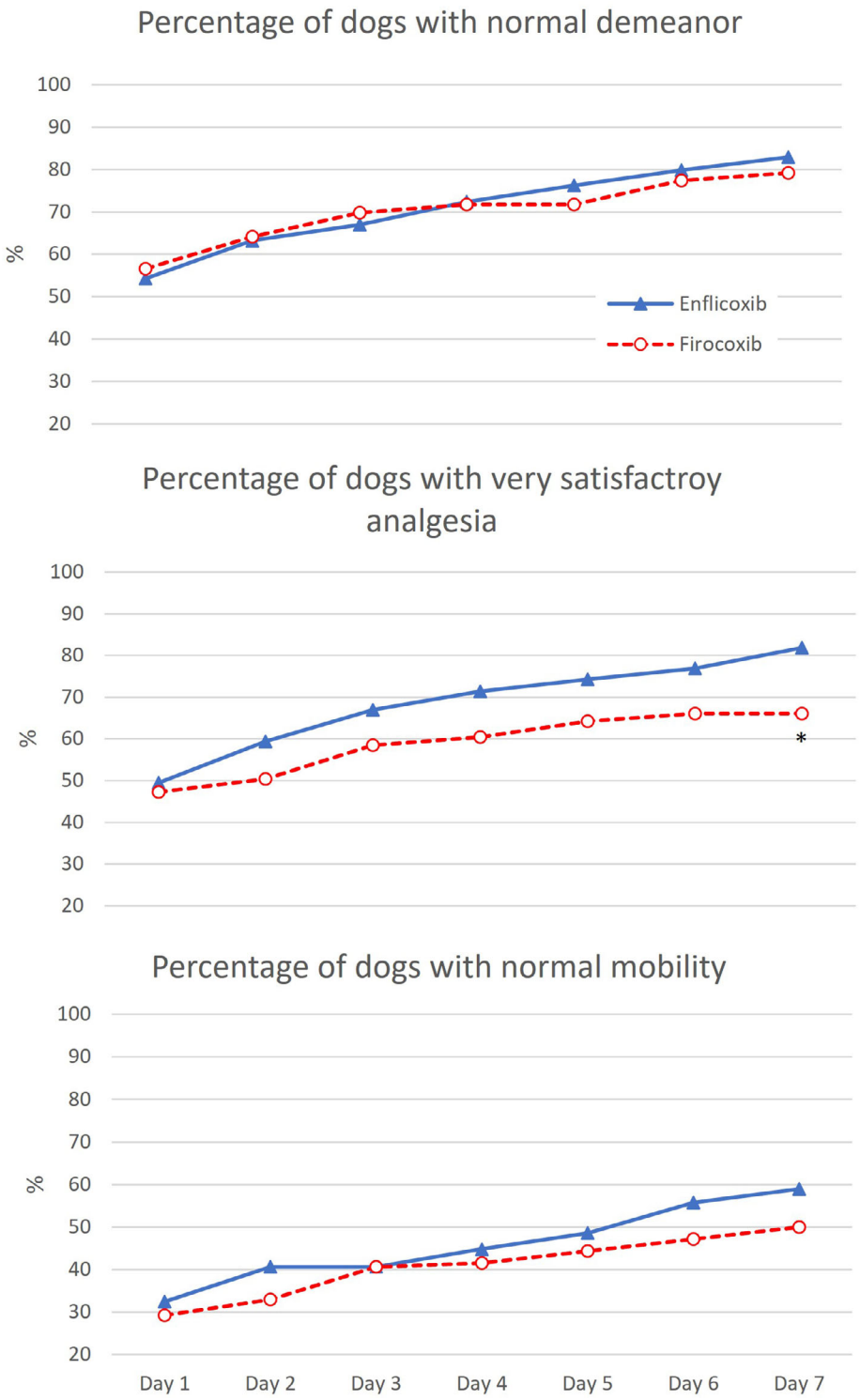

FIGURE 5 Owner assessments of demeanour, mobility and quality of analgesia from day 1 to day 7 in each treatment group.

ulatory and guideline-oriented studies commonly emphasise responder-based outcomes, as they capture pain control over time and better reflect overall clinical benefit than isolated timepoint scores.[2,8] Demonstrating non-inferiority for the primary endpoint, together with comparable responder rates provides strong evidence of enflicoxib effectiveness under real-world conditions, supporting the clinical relevance and external validity of the findings. However, non-inferiority between treatments should not be interpreted as evidence of uniformly optimal analgesia in all dogs during the postoperative period. In the present study, non-response occurred during the immediate postoperative period in both groups, suggesting that treatment with NSAIDs alone may be insufficient in a subset of dogs during this critical phase after some orthopaedic surgeries, and additional multimodal analgesic support may be required. Additional exploratory analyses suggested that early non-response may vary according to the type of orthopaedic procedure, although these findings should be interpreted cautiously because the analyses were post hoc and several procedure categories were small or unspecified.

Both treatments were well tolerated. AEs were infrequent, predominantly mild gastrointestinal signs, and consistent with the known safety profile of COX-2-selective NSAIDs.[8,23,24] The type, frequency and severity of AEs did not differ meaningfully between groups, all resolved by the end of the study, and no clinically relevant changes in clinical pathology variables were detected. These findings are in line with previous reports on the safety of enflicoxib,[10–13,25,26] and support its use under field conditions in orthopaedic patients.

Despite this favourable safety profile, reluctance to administer NSAIDs before general anaesthesia remains common in clinical practice, largely driven by concerns regarding peri-anaesthetic hypotension and potential renal compromise. Such concerns are not supported by available evidence when NSAIDs are used in appropriately selected and managed patients.[2,4,8] Current analgesia guidelines emphasise that perioperative NSAID use, including preoperative administration, is recommended if patients are adequately hydrated, haemodynamic stability is actively monitored, and hypotension is promptly addressed.[2]

In the present study, enflicoxib was administered preoperatively under routine clinical conditions, and no hypotension-related AEs or clinically relevant changes in renal biochemical or urinalysis variables were detected. These findings are consistent with previous studies reporting a favourable renal safety profile for enflicoxib.[11–13,25,26] Moreover, effective preoperative analgesia may improve cardiovascular stability by reducing nociceptive input and anaesthetic requirements, thereby potentially mitigating rather than exacerbating peri-anaesthetic risk. Large-scale observational data have shown that the preoperative use of NSAIDs in combination with opioids is associated with a reduced odds of anaesthetic-related death in dogs.[5]

The study has several strengths. The multicentre design, randomisation and masking enhance internal validity and reduce selection and observer bias. Use of an active comparator that reflects routine clinical practice improves the clinical relevance and interpretability of the findings. Application of a validated behavioural pain scale, supported by structured sedation assessments, is likely to have reduced misclassification of sedation or anxiety as pain. Conducting the trial under field conditions and including a broad range of orthopaedic procedures enhances generalisability to typical first opinion and referral caseloads rather than to a narrowly defined experimental population. The combination of veterinarian-based and owner-reported outcomes provides a multidimensional view of recovery that reflects both clinical and caregiver perspectives.

Limitations should also be acknowledged. The non-inferiority margin has not undergone formal validation. Clinical heterogeneity inevitably introduces variability, reflecting real-world practice and representing a trade-off between experimental control and external validity. Finally, missing SF-GCPS values were replaced using mean imputation, which has known limitations. However, the consistency of results across the different population sets (ITT and PP) and several sensitivity analyses supports the robustness of the conclusions.

In summary, a single preoperative administration of enflicoxib provided sustained postoperative analgesia that was non-inferior to daily firocoxib, with a good safety profile. The long duration of action of enflicoxib offers practical advantages by eliminating the need for daily postoperative NSAID dosing, with the potential to improve treatment adherence and maintain more consistent analgesic cover. These findings support the inclusion of enflicoxib in multimodal perioperative analgesia protocols for dogs undergoing orthopaedic procedures. Further work should investigate procedure-specific outcomes, potential opioid-sparing effects and longer-term functional recovery, including objective functional and quality-of-life measures.

AUTHOR CONTRIBUTIONS

Marta Salichs, Josep Homedes, Anabel Blasco and Llorenç Badiella have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, and drafting the manuscript. Jose I. Redondo has been involved in writing and reviewing the manuscript critically for important intellectual content. All the authors approved the final version of the manuscript and agree to be accountable for its contents.

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CONFLICT OF INTEREST STATEMENT

Marta Salichs and Josep Homedes are employees of Ecuphar Veterinaria SLU (Animalcare Group). Anabel Blasco, Llorenç Badiella and José I. Redondo have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval was obtained from the Spanish (AEMPS) and French (ANSES) regulatory authorities and satisfied national regulatory and animal welfare standards and requirements. The study was conducted in compli-

ance with the Veterinary International Conference on Harmonisation guideline for Good Clinical Practice (VICH 2000). Written informed consent was obtained from all dog owners before enrolment of their dogs in the study. Dogs remained under the care of their owners at home during and after the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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