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Multicentre, blinded, randomised clinical trial comparing the use of flunixin meglumine with firocoxib in horses with small intestinal strangulating obstruction

A. L. ZIEGLER[†], C. K. FREEMAN[†], C. A. FOGLE[†], M. J. BURKE[†], J. L. DAVIS[‡], V. L. COOK[§], L. L. SOUTHWOOD[¶], A. T. BLIKSLAGER^{†,*}

[†]Department of Clinical Sciences, North Carolina State University, Raleigh, North Carolina, USA

[‡]Department of Biomedical Sciences and Pathobiology, Virginia Tech, Blacksburg, Virginia, USA

[§]Department of Large Animal Clinical Sciences, Michigan State University, East Lansing, Michigan, USA

[¶]Department of Clinical Studies, University of Pennsylvania, Kennett Square, Pennsylvania, USA.

Summary

Background: Small intestinal strangulating obstruction (SISO) is associated with endotoxaemia which leads to an increased risk of death. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat signs of endotoxaemia by inhibiting cyclo-oxygenases (COX). COX-1 is expressed constitutively and promotes gut barrier function, whereas COX-2 is inducible and contributes to the signs of endotoxaemia. In preclinical SISO trials, intestinal barrier recovery was more complete with reductions in endotoxin permeability in horses treated with COX-2 selective NSAIDs as compared with horses treated with flunixin meglumine.

Objectives: We hypothesised that treatment of post-surgical SISO horses with firocoxib (COX-2 selective) would reduce the signs of endotoxaemia to a greater extent than flunixin meglumine (nonselective COX inhibitor) while continuing to provide similar levels of pain control.

Study design: Blinded randomised clinical trial.

Methods: In addition to clinical monitoring, preoperative and 12-, 24- and 48-h post-operative plasma samples were assessed for prostaglandin E₂ (PGE₂), thromboxane B₂ (TXB₂), TNF α and soluble CD14 (sCD14).

*Correspondence: anthony_blikslager@ncsu.edu;

Authorship

Manuscript was prepared by A. Ziegler, reviewed by J. Davis, C. Fogle, M. Burke, L. Southwood and V. Cook and final draft approved by A. Blikslager. C. Freeman performed ELISA assays and mined medical records for clinical data.

Authors' declaration of interests

No competing interests have been declared.

Ethical animal research

This randomised clinical trial was approved by Institutional Animal Care and Use protocols at each University. All owners or responsible parties of horses enrolled in this clinical trial gave informed consent.

Manufacturers' addresses

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Results: In 56 recruited SISO horses, either flunixin meglumine (1.1 mg/kg, i.v., q12h) or firocoxib (0.3 mg/kg, i.v. loading dose; 0.1 mg/kg, i.v., q24h) was given in the post-operative period in three university hospitals from 2015 to 2017.

COX-2 selectivity was confirmed by a relative lack of inhibition of the COX-1 prostanoid TXB₂ by firocoxib and significant inhibition by flunixin meglumine ($P = 0.014$). Both drugs inhibited the COX-2 prostanoid PGE₂. There were no significant differences in pain scores between groups ($P = 0.2$). However, there was a 3.23-fold increased risk ($P = 0.04$) of increased plasma sCD14 in horses treated with flunixin meglumine, a validated biomarker of equine endotoxaemia.

Main limitations: Horses were all treated with flunixin meglumine prior to referral. In addition, many horses were treated with lidocaine, which has been shown to mitigate the deleterious effects of flunixin meglumine.

Conclusions: In SISO cases, firocoxib reduced a biomarker of endotoxaemia as compared with flunixin meglumine while continuing to provide similar levels of pain control.

Keywords

horse; colic; endotoxaemia; flunixin meglumine; firocoxib; clinical study

Introduction

Colic-related deaths account for greater than 30% of all mortalities in horses between 1 and 20 years of age [1]. Approximately 10% of horses in the United States experience an episode of colic annually and ~10% of these cases require surgical intervention [2,3]. While survival rates in surgical cases have steadily increased over the past few decades, complications associated with endotoxaemia continue to be highly problematic in postoperative colic cases, especially in those affected by small intestinal strangulating obstruction (SISO) [4,5]. Clinical endotoxaemia following SISO has been associated with post-operative complications such as recurrent colic, post-operative reflux and ultimately increased mortality due to carefully validated signs consistent with systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) [6–8].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are key components of the standard of care to treat endotoxaemic shock. NSAIDs inhibit cyclooxygenases (COX), thereby reducing the production of prostanoids, which are key mediators of shock [9]. The two principal isoenzymes of COX (COX-1 and COX-2) are inhibited by NSAIDs to varying degrees [10]. Most NSAIDs used to treat horses are nonselective COX inhibitors, such as flunixin meglumine or phenylbutazone, and inhibit both enzymes at clinical dosages, whereas one NSAID in particular that is labelled for use in horses is highly COX-2 selective (or COX-1 sparing): firocoxib. This is important because COX-1 is expressed constitutively and mediates homeostasis of gut barrier function, whereas COX-2 is induced in pro-inflammatory states and is in part responsible for the clinical signs of endotoxaemia [11–13]. Flunixin meglumine is routinely used to treat pain and signs of endotoxaemia in post-surgical colic cases. However, preclinical trials have shown that inhibition of both COX isoenzymes with flunixin meglumine leads to increased intestinal permeability to LPS in horses with experimental SISO [11]. Conversely, horses in these studies treated with the

modestly COX-2 selective NSAID meloxicam or the highly COX-2 selective NSAID firocoxib had significantly lower intestinal permeability vs. horses treated with flunixin meglumine [14]. Behavioural pain scores were significantly reduced by treatment with both flunixin meglumine and COX-2 inhibitors in these trials [11,15]. Based on these findings, we hypothesised that treatment of post-surgical SISO horses with firocoxib (COX-2 selective) would reduce endotoxaemia and associated shock syndromes (SIRS and MODS) to a greater extent than flunixin meglumine (nonselective COX inhibitor) while continuing to provide similar levels of pain control.

Materials and methods

Inclusion criteria

Horses 1 year of age that were admitted to one of the participating university equine hospitals for evaluation of acute colic that underwent surgical correction of SISO and subsequently recovered from surgery were eligible for inclusion in the study and were recruited at the time of recovery from surgery (Fig 1). Ponies and miniature horses were excluded due to the potential for differing pathophysiological responses to colic. Owners or responsible parties of horses eligible for enrolment were given the opportunity to participate in the study, and informed consent was obtained prior to enrolment.

Sample size

Using the difference and variance in plasma sCD14 measurements in clinical SISO cases with or without clinical signs of endotoxaemia (302.6 ± 465.0 [s.d.] ng/mL, an unpublished data set from Fogle *et al.* [7]), a statistical power of 0.8 and an α of 0.05, enrolment of 76 horses ($n = 38$ in each treatment group) was initially considered. However, during interim analysis, a statistically significant difference in sCD14 measurements was identified following analysis of 56 enrolled horses after 2 years, and the study was concluded.

Treatments

Based on the history of the caseloads at each University, it was known that the majority of horses would have received at least one dose of flunixin meglumine prior to admission for evaluation of colic, so randomisation prior to colic surgery was not possible. Therefore, subjects received routine colic treatments preoperatively, including flunixin meglumine (1.1 mg/kg, i.v.), unless the horse was within 12 h of administration of a full dosage of flunixin meglumine by the referring veterinarian. At recovery, horses were randomly allocated 1:1 into two parallel groups for post-operative NSAID therapy by simple sequential randomisation (flip of a coin) or by simple randomisation (first doses prepared, concealed and shuffled in advance by pharmacy staff) depending on hospital site. Horses were treated with either flunixin meglumine (Banamine®,^a 1.1 mg/kg, i.v., q12h) or firocoxib (Equioxx®^b, 0.3 mg/kg, i.v., loading dose; 0.1 mg/kg, i.v., q24h thereafter) as close as reasonably possible to 12 h following the last preoperative dose of flunixin meglumine [16]. Hospital personnel making clinical decisions or who were responsible for pain scoring were

^aMerck Animal Health, Madison, New Jersey, USA.

^bMerial Inc., Duluth, Georgia, USA; acquired during the study by Boehringer Ingelheim, Ingelheim am Rhein, Germany.

blinded to NSAID treatment allocation. Fluid therapy and antimicrobial administration were discussed by all investigators and a standard of care was established including administration of lactated Ringer's solution and potassium penicillin (22,000 U i.v. q6h) and gentamicin (6.6 mg/kg i.v. q24h). Additional pain management with butorphanol was permitted for breakthrough pain at the discretion of the attending veterinarian. Nasogastric intubation was performed if there were concerns regarding the presence of post-operative reflux (POR), and treatment with lidocaine for POR or analgesia was also permitted at the discretion of the attending veterinarian and was recorded.

Clinical parameters

Physical examination parameters (rectal temperature, pulse, respiratory rate, mucous membrane colour and capillary refill time) were assessed and recorded every 12 h in the first 3 days post-operatively, and then every 24 h for the following 3 days. Volumes of net gastric reflux exceeding 2 L at any one time were considered positive for POR [17]. Complete blood counts and serum chemistry panels were obtained at the discretion of the attending clinician for assessment of the clinical management of each individual case and were not required for purposes of this study. Any changes in white blood cell counts, use of additional pain control (butorphanol, detomidine, xylazine) or lidocaine administration and any complications occurring during hospitalisation as defined by the attending clinician were recorded. Short-term survival was defined as alive at the time of discharge from the hospital.

SIRS was identified as any horse having two or more of the following post-operatively throughout hospitalisation: hyperthermia ($>38.6^{\circ}\text{C}$) or hypothermia ($<36.7^{\circ}\text{C}$), leucopenia ($<4800/\mu\text{L}$) or leucocytosis ($>14,300/\mu\text{L}$), tachycardia (>48 beats/min) and tachypnoea (>24 breaths/min) [18]. MODS was identified in any horse having two or more of the following postoperatively throughout hospitalisation: haemodynamic dysfunction detected as congested mucous membranes with increased capillary refill time, haemostatic dysfunction detected as jugular vein thrombosis and/or platelet count $<100,000/\mu\text{L}$, renal dysfunction as indicated by creatinine >2 mg/dL, intestinal dysfunction identified by nasogastric reflux >2 L and decreased motility on abdominal ultrasound, hepatic dysfunction indicated by bilirubin >6 mg/dL, clinical signs of laminitis including subjective increases in digital pulses and evidence of foot pain in response to hoof testers, respiratory distress as indicated by persistent tachypnoea and neurological function detected as stupor and incoordination. The criteria for MODS have been previously published by Blikslager *et al.* in 1994 and in a study of the post-operative complications of large colon volvulus by one of the participating hospitals [17,19].

Pain scoring

Hospital personnel blinded to NSAID allocation were responsible for assessing behavioural pain scores using a standardised system (Supplementary Item 1). A score of 9 indicates no behavioural evidence of pain (a score of one in each of nine behavioural categories), with a maximal score of 36 [20]. Pain scores were assessed and recorded every 12 h in the first 3 days post-operatively and then every 24 h for the following 3 days.

Plasma sample collection

Blood samples were collected from enrolled horses into plasma separator tubes (Vacutainer® PPT™ Plasma Preparation Tube^c) via jugular catheter or jugular venepuncture preoperatively, at 6–8, 24 and 48 h post-operatively. Samples were immediately centrifuged to separate plasma and frozen at –20°C, then transferred to –80°C for storage prior to analysis.

Plasma biomarkers

Plasma was assayed for TNF α concentration using a commercial ELISA assay^d validated for the horse. Differential prostanoid inhibition by flunixin meglumine and firocoxib treatment were assessed using ELISA kits for PGE₂ and TXB₂^e validated at NC State in previous studies evaluating effects of flunixin meglumine and COX-2 inhibitors on intestinal recovery [11,15]. Plasma samples were shipped to the Animal Health Diagnostic Center at Cornell University, Ithaca, NY, USA, for sCD14 analysis. The Center's established reference range for sCD14 in normal horses is 311–1716 ng/mL.

Data analysis

All statistics were performed on Prism 7 software.^f Data for the two groups were compared using two-way ANOVA for the effect of time and treatment on each parameter. For nonparametric data, ANOVA was run on ranks. For elevated sCD14, elevated TNF α , survival, and SIRS/MODS outcomes, the distributions of horses between groups were compared using a Chi-square test with one-tailed assumption based on our hypothesis that horses in the firocoxib group would have reduced endotoxaemia and associated shock syndromes. Enrolment data were analysed by Chi-square tests with two-tailed assumption. The relative risk of clinical abnormalities and survival were also analysed between the two groups. $P < 0.05$ was considered statistically significant.

Results

Enrolment

A total of 63 horses were enrolled in the randomised control trial (RCT), including 32 horses that received flunixin meglumine in the post-operative period and 31 horses that received firocoxib in the post-operative period; however to focus on SISO, seven horses with ileal impaction were excluded from analysis (Fig 1). Randomisation was assessed between the two groups (Table 1), and there was no significant difference in age ($P = 0.2$), breed ($P = 0.4$) or whether intestine was resected ($P = 0.3$). However, there was a significantly different distribution of sex ($P = 0.03$). There was no difference in the use of intra- or post-operative i.v. lidocaine between groups; 73 and 82% of horses were treated with lidocaine in the flunixin meglumine and firocoxib groups, respectively ($P = 0.5$).

^cBecton Dickinson and Company, Franklin Lakes, New Jersey, USA.

^dPierce Protein Biology Products, Rockford, Illinois, USA.

^eCayman Chemical, Ann Arbor, Michigan, USA.

^fGraphPad Software Inc., La Jolla, California, USA.

COX selectivity

COX-1 inhibition in horses treated with flunixin meglumine was confirmed post-operatively by a significant reduction in plasma TXB₂ over the initial 48 h [11]. No significant difference in plasma TXB₂ was noted between groups prior to surgery or at 6 and 24 h post-operatively. However, horses treated with flunixin meglumine had significantly lower plasma TXB₂ compared with firocoxib-treated horses by 48 h post-operatively (22.14 ± 6.13 vs. 49.14 ± 9.24 pg/mL, respectively, $P = 0.01$, Fig 2a). Both NSAID groups had similar levels of PGE₂ ($P = 0.20$ Fig 2b).

Pain scoring

Amongst the 56 horses enrolled in the RCT, there was no significant difference in behavioural pain scores between the two groups throughout the post-operative period ($P = 0.20$). However, use of either flunixin meglumine or firocoxib had similar significant reductions in behavioural pain score. For instance, in the flunixin meglumine group, the mean behavioural pain score at 12 h post-operatively was 18, and this was reduced significantly by 96 h post-operatively to 12. Similarly, the pain score in the firocoxib group at 12 h post-operatively was 18 and this was reduced significantly to 11 by 96 h post-operatively ($P < 0.01$, Fig 3a).

There was no significant difference in the use of additional pain control medications (butorphanol, detomidine or xylazine) between groups, though there was a trend towards lower use of these medications in the firocoxib-treated horses. More specifically, in the firocoxib group, 9% of horses were treated with additional pain control medications as compared with 27% of horses in the flunixin meglumine group. This represents a threefold increased relative risk, though this was not statistically significant at this sample size (95% confidence interval [21] 0.80–11.85, $P = 0.2$).

Clinical parameters

As a measure of both pain and clinical endotoxaemia, heart rates were compared, and no significant differences were found between the two groups of horses throughout hospitalisation ($P = 0.5$, Fig 3b). Both groups had similar reduction in heart rate by 48 h post-operatively as compared with 12 h post-operatively. Across those two time points, the mean heart rate for horses treated with flunixin meglumine decreased from a mean heart rate of 55–44 ($P < 0.001$) and firocoxib-treated horses 54–45 ($P = 0.05$).

There were no significant differences in the incidence of clinical signs attributable to SIRS or MODS between groups (Table 2). SIRS or MODS was diagnosed in 34.6 and 42.9% of horses treated with flunixin meglumine, respectively, after 48 h post-operatively as compared with 22.3 and 36.0% of horses treated with firocoxib ($P = 0.18$ and $P = 0.31$, respectively, between groups).

On evaluation of short-term survival (Table 3), 26.7% of horses treated with flunixin meglumine did not survive to discharge as compared with 19.2% of horses treated with firocoxib. This represents a 1.4-fold increased relative risk of nonsurvival in the flunixin meglumine group. However, this was not statistically significant (CI 0.54–3.66, $P = 0.5$).

Endotoxaemia parameters

Increase in plasma sCD14 above the established reference range was significantly associated with the incidence of either SIRS or MODS, or both SIRS and MODS, as one parameter ($P < 0.001$). Increased sCD14 detected SIRS/MODS with a sensitivity of 69% (CI 53–82%) and a specificity of 100% (CI 76–100%).

As plasma markers of endotoxaemia, the incidence of sCD14 exceeding the established reference range and TNF α exceeding zero were recorded and compared (Table 3) [7]. There were no significant differences in TNF α levels between the two groups at any time period (Fig 4a, $P = 0.50$) or in the proportion of horses with detectable plasma TNF α in each group (Fig 4b, $P = 0.40$). In addition, there were no significant differences in mean sCD14 levels between the two groups at any time period (Fig 4a, $P = 0.5$) However, at 48 h post-operatively, 26.9% of horses treated with flunixin meglumine had sCD14 levels exceeding the upper limit of the reference range as compared with 8.33% of horses treated with firocoxib (Fig 4c, d, $P = 0.044$). This corresponds to a 3.23-fold increased risk of increased biomarker of endotoxaemia in horses treated with flunixin meglumine as compared with those treated with firocoxib (CI 0.86–12.94, $P = 0.04$).

Discussion

Horses with SISO lesions had evidence of behavioural signs of pain in the post-operative period, and these signs were significantly reduced by 96 h post-operatively by both flunixin meglumine and firocoxib. There was no difference in pain scores or incidence of use of additional pain management during the study period between the flunixin meglumine and firocoxib groups, suggesting similar levels of pain control with either of these NSAIDs. In keeping with this finding, there was also no significant difference in heart rate over time between the two treatment groups. This contrasts to findings in a UK-based RCT using client-owned cases with SISO in which behavioural pain scores were significantly higher in horses treated with meloxicam as compared with those treated with flunixin meglumine. While, it is important to consider the implications of the lack of blinding of the veterinarians to medication administered in this UK study, it is also important to note that meloxicam was double dosed (given q12h instead of the labelled q24h), to match double dosing of flunixin meglumine (given q12h instead of the labelled q24h for horses), but still resulted in higher pain scores, which were evaluated in a blinded manner. Additionally, it is possible that double dosing meloxicam may result in a lack of COX-2 selectivity, although this was not evaluated in the UK study [14]. In the present study, firocoxib was also administered at an off-label loading dose (0.3 mg/kg), although the reason for this was the scientific finding that firocoxib does not reach steady state concentrations within the first 72 h without a loading dose [16].

An important finding in horses treated with firocoxib was the significant reduction in the number of horses with increased sCD14, a validated serum marker of clinical endotoxaemia, as compared with the flunixin meglumine group at the 48 h time period. Over 25% of horses treated with flunixin meglumine had increased sCD14 at 48 h as compared with less than 10% for firocoxib horses. This may be due to a reduction in the rapidity of mucosal repair as a result of nonselective COX inhibition by flunixin meglumine, and an associated reduction

in COX-1 reparative prostanoids, as has been documented in preclinical trials. More precisely, these trials showed that the permeability of LPS across ischaemic-injured mucosa following an 18 h recovery period was significantly increased in horses treated with flunixin meglumine as compared with firocoxib [11]. In the prior RCT evaluating flunixin meglumine and meloxicam, there were no measurable differences in endotoxaemia [14]. However, in that study, LPS was measured rather than sCD14. The latter has been shown to be more accurate for distinguishing horses with clinical signs of endotoxaemia, possibly due to increased persistence of this mediator following stimulation by the more labile LPS [7]. Nonetheless, it is arguably more important to emphasise differences in signs of SIRS or MODS and survival because these syndromes more directly translate to the clinical outcomes. There was no significant difference in the incidence of these outcomes comparing horses treated with flunixin meglumine vs. firocoxib. However, there were notable trends, particularly for survival, when comparing the two NSAIDs.

Validating trends towards increased survival in horses treated with firocoxib will require additional study of greater numbers of horses. Study funding necessitated closure of enrolment after 63 horses, at which point interim analyses determined, there was sufficient enrolment to detect differences in sCD14 elevations. However, the study as a whole is underpowered to detect differences in survival outcomes which is a weakness of the present RCT. A power analysis on the short-term survival outcomes shows that a sample size of over 500 horses per group for this RCT may detect a significant protective effect of firocoxib use on survival. In addition to increased numbers, what would likely be most helpful in evaluating differences in effects of NSAIDs would be a combined field and referral hospital trial in which horses with colic are given flunixin meglumine or firocoxib in the field for treatment of colic prior to referral. This would be predicted to preserve COX-1 activity in firocoxib horses in the full perioperative period in an attempt to further promote mucosal repair, thereby further reducing endotoxaemia, and hopefully increasing survival.

Analysis of prostanoids indicated that firocoxib spared COX-1 and selectively inhibited COX-2 by the 48 h post-operative time point, based on the finding that blood levels of PGE₂ (associated with peripheral COX-2 activity in mononuclear cells) were inhibited, whereas levels of TXB₂ (associated with peripheral COX-1 activity in platelets) increased within 48 h. The initial inhibition of COX-1 in the flunixin meglumine and firocoxib groups was attributed to the initial preoperative administration of flunixin meglumine to all horses in the trial. However, it is also important to consider the effect of the current recommended loading dose in firocoxib-treated horses on COX selectivity in the earlier time points. This was considered during study design and the decision was made to prioritise pain control and follow the current recommendations for optimal standard of care. Whether this loading dose diminishes the selectivity of firocoxib is not known.

Additional limitations of this study include the varying interpretations of what “the discretion of the attending veterinarian” means, and the reality that not all aspects of care could be practically controlled across institutions. To foster clinician participation and case enrolment, we did not attempt to restrict their clinical freedoms by controlling all aspects of horse care and requiring extensive reporting. Due to the nature of a multi-institutional study, there are data points missing in some cases. Parameters analysed for SIRS had higher

reporting rate because these parameters were requested directly on the study forms provided to all three institutions. Besides POR, capillary refill time and mucous membrane colour, other MODS parameters were data mined from medical records after conclusion of the study and from only one site, so the reporting level was very low. This introduces a bias for abnormal findings and complicates interpretation, as only horses with a clinical picture prompting further diagnostics (serum chemistry or complete blood counts, abdominal ultrasound) were tested and reported in the horse medical record. As an example, if a horse had one parameter of SIRS (increased heart rate) but did not have other diagnostics performed and thus a second parameter (such as a leucocytosis) was missed, this horse would not have been classified as in SIRS incorrectly. In spite of these difficulties and limitations, this RCT provides important preliminary evidence that firocoxib offers clinical benefits in managing SISO cases compared with flunixin meglumine.

Conclusion

The clinical relevance of this study is that the use of firocoxib following surgery for SISO results in similar levels of pain control as compared with horses treated with flunixin meglumine, but firocoxib horses have reduced evidence of endotoxaemia at 48 h post-operatively as detected by measuring sCD14. Additional studies to establish the impact on short-term survival and risk of complications, to achieve earlier COX-selectivity with preoperative drug randomisation as well as to extend data collection beyond 48 h post-operatively will be important to establish whether or not firocoxib is a preferred treatment for horses with SISO.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1:
CONSORT 2010 flow diagram outlining process for study recruitment.

Fig 2:

Effects of flunixin meglumine (FM) and firocoxib (Firo) on plasma concentrations of COX-1 and COX-2 activity biomarkers TXB₂ and PGE₂, respectively. a) TXB₂ levels rebounded by 48 h post-operatively in horses treated with firocoxib as compared with continued suppression of TXB₂ in horses treated with flunixin meglumine. b) Both drugs suppress PGE₂ equally. *P = 0.014 by two-way ANOVA with Sidak's multiple comparisons test.

Fig 3:

Effects of flunixin meglumine (FM) and firocoxib (Firo) on post-operative pain scores and heart rates. a) Both drugs control pain equally throughout the post-operative period ($P = 0.20$). There is a significant reduction in pain scores over time across both groups ($P = 0.0002$). b) Both drugs reduce heart rate equally ($P = 0.51$). There is a significant reduction in heart rate over time in both groups ($P < 0.0001$). Statistical analyses assessed by two-way ANOVA.

Fig 4:

Effects of flunixin meglumine (FM) or firocoxib (Firo) on plasma TNFα and sCD14 levels.

a) Individual plasma TNFα levels plotted for each time point (two-way ANOVA, effect of drug $P = 0.50$). b) Proportion of horses with TNFα levels exceeding 0 (Chi-square analysis with one-tailed assumption, $P = 0.44$). c) Individual plasma sCD14 levels plotted for each time point (two-way ANOVA, effect of drug $P = 0.50$). d) Proportion of horses with sCD14 levels exceeding reference range of 1716 ng/mL. Note, the significant difference in numbers of horses exceeding reference range in the flunixin meglumine group at 48 h post-operatively (Chi-square analysis with one-tailed assumption, $*P = 0.044$).

TABLE 1:

Distribution of breed, age, sex and surgical procedure between groups

Parameter	Flunixin (%)	Firocoxib (%)	Chi-square P-value
Breed			
TB/STB/Arab	23	27	0.3831
QH/Paint/App	23	36	
WB	8	14	
Other	46	23	
Age (years)			
<5	15	0	0.1552
5–15	31	50	
15–25	50	41	
>25	4	9	
Sex			
Gelding	76	59	*0.0273
Stallion	12	0	
Mare	12	41	
Surgical procedure			
Resection	73	59	0.3057
No resection	27	41	

Data presented as percentage of the total enrolment for each group. P-values represent results of Chi-square analysis of the distributions with two-tailed assumption.

* P-value considered significant.

TABLE 2:

Incidence of clinical abnormalities associated with SIRS and MODS observed during hospitalisation after 48 h post-operatively

Clinical abnormality	Flunixin affected/observed (%)	Firocoxib affected/observed (%)	Relative risk Flunixin vs. Firocoxib (confidence interval)	P-value
SIRS				
Hypothermia/hyperthermia	6/26 (23.1)	4/19 (21.1)	1.096 (0.3831–3.275)	0.4359
Leucocytosis/leucopenia	8/25 (32.0)	4/21 (19.0)	1.556 (0.5807–4.418)	0.2005
Tachycardia	9/26 (34.6)	5/18 (27.8)	1.246 (0.5283–3.140)	0.3161
Tachypnoea	11/26 (42.3)	13/18 (72.2)	0.5858 (0.3353–1.000)	0.250
MODS				
Abnormal CRT or mucous membranes	13/26 (50.0)	8/20 (40.0)	1.250 (0.6641–2.494)	0.2498
Thrombopenia	1/7 (14.3)	0/4 (0.00)	∞ (0.1565– ∞)	0.2301
Thrombophlebitis	2/26 (8.70)	0/18 (0.00)	∞ (0.3872– ∞)	0.1142
Elevated creatinine	0/7 (0.00)	1/4 (25.0)	0.000 (0.000–1.963)	0.0827
Elevated bilirubin	1/7 (14.3)	0/4 (0.00)	∞ (0.179– ∞)	0.2139
Post-operative reflux	11/26 (42.3)	7/20 (35.0)	1.209 (0.5908–2.605)	0.3073
Decreased intestinal motility	4/7 (57.1)	1/3 (33.3)	1.714 (0.4573–9.936)	0.2451
SIRS	9/26 (34.6)	5/22 (22.3)	1.523 (0.6299–3.874)	0.1833
MODS	12/28 (42.9)	9/25 (36.0)	1.190 (0.6154–2.368)	0.3052
SIRS or MODS	15/26 (57.7)	8/19 (42.0)	1.370 (0.7637–2.661)	0.1508

Systemic inflammatory response syndrome (SIRS) was identified as any horse having two or more of the following during the post-operative period: hyperthermia ($>101.5^{\circ}\text{F}$) or hypothermia ($<98^{\circ}\text{F}$), leucopenia ($<4800/\mu\text{L}$) or leucocytosis ($>14,300/\mu\text{L}$), tachycardia (>48 beats/min) and tachypnoea (>24 breaths/min). Multiple organ dysfunction syndrome (MODS) was identified in any horse having two or more of the following during the post-operative period: haemodynamic dysfunction detected as congested mucous membranes with increased capillary refill time (CRT), haemostatic dysfunction detected as jugular vein thrombosis and/or platelet count $<100,000/\mu\text{L}$, renal dysfunction as indicated by creatinine >2 mg/dL, intestinal dysfunction identified by nasogastric reflux >2 L and decreased motility on abdominal ultrasound, hepatic dysfunction indicated by bilirubin >6 mg/dL. P-values calculated from Chi-square tests with one-tailed assumption based on hypothesis.

TABLE 3:

Incidence of plasma sCD14 exceeding established reference range, plasma TNF α exceeding zero and short-term nonsurvival (case subjected to euthanasia or deceased during hospitalisation)

Parameter	Flunixin affected/observed (% affected)	Firocoxib affected/observed (% affected)	Relative risk Flunixin vs. Firocoxib (confidence interval)	P-value
Elevated plasma sCD14				
At 24 h post-operative	5/26 (19.2)	4/24 (16.7)	1.154 (0.3736–3.623)	0.4068
At 48 h post-operative	7/26 (26.9)	2/24 (8.33)	3.231 (0.8632–12.94)	0.0437 *
Elevated plasma TNF α				
At 24 h post-operative	7/26 (26.9)	6/25 (24.0)	1.122 (0.4507–2.826)	0.4054
At 48 h post-operative	7/26 (26.9)	6/25 (24.0)	1.122 (0.4507–2.826)	0.4054
Short-term nonsurvival	8/30 (26.7)	5/26 (19.2)	1.387 (0.5432–3.662)	0.2555

P values calculated by Chi-square tests with one-tailed assumption.

* P-value considered significant.