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Letter to the Editor: Bias in statistics or bias in equine veterinary medicine?

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Please find our point-by-point responses to D. E. Freeman's letter to the Editor regarding our article reporting the results of a randomised clinical trial (RCT) comparing flunixin meglumine and firocoxib for the control of postoperative pain and endotoxaemia in horses after surgical correction of small intestinal strangulating obstruction (SISO) [1].

- We agree that using the word "trend" to suggest data is "close to significance" is incorrect. However, the authors were careful not to use the term trend in this manner. Our discussion in the article proposes that validating a trend towards improved survival in horses treated with firocoxib would require additional studies with greater numbers of horses and likely modification of the study design to include preoperative drug randomisation. The suggestion by Dr Freeman that changes are unlikely no matter how many horses are assessed simply implies bias, rather than a true understanding of statistical power. Furthermore, the discussion regarding sCD14 values, which were significantly higher in patients on flunixin meglumine as compared to firocoxib ($P = 0.044$), is incoherent.
- A one-tailed assumption is appropriate when the hypothesis states a predicted directionality. Our hypothesis was that "treatment of post-surgical SISO horses with firocoxib **would reduce endotoxaemia and associated shock syndromes (SIRS and MODS) to a greater extent** than flunixin meglumine while continuing to provide similar levels of pain control".
- The differences in the surgical treatments between drug groups is a reasonable point. We agree that future studies with even randomisation into both resection and nonresection groups to account for this variable would be informative. Nonetheless, Dr. Freeman has previously indicated that horses in which SISO is not resected are arguably more critical patients to manage because of the known presence of ischaemic-injured intestine [2], so it could be argued that more nonresected cases in the firocoxib group is an allocation bias against that group.
- The authors are aware of and have discussed prothrombotic side effects of COX-2 inhibitors in human beings previously [3]. Horses are not known to be susceptible to these prothrombotic side effects of COX selective NSAIDs, and no

significant increase in such side effects (such as thrombosed jugular veins) were noted in horses on firocoxib in the present RCT.

- The authors were careful not to overstate the results indicating that ‘this RCT ***provides important preliminary evidence that*** firocoxib offers clinical benefits.’ In the letter by Dr Freeman, the bolded part of the statement was omitted to make a point not intended by the authors. In the referenced study, Fogle *et al.* [4] found that sCD14 was significantly higher in horses classified as clinically endotoxaemic compared to clinically nonendotoxaemic horses, whereas there were no significant differences in LPS. This likely relates to rapid clearing of LPS by LPS-binding protein whereas macrophages remain activated and capable of continued secretion of sCD14. Therefore, at present, sCD14 may provide a more accurate means of quantifying endotoxaemia than assays of LPS.

Ultimately, readers should assess the evidence for themselves as to whether there is cause for concern about the use of flunixin in horses with SISO now that we have shown both preclinically [5–9] and clinically [10] that flunixin increases evidence of endotoxaemia in horses with SISO by retarding recovery of injured mucosa. Furthermore, there is an alternative nonsteroidal anti-inflammatory drug labelled for horses in the form of firocoxib that is COX-2 selective, and avoids the potential complications of flunixin meglumine while providing similar levels of pain control [10]. We propose that current therapy for horses with colic should be assessed with RCTs that seek to provide evidence as a basis to support the efficacy of these treatments rather than relying on potentially biased clinical experience alone.

References

1. Freeman DE (2019) Letter to the editor: Multicentre, blinded, randomised clinical trial comparing the use of flunixin meglumine with firocoxib in horses with small intestinal strangulating obstruction. *Equine Vet. J* 51, 422. [PubMed: 30714186]
2. Freeman DE (2018) Post-operative ileus reflux – a surgeon’s perspective. *Equine Vet. Educ* 30, 671–680.
3. Ziegler A, Fogle C and Blikslager AT (2017) Update on the use of cyclooxygenase-2-selective nonsteroidal anti-inflammatory drugs in horses. *J. Am. Vet. Med. Ass* 250, 1271–1274. [PubMed: 28509650]
4. Fogle J, Jacob M, Blikslager A, Edwards A, Wagner B, Dean K and Fogle C (2016) Comparison of lipopolysaccharides and soluble CD14 measurement between clinically endotoxaemic and nonendotoxaemic horses. *Equine Vet. J* 49, 155–159. [PubMed: 27060869]
5. Tomlinson JE, Wilder BO, Young KM and Blikslager AT (2004) Effects of flunixin meglumine or etodolac treatment on mucosal recovery of equine jejunum after ischemia. *Am. J. Vet. Res* 65, 761–769. [PubMed: 15198216]
6. Tomlinson JE and Blikslager AT (2005) Effects of cyclooxygenase inhibitors flunixin and deracoxib on permeability of ischaemic-injured equine jejunum. *Equine Vet. J* 37, 75–80. [PubMed: 15651739]
7. Little D, Brown SA, Campbell NB, Moeser AJ, Davis JL and Blikslager AT (2007) Effects of the cyclooxygenase inhibitor meloxicam on recovery of ischemia-injured equine jejunum. *Am. J. Vet. Res* 68, 614–624. [PubMed: 17542694]
8. Cook VL, Jones Shults J, McDowell M, Campbell NB, Davis JL and Blikslager AT (2008) Attenuation of ischaemic injury in the equine jejunum by administration of systemic lidocaine. *Equine Vet. J* 40, 353–357. [PubMed: 18321812]

9. Cook VL, Meyer CT, Campbell NB and Blikslager AT (2009) Effect of firocoxib or flunixin meglumine on recovery of ischemic-injured equine jejunum. *Am. J. Vet. Res* 70, 992–1000. [PubMed: 19645580]
10. Ziegler AL, Freeman CK, Fogle CA, Burke MJ, Davis JL, Cook VL, Southwood LL and Blikslager AT (2018) Multicentre, blinded, randomised clinical trial comparing the use of flunixin meglumine with firocoxib in horses with small intestinal strangulating obstruction. *Equine Vet. J* 51, 329–335. [PubMed: 30156312]