**Epidural administration of opioid analgesics improves quality of recovery in horses anaesthetised for treatment of hindlimb synovial sepsis**

BACKGROUND:

Opioid epidural analgesia (OEA) has been shown to provide effective analgesia in horses. There is a lack of evidence regarding the effect of OEA on quality of recovery (QR) in horses.

OBJECTIVES:

Identify whether OEA influences QR in horses undergoing general anaesthesia required for management of hindlimb synovial sepsis.

STUDY DESIGN: Single centre retrospective cross-sectional study.

METHODS:

Data were obtained from the clinical records of horses which had undergone arthroscopic or tenoscopic surgery for management of hindlimb synovial sepsis over a 9-year period in a referral hospital population. Multivariable logistic regression analysis was used to identify the perioperative factors that impact on QR.

RESULTS:

Records from 149 horses, undergoing 170 general anaesthetics were included. Multivariable logistic regression analysis showed that OEA (OR 3.0, 95% CI 1.2 to 7.2, P = 0.02) was associated with good QR, whereas Cob breeds (OR 0.16, 95% CI 0.06 to 0.46, P = 0.001), age (in years) (OR 0.90, 95% CI 0.83 to 0.97, P = 0.004) increasing intraoperative dosages (in mg/kg) of thiopental (OR 0.64, 95% CI 0.46 to 0.90, P = 0.01) or ketamine (OR 0.42, 95% CI 0.18 to 0.98, P = 0.04) were linked to poor QR.

MAIN LIMITATIONS:

Certain variables that may influence QR, such as patient temperament and hindlimb orthopaedic co-morbidities were not recorded. The clinical prediction model obtained is only applicable to the specific facilities, population and peri-anaesthetic management practiced at our institution.

CONCLUSIONS:

This study concludes that OEA is significantly associated with good QR in horses undergoing general anaesthesia required for management of hindlimb synovial sepsis. Other risk factors, such as increasing age, cob breed, use of higher intra-operative dosages (in mg/kg) of ketamine and/or thiopental, were associated with poor QR.

KEYWORDS: “Anaesthesia”; “Analgesia”; “Recovery”: “Epidural”; “Opioid”; “Synovial sepsis”

INTRODUCTION

Epidural administration of opioids with or without local anaesthetics has been considered by many authors to be a safe and effective method of providing long-lasting analgesia in small animals undergoing pelvic limb orthopaedic surgeries [1–3]. In these species, opioid epidural analgesia (OEA) decreases central sensitization, volatile anaesthetic and perioperative systemic opioid requirements, stress response during surgery and post-operative rescue analgesia [4–7].

In horses, several studies demonstrate a beneficial effect of OEA without motor effects [8–11]. Experimental studies assessing the analgesic effects of intercoccygeal epidural administration of opioids, with or without combination with local anaesthetics, demonstrate an increase in pain threshold to electrical stimulation of the perineal and lumbosacral areas in conscious horses [8,9]. Clinical studies show that epidural administration of morphine alone, or in combination with detomidine, produces significantly lower post-operative pain scores in horses undergoing surgical procedures under general anaesthesia (GA) [10,11].

Complications arising from poor quality of recovery (QR) in horses undergoing GA have been extensively reported and considered as key risk factors in the prevalence of perioperative equine fatalities [12,13]. Administration of morphine in the epidural space reduced volatile anaesthetic requirements and improved QR in experimental ponies [14,15]. However, some studies do not show an improvement in recovery quality after OEA within a clinical setting [11] whereas others demonstrate a beneficial effect of systemic administration of opioids in terms of QR score [16–18]. In addition, at high doses, opioid use can produce detrimental behavioural effects, resulting in a negative effect on QR [19].

A number of studies have investigated the use of systemic opioids and their combination with other agents in an attempt to provide adequate analgesia, reduce volatile anaesthetic requirements, and improve recovery qualities [18,20–22]. OEA has been consistently shown to provide reliable analgesia in horses under experimental conditions, although, to the author’s knowledge, a positive impact on QR has not been demonstrated in a clinical setting.

The aim of this study was to identify perioperative factors associated with QR in horses undergoing GA required for management of hindlimb synovial sepsis. Our hypothesis was that OEA will improve QR in this subset of horses.

MATERIAL AND METHODS

Data collection

The case records of horses presented to the University of Liverpool Philip Leverhulme Equine Hospital for management of hindlimb synovial sepsis between January 2010 and December 2019 were reviewed. Cases were included if horses were >6 months of age, sepsis of a hindlimb synovial structure had been diagnosed, surgical management under GA had been performed with unassisted recovery from anaesthesia and QR score was recorded. Horses subjected to euthanasia during surgery or recovered using assisted methods were excluded from the study. Perioperative variables included in analysis are given in Table 1.

Table 1. Perioperative variables recorded from the clinical records. MAC: minimum alveolar concentration, OEA: opioid epidural analgesia, GA: general anaesthesia, PIVA: partial intravenous anaesthesia.

|  |
| --- |
| **Pre-operative variables** |
| Age | Years |
| Breed | Cob or non-cob breed |
| Sex | Stallion, gelding or mare |
| Weight | Kilograms |
| ASA physical status classification | I to V (E for emergency) |
| Out-of-hours surgery | Yes or no |
| Time between hospital admission and induction of GA | Minutes |
| **Intra-operative variables** |
| Acepromazinea | Yes or no |
| Non-steroidal anti-inflammatory drug | Specific agent |
| Alpha-2-agonist | Specific agent |
| Opioid | Specific agent |
| Total opioid dose  | Total dose of opioids administered intravenously, epidurally and intra-articularly, expressed in mg/kg. |
| Induction agent | Specific agent |
| Co-induction agent | Specific agent |
| Volatile anaesthetic agent | Specific agent |
| MAC multiple | End-tidal anaesthetic agent was recorded at 5 minutes intervals during anaesthesia, all values were summed, divided by the number of observations, and divided by stated MAC for the agent used. |
| OEA administered | Yes or no; including agent(s) used and dose in mg/kg |
| Time from OEA administration to induction of GA | Minutes |
| Time from OEA administration to recovery from GA | Minutes |
| Peripheral nerve block | Yes or no; including agent(s) used and dose in mg/kg |
| Intra-articular injection of opioids and/or local anaesthetics | Yes or no; including agent(s) used and dose in mg/kg |
| Intra-operative administration of ketamineb | Total dose in mg/kg |
| Intra-operative administration of thiopentalc | Total dose in mg/kg |
| Intra-operative administration PIVA | Specific agent |
| Intra-operative administration of analgesic agents as a bolus(es) | Specific agent |
| **Post-operative variables** |
| Sedation for recovery | Yes or no |
| Quality of recovery score | Descriptive scale [23,24] (Table S1) |
| Number of attempts to stand |  |
| Recovery duration | Minutes |
| Surgery duration | Minutes |
| GA duration | Minutes |
| Morbidity/mortality | Yes or no |

Quality of recovery was evaluated using a descriptive scale, previously reported and correlated [23,24] with other composite scales [25] (Table S1). QR scores of 1 and 2 were defined as good recovery and QR scores higher than 2 were defined as poor recovery.

A post hoc power calculation determined that the sample obtained in this study had 100% power to detect, as significant at the 5% level, a clinically significant difference in QR (determined as a change in category from poor to good recovery quality score). The outcome variable was QR, a binary categorical variable, (with odds ratio [OR] >1 indicating greater odds of good QR and OR <1 indicating reduced odds of good QR).

Data analysis

Statistical analysis was performed using SPSS Statistic version 25 for Windowsd. Normality of data was evaluated using the Shapiro-Wilk test. All variables were screened for association with outcome (good QR) using a univariable logistic regression model for continuous and categorical variables with an alpha level of 0.05. For categorical variables, reference categories were attributed to the highest number of occurrences in such category, with the exception of the categorical variable OEA where the reference category was attributed to horses where OEA was not administered. Pearson’s rank correlation was used to establish signiﬁcance and strength of association between each of these variables and outcome. For highly correlated covariates only those with the smallest P-values were selected.

A backward stepwise elimination procedure was used to determine the final multivariable logistic regression model; covariates with univariable P-values <0.2 were incorporated, with retention of covariates with Wald P-values <0.05 at each step, in order to determine which explanatory variables would be included in the final model. The ﬁt of the ﬁnal multivariable model was assessed using the Hosmer–Lemeshow goodness-of-ﬁt test. Correlation of estimates were used to evaluate the strength of the linear relationship between variables and the outcome. Specificity and sensitivity (95% CI) were calculated via classification table using the predicted values produced by the ﬁnal multivariable model and the observed values (poor and good QR).

A formula was generated to predict the probability (P) of a good QR based on the ﬁnal multivariable model obtained:

$$P = \frac{e^{\left(β+α\_{1}\*X\_{1}+…α\_{n}\*X\_{n}\right)}}{1+e^{\left(β+α\_{1}\*X\_{1}+…α\_{n}\*X\_{n}\right)}}$$

Differences in continuous variables between OEA and non-OEA groups, as well as between good and poor QR groups, were analysed using two-tailed hypothesis tests. Where variables were normally distributed, an independent T-test was used, where data were not normally distributed, the Mann-Whitney U test was utilised. Results are reported as mean (± standard deviation) for normally distributed variables and median (interquartile range) for non-normally distributed ones. In all cases significance was assumed if P <0.05.

RESULTS

Case details

A total of 230 arthroscopic and tenoscopic surgeries, performed under GA, for management of hindlimb synovial sepsis were identified. Only 170 general anaesthetics (149 horses) fulfilled the study inclusion criteria. Of the 60 excluded general anaesthetics: 11 (4.8%; 95% CI 2.4 to 8.4%) were performed on horses euthanised during GA, two (0.87%; 95% CI 0.1 to 3.1%) were performed on horses under six months old, 29 (12.6%; 95% CI 8.6 to 17.6%) recoveries from GA used an assisted method, and 18 (7.8%; 95% CI 4.7 to 12.1%) anaesthetic records were incomplete, with recovery score not recorded (Figure 1). Twenty different breeds were identified, of which Thoroughbreds (30.6%; 95% CI 23.8 to 38.1%), Sport Horses (15.3%; 95% CI 10.2 to 21.6%), Cob breeds (14.7%; 95% CI 9.6 to 20.9%) and Warmbloods (13.5%; 95% CI 8.8 to 19.6%) were the most represented ones. When all breeds were analysed in a univariable logistic regression, only cob breeds were significantly associated with poor recovery scores (OR 3.4, 95% CI 1.2 to 9.6, P = 0.02), therefore, the data was reorganised in two categories (cob breeds and non-cob breeds). Median (IQR) age was 9 (9.75) years. Detailed demographic information is included as supplementary data (Table S2).

Epidural administration of opioids

All epidural procedures were performed in the preoperative period and technique success was based on positive hanging drop, lack of resistance to injection and/or loss of resistance during needle placement. OEA was performed in 84 horses (49.4%; 95% CI 41.7 to 57.2%), in 81 horses (47.6%; 95% CI 40.0 to 55.4%) OEA was not performed and in five cases (3.0%; 95% CI 0.96 to 6.7%) OEA was attempted but the procedure was unsuccessful. A combination of preservative free morphinee and methadonef was used in 69 cases (82.1%; 95% CI 72.3 to 89.7%), preservative free morphine alone in eight cases (9.5%; 95% CI 4.2 to 17.9%) and preservative free methadone alone in seven cases (8.3%; 95% CI 3.4 to 16.4%). Mean (± standard deviation) dose of opioid administered epidurally was 0.19 (± 0.04) mg/kg. Median time (IQR) from administration of OEA to induction of anaesthesia was 26.5 (16.5) minutes, median time (IQR) from administration of OEA to recovery from anaesthesia was 154 (38.8) minutes.

Total opioid dose (mean, ± standard deviation) administered was significantly different between OEA and non-OEA groups (OEA: 0.41 (± 0.08) mg/kg; non-OEA: 0.22 (± 0.07) mg/kg, P = 0.001). Minimum alveolar concentration (MAC) multiple (mean, ± standard deviation) of volatile anaesthetic agent was significantly different between groups (OEA: 0.89 (± 0.12) MAC; non-OEA 0.96 (± 0.13) MAC, P < 0.001). Median (IQR) number of attempts to stand was significantly lower in the OEA group than the non-OEA group (1.5 (1.0) and 2.0 (2.0) respectively; Mann–Whitney U = 2443.5, P = 0.03). Median (IQR) recovery duration was not different between groups (OEA 31 (22) minutes; non-OEA 35 (22) minutes; Mann–Whitney U = 3423, P = 0.6).

Recovery Quality

With 132 (77.6%; 95% CI 70.6 to 83.7%) anaesthetics QR was rated as good and 38 (22.4%; 95% CI 16.3 to 29.4%) anaesthetic recoveries were rated as poor. Details of the anaesthetic protocols used and recovery variables of both groups are presented as supporting information (Tables S3 and S4).

The results obtained from univariable logistic regression analysis, based on perioperative variables with an outcome of good QR, are presented as supporting information (Table S5). Total opioid dose (mean, ± standard deviation) administered was not significantly different between good and poor QR groups (good QR: 0.32 (± 0.12) mg/kg; poor QR: 0.29 (± 0.13) mg/kg, P = 0.23).

The final multivariable logistic regression model based on perioperative variables with an outcome of good QR is shown in Table 2. The Hosmer and Lemeshow test indicated no evidence of poor fit for the model (P = 0.9). Five variables were found significantly associated with QR: OEA, age, cob breed and intraoperative administration of ketamine and thiopental (as continuous variables, expressed in mg/kg). Our results show that the provision of OEA increases the odds of a good QR by three times when compared to patients not receiving OEA (OR 3.0, 95% CI 1.2 to 7.2, P = 0.02). For cob breeds, the odds of a good QR decrease by 84% when compared to non-cob breeds (OR 0.16, 95% CI 0.06 to 0.46, P = 0.001). As age increases by 1 year, the odds of a good QR decrease by 10% (OR 0.90, 95% CI 0.83 to 0.97, P = 0.004). For each 1 mg/kg increase in intraoperative administration of ketamine the odds of a good QR decrease by 58% (OR 0.42, 95% CI 0.18 to 0.98, P = 0.04). For each 1 mg/kg increase in intraoperative administration of thiopental the odds of a good QR decrease by 36% (OR 0.64, 95% CI 0.46 to 0.90, P = 0.01).

The model was able to correctly predict QR in 78.2% (95% CI 70.5% to 83.5%) of the cases with a sensitivity of 93.2% (95% CI 87.1% to 96.6%) and specificity of 26.3% (95% CI 14.0% to 43.4%). Based on the final model, predictive probabilities were calculated to examine the effects of OEA on quality of recovery in this subset of horses (Figure 2). A formula was generated to predict the probability (P) of a good QR (age displayed in years; cob breeds represented as 1 and non-cob breeds as 0; administration of OEA represented as 1 and no OEA administered as 0; intraoperative administration of thiopental in mg/kg; intraoperative administration of ketamine in mg/kg):

$$P = \frac{e^{\left(2.77+\left[-0.11\*\left(age\right)\right]+\left[-1.84\*\left(breed\right)\right]+\left[1.09\*\left(OEA\right)\right]+\left[-0.44\*\left(thiopental\right)\right]+\left[-0.87\*\left(ketamine\right)\right]\right)}}{1+e^{\left(2.77+\left[-0.11\*\left(age\right)\right]+\left[-1.84\*\left(breed\right)\right]+\left[1.09\*\left(OEA\right)\right]+\left[-0.44\*\left(thiopental\right)\right]+\left[-0.87\*\left(ketamine\right)\right]\right)}}$$

Our model was able to predict at what age OEA will have the strongest impact on QR. For cob breeds, from 4 to 14 years, performing OEA is associated with maintaining probability of a good QR above 50%. For non-cob breeds, from 20 to 30 years of age, OEA has a positive impact on QR by keeping the probability of a good QR above 50%. Also, for a patient with the average signalment of this subset of the population (9-year-old, non-cob breed), not receiving OEA, the intraoperative administration of a total dose of 4 mg/kg of thiopental or 2 mg/kg of ketamine will decrease the probability of a good QR to below 50%.

Table 2. Multivariable logistic regression model for perioperative factors associated with good quality of recovery following 170 arthroscopic or tenoscopic surgeries under general anaesthesia (in 149 horses) for management of hindlimb synovial sepsis performed at the University of Liverpool Philip Leverhulme Equine Hospital between January 2010 and December 2019.

|  |  |
| --- | --- |
|  | 95% C.I. for Odds Ratio |
| Outcome | Perioperative Variable | B value\* | P value | Odds Ratio | Lower | Upper |
| Good Quality of Recovery | Opioid Epidural Analgesia | Yes | 1.1 | 0.02 | 3.0 | 1.2 | 7.2 |
| No | Reference  |
| Breeds | Cob | -1.8 | 0.001 | 0.16 | 0.06 | 0.46 |
| Others | Reference  |
| Age (years) | -0.11 | 0.004 | 0.90 | 0.83 | 0.97 |
| Intraoperative Ketamine (mg/kg) | -0.87 | 0.04 | 0.42 | 0.18 | 0.98 |
| Intraoperative Thiopental (mg/kg) | -0.44 | 0.01 | 0.64 | 0.46 | 0.90 |
| Intercept | 2.8 | 0.000 | 16.00 |  |  |

\*B Value or beta coefficient is the degree of change in the outcome variable for every 1-unit of change in the predictor variable.

\*$ Multivariable logistic regression equation=2.77+\left[-0.11\*\left(age\right)\right]+\left[-1.84\*\left(breed\right)\right]+\left[1.09\*\left(OEA\right)\right]+\left[-0.44\*\left(thiopental\right)\right]+\left[-0.87\*\left(ketamine\right)\right]$

DISCUSSION

In our study population, OEA was associated with a better quality of recovery in horses undergoing general anaesthesia for surgical management of hindlimb synovial sepsis. Other risk factors, such as increasing age, cob-breed, use of higher intra-operative dosages of ketamine and/or thiopental, were associated with poor QR.

Therefore, the model predicts that a good QR score will be associated with providing OEA, in younger non-cob breeds, and using lower intraoperative dosages of thiopental and ketamine.

An improvement in QR, associated with OEA, has been reported for experimental ponies undergoing orthopaedic surgical procedures [15] whereas other authors have failed to show a significant improvement in recovery quality after OEA in a clinical setting [11]. The invasiveness of a surgical procedure is a risk factor that negatively influences QR, likely due to more invasive procedures being associated with greater post-operative pain. This may make horses less likely to rest quietly in the recovery box and attempt to rise earlier, making signs of ataxia more evident [24]. Evidence indicates that OEA significantly increased recovery duration in ponies [15] but our data showed no difference in recovery duration between OEA and non-OEA groups, although horses in the OEA group made fewer attempts to stand. From our findings we suggest that OEA provides additional effective and long-lasting analgesia, facilitating recovery in horses by reducing the number of attempts to stand, without increased recovery duration.

In the present study, opioids were administered via various routes, however there was no significant difference observed between total opioid dose with each route (combined systemically, intra-articularly and epidurally administered opioids in mg/kg) for the different QR groups. There was no effect of total opioid dose, intravenous (IV) and intra-articular routes or inclusion of peripheral nerve blocks (PNBs) in the final model relating to recovery quality. It is likely then that it is the route of administration of opioids providing a direct benefit in terms of QR in the population studied. Additionally, older horses may benefit more from analgesia provided by OEA, from our observations of a better QR in this particular subset of the population. Previous studies have reported variable associations between age and QR, ranging from no influence [24], to a suggestion of some influence [13]. However, in the latter study, age was not retained in the final multivariable logistic model produced, as it was highly associated with higher ASA physical status and colic surgery [13]. Older horses are more likely to display certain comorbidities such as osteoarthritis, osteopenia, sarcopenia and weakness related to Cushing’s disease [27–29], and may experience more difficulties in standing following surgery. OEA would also provide additional analgesia for other hindlimb orthopaedic co-morbidities not directly related to the surgery. This may explain why OEA showed a strong impact on QR but PNBs and intra-articular injection of opioids and/or local anaesthetics failed to do so. Hindlimb orthopaedic co-morbidities were not assessed in the present study, which represents a limitation when interpreting our findings.

In previous studies, breed has been associated with poorer recovery scores and shorter recovery duration [30–32]. Welsh cobs have been reported to be considerably more excitably and anxious than other types [33]. Other authors demonstrated that horses with higher subjective temperament scores, anaesthetised for MRI scans, displayed worse recoveries, suggesting that temperament may be an important factor associated with poor QR scores [34]. Similarly, certain temperaments have been associated with poor QR in human paediatric anaesthesia [33]. Preoperative anxiety is an important risk factor related to emergence delirium during recovery from anaesthesia in children [33]. It may be that certain breeds have a predisposition to more excitable temperaments. Temperament, however, was not assessed in this study, so we cannot state whether this is an individual animal phenomenon rather than an overall breed characteristic.

Our data show that QR is also influenced by total additional doses of ketamine and thiopental. In horses, administration of high doses of thiopental and ketamine may result in excitement and poor recovery quality [35,36]. These undesirable effects are attributed to the recovery from thiopental and ketamine depending on redistribution of the drug rather than elimination, as well as active metabolite formation in the case of ketamine [36–38].

Muscle tremor and rigidity, involuntary limb movements, excitation, and ataxia were observed during recovery from anaesthesia in horses receiving high doses of ketamine (6.6 mg/kg) [35]. This is partially due to formation and accumulation of the active metabolite norketamine, which displays a longer half-life than ketamine [37,39]. Our results support the observations of other authors, that additional IV doses of ketamine amounting to more than 2 mg/kg may have a detrimental impact on recovery [37].

In experimental and clinical studies evaluating the efficacy of different partial intravenous anaesthesia (PIVA) protocols, the total dose of thiopental administered intraoperatively was not correlated with a poor recovery [16,40–42]. In these studies, the total dose of thiopental administered averaged between 0.61-1.8 mg/kg which, considering our model, does not significantly impact QR.

Preservative free morphine and methadone was the most common opioid combination administered epidurally in our study population. When administered in the epidural space, morphine has a slower onset (up to six hours) but longer duration of action and methadone has a more rapid onset (15 minutes) but shorter duration of action [8–10]. These pharmacokinetic differences relate to the differences in lipid solubility between these drugs [8–10]. This combination therefore allows provision of efficacious analgesia during surgery as well as during recovery of anaesthesia and in the immediate post-operative period.

Horses with hind limb synovial sepsis were chosen as the study population in which to assess the influence of OEA on QR. These patients usually manifest a significant degree of lameness, therefore it is more likely that the analgesia provided by OEA will impact on QR. Experimental synovial sepsis models have been used to assess the efficacy of intra-articular and epidural opioid administration in horses [43–45]. Contamination of a synovial cavity causes a marked inflammatory response which produces up regulation of opioid receptors, evident lameness, pain and swelling of the affected structure [46,47].

Our clinical prediction model was not tested prospectively, or in different centres. Consequently, its performance under different conditions to those at the University of Liverpool Philip Leverhulme Equine Hospital is unknown, and its value must be interpreted with this caveat.

This study concludes that OEA significantly improves QR in horses undergoing GA for treatment of hindlimb synovial sepsis. OEA showed a superior impact in QR than PNBs, intra-articular administration of opioids and/or local anaesthetics and intravenous administration of opioids. Increasing age, cob breeds and high doses of thiopental and ketamine administered intraoperatively are significantly correlated with the likelihood of poor QR.

MANUFACTURERS’ ADDRESSES

a Vetoquinol UK Ltd, Towcester, Northamptonshire, United Kingdom

b Vetoquinol UK Ltd, Towcester, Northamptonshire, United Kingdom.

c Troy Laboratories Australia Pty Ltd, Glendenning, New South Wales, Australia

d IBM, Chicago, Illinois, United States of America

e Macarthys Laboratories Ltd, Romford, Essex, United Kingdom

f Macarthys Laboratories Ltd, Romford, Essex, United Kingdom

LIST OF FIGURE LEGENDS

Figure 1.Flow chart illustrating reasons for exclusion of anaesthetic records identified representing general anaesthesia events required for management of hindlimb synovial sepsis at the University of Liverpool Philip Leverhulme Equine Hospital between January 2010 and December 2019.

Figure 2. Influence of opioid epidural analgesia on recovery quality of 170 arthroscopic or tenoscopic surgeries under general anaesthesia (in 149 horses) for management for hindlimb synovial sepsis performed at the University of Liverpool Philip Leverhulme Equine Hospital between January 2010 and December 2019. Negative unstandardised beta weights correspond to older horses, cob breeds and higher intraoperative dosages of thiopental and ketamine. Positive unstandardised beta weights correspond to younger horses, non-cob breeds and lower intraoperative dosages of thiopental and ketamine (Table 2.). Note that, for the same unstandardised beta weight, the predictive probability for a good QR is higher for patients receiving OEA than for patients in the non-OEA group. The difference in predictive probability between OEA and non-OEA groups is higher for more negative unstandardised beta weights (older horses, cob breeds and higher intraoperative dosages of thiopental and ketamine).

LIST OF LEGENDS FOR SUPPLEMENTARY ITEMS

Table S1. Descriptive scale for evaluation of recovery quality in horses [23,24].

Table S2. Demographic variables of 170 arthroscopic or tenoscopic surgeries under general anaesthesia (in 149 horses) for management for hindlimb synovial sepsis performed at the University of Liverpool Philip Leverhulme Equine Hospital between January 2010 and December 2019. The data is divided into two groups according to the quality of recovery score (QR), poor QR and good QR. Differences in continuous variables between good and poor QR groups, were analysed using two-tailed hypothesis tests. For normally distributed variables, an independent T-test, with an alpha level of 0.05, was used to analyse the difference in means (± SD) of continuous variables between both groups (poor QR and good QR). For non-normally distributed data, a Mann-Whitney U test, with an alpha level of 0.05, was used to analyse the difference in median (IQR) of continuous variables between both groups (poor QR and good QR). Data are presented as mean (standard deviation (SD)) if normally distributed and as median (interquartile range (IQR)) if not normally distributed. For categorical variables an univariable regression analysis, with an alpha level of 0.05, was used to analyse the difference between groups (poor QR and good QR).

 Table S3. Recovery variables of 170 arthroscopic or tenoscopic surgeries under general anaesthesia (in 149 horses) for management for hindlimb synovial sepsis performed at the University of Liverpool Philip Leverhulme Equine Hospital between January 2010 and December 2019. The data is divided into two groups according to the quality of recovery score (QR), poor QR and good QR. Differences in continuous variables between good and poor QR groups, were analysed using two-tailed hypothesis tests. For normally distributed variables, an independent T-test, with an alpha level of 0.05, was used to analyse the difference in means (± SD) of continuous variables between both groups (poor QR and good QR). For non-normally distributed data, a Mann-Whitney U test, with an alpha level of 0.05, was used to analyse the difference in median (IQR) of continuous variables between both groups (poor QR and good QR). Data are presented as mean (standard deviation (SD)) if normally distributed and as median (interquartile range (IQR)) if not normally distributed. For categorical variables an univariable regression analysis, with an alpha level of 0.05, was used to analyse the difference between groups (poor QR and good QR).

Table S4. Anaesthetic variables of 149 horses undergoing 170 arthroscopic or tenoscopic surgeries under general anaesthesia for management for hindlimb synovial sepsis performed at the University of Liverpool Philip Leverhulme Equine Hospital between January 2010 and December 2019. The data is divided into two groups according to the quality of recovery score (QR), poor QR and good QR. Differences in continuous variables between good and poor QR groups, were analysed using two-tailed hypothesis tests. For normally distributed variables, an independent T-test, with an alpha level of 0.05, was used to analyse the difference in means (± SD) of continuous variables between both groups (poor QR and good QR). For non-normally distributed data, a Mann-Whitney U test, with an alpha level of 0.05, was used to analyse the difference in median (IQR) of continuous variables between both groups (poor QR and good QR). Data are presented as mean (standard deviation (SD)) if normally distributed and as median (interquartile range (IQR)) if not normally distributed. For categorical variables an univariable regression analysis, with an alpha level of 0.05, was used to analyse the difference between groups (poor QR and good QR). OEA: opioid epidural analgesia, NSAIDs: Non-steroidal anti-inflammatory drugs.

Table S5. Univariable logistic regression model for perioperative factors associated with good quality of recovery following 170 arthroscopic or tenoscopic surgeries under general anaesthesia (in 149 horses) for management of hindlimb synovial sepsis performed at the University of Liverpool Philip Leverhulme Equine Hospital between January 2010 and December 2019.

REFERENCES

1. O, O. and Smith, L.J. (2013) A comparison of epidural analgesia provided by bupivacaine alone, bupivacaine + morphine, or bupivacaine + dexmedetomidine for pelvic orthopedic surgery in dogs. *Vet. Anaesth. Analg.* **40**, 527–536.

2. Cerasoli, I., Tutunaru, A., Cenani, A., Ramirez, J., Detilleux, J., Balligand, M. and Sandersen, C. (2017) Comparison of clinical effects of epidural levobupivacaine morphine versus bupivacaine morphine in dogs undergoing elective pelvic limb surgery. *Vet. Anaesth. Analg.* **44**, 337–345.

3. Troncy, E., Junot, S., Keroack, S., Sammut, V., Pibarot, P., Genevois, J.P. and Cuvelliez, S. (2002) Results of preemptive epidural administration of morphine with or without bupivacaine in dogs and cats undergoing surgery: 265 Cases (1997-1999). *J. Am. Vet. Med. Assoc.* **221**, 666–672.

4. Golder, F.J., Pascoe, P.J., Bailey, C.S., Ilkiw, J.E. and Tripp, L.D. (1998) The effect of epidural morphine on the minimum alveolar concentration of isoflurane in cats. *Vet. Anaesth. Analg.* **25**, 52–56.

5. Campagnol, D., Teixeira-Neto, F.J., Peccinini, R.G., Oliveira, F.A., Alvaides, R.K. and Medeiros, L.Q. (2012) Comparison of the effects of epidural or intravenous methadone on the minimum alveolar concentration of isoflurane in dogs. *Vet. J.* **192**, 311–315.

6. Steagall, P.V.M., Simon, B.T., Teixeira Neto, F.J. and Luna, S.P.L. (2017) An update on drugs used for lumbosacral epidural anesthesia and analgesia in dogs. *Front. Vet. Sci.* **4**, 68.

7. Romano, M., Portela, D.A., Breghi, G. and Otero, P.E. (2016) Stress-related biomarkers in dogs administered regional anaesthesia or fentanyl for analgesia during stifle surgery. *Vet. Anaesth. Analg.* **43**, 44–54.

8. Olbrich, V.H. and Mosing, M. (2003) A comparison of the analgesic effects of caudal epidural methadone and lidocaine in the horse. *Vet. Anaesth. Analg.* **30**, 156–164.

9. Natalini, C.C. and Robinson, E.P. (2000) Evaluation of the analgesic effects of epidurally administered morphine, alfentanil, butorphanol, tramadol, and U50488H in horses. *Am. J. Vet. Res.* **61**, 1579–1586.

10. Goodrich, L.R., Nixon, A.J., Fubini, S.L., Ducharme, N.G., Fortier, L.A., Warnick, L.D. and Ludders, J.W. (2002) Epidural morphine and detomidine decreases postoperative hindlimb lameness in horses after bilateral stifle arthroscopy. *Vet. Surg.* **31**, 232–239.

11. Martin-Flores, M., Campoy, L., Kinsley, M.A., Mohammed, H.O., Gleed, R.D. and Cheetham, J. (2014) Analgesic and gastrointestinal effects of epidural morphine in horses after laparoscopic cryptorchidectomy under general anesthesia. *Vet. Anaesth. Analg.* **41**, 430–437.

12. Johnston, G.M., Eastment, J.K., Wood, J.L.N. and Taylor, P.M. (2002) The confidential enquiry into perioperative equine fatalities (CEPEF): Mortality results of Phases 1 and 2. *Vet. Anaesth. Analg.* **29**, 159–170.

13. Dugdale, A.H., Obhrai, J. and Cripps, P.J. (2016) Twenty years later: A single-centre, repeat retrospective analysis of equine perioperative mortality and investigation of recovery quality. *Vet. Anaesth. Analg.* **43**, 171–178.

14. Doherty, T.J., Geiser, D.R. and Rohrbach, B.W. (1997) Effect of high volume epidural morphine, ketamine and butorphanol on halothane minimum alveolar concentration in ponies. *Equine Vet. J.* **29**, 370–373.

15. Natalini, C.C., Crosignani, N. and Polidoro, A. da S. (2007) Comparative evaluation of the effects of epidural morphine and 0.9% sodium chloride on cardiorespiratory function and anesthetic recovery in ponies. *Acta Sci. Vet.* **35**, 315–320.

16. Love, E.J., Geoffrey Lane, J. and Murison, P.J. (2006) Morphine administration in horses anaesthetized for upper respiratory tract surgery. *Vet. Anaesth. Analg.* **33**, 179–188.

17. Mircica, E., Clutton, R.E., Kyles, K.W. and Blissitt, K.J. (2003) Problems associated with perioperative morphine in horses: a retrospective case analysis. *Vet. Anaesth. Analg.* **30**, 147–155.

18. Clark, L., Clutton, R.E., Blissitt, K.J. and Chase-Topping, M.E. (2008) The effects of morphine on the recovery of horses from halothane anaesthesia. *Vet. Anaesth. Analg.* **35**, 22–29.

19. Steffey, E.P., Eisele, J.H. and Baggot, J.D. (2003) Interactions of morphine and isoflurane in horses. *Am. J. Vet. Res.* **64**, 166–175.

20. Love, E.J., Geoffrey Lane, J. and Murison, P.J. (2006) Morphine administration in horses anaesthetized for upper respiratory tract surgery. *Vet. Anaesth. Analg.* **33**, 179–188.

21. Gozalo-Marcilla, M., Hopster, K., Gasthuys, F., Krajewski, A.E., Schwarz, A. and Schauvliege, S. (2014) Minimum end-tidal sevoflurane concentration necessary to prevent movement during a constant rate infusion of morphine, or morphine plus dexmedetomidine in ponies. *Vet. Anaesth. Analg.* **41**, 212–219.

22. Clark, L., Clutton, R.E., Blissitt, K.J. and Chase-Topping, M.E. (2005) Effects of peri-operative morphine administration during halothane anaesthesia in horses. *Vet. Anaesth. Analg.* **32**, 10–15.

23. Scarabelli, S. and Rioja, E. (2018) Retrospective evaluation of correlation and agreement between two recovery scoring systems in horses. *Vet. Rec.* **182**, 169.

24. Young, S.S. and Taylor, P.M. (1993) Factors influencing the outcome of equine anaesthesia: a review of 1,314 cases. *Equine Vet. J.* **25**, 147–151.

25. Donaldson, L.L., Dunlop, G.S., Holland, M.S. and Burton, B.A. (2000) The Recovery of Horses From Inhalant Anesthesia: A Comparison of Halothane and Isoflurane. *Vet. Surg.* **29**, 92–101.

26. Natalini, C.C., Crosignani, N. and Polidoro, A. da S. (2007) Comparative evaluation of the effects of epidural morphine and 0.9% sodium chloride on cardiorespiratory function and anesthetic recovery in ponies. *Acta Sci. Vet.* **35**, 315–320.

27. Matthews, N.S. (2002) Anesthetic considerations of the older equine. *Vet. Clin. North Am. - Equine Pract.* **18**, 403–409.

28. Fürst, A., Meier, D., Michel, S., Schmidlin, A., Held, L. and Laib, A. (2008) Effect of age on bone mineral density and micro architecture in the radius and tibia of horses: An Xtreme computed tomographic study. *BMC Vet. Res.* **4**, 1–12.

29. Aleman, M., Watson, J.L., Williams, D.C., LeCouteur, R.A., Nieto, J.E. and Shelton, G.D. (2006) Myopathy in horses with pituitary pars intermedia dysfunction (Cushing’s disease). *Neuromuscul. Disord.* **16**, 737–744.

30. Niimura Del Barrio, M.C., David, F., Hughes, J.M.L., Clifford, D., Wilderjans, H. and Bennett, R. (2018) A retrospective report (2003-2013) of the complications associated with the use of a one-man (head and tail) rope recovery system in horses following general anaesthesia. *Ir. Vet. J.* **71**, 1–9.

31. Woodhouse, K.J., Brosnan, R.J., Nguyen, K.Q., Moniz, G.W. and Galuppo, L.D. (2013) Effects of postanesthetic sedation with romifidine or xylazine on quality of recovery from isoflurane anesthesia in horses. *J. Am. Vet. Med. Assoc.* **242**, 533–539.

32. Voulgaris, D.A. and Hofmeister, E.H. (2009) Multivariate analysis of factors associated with post-anesthetic times to standing in isoflurane-anesthetized horses: 381 cases. *Vet. Anaesth. Analg.* **36**, 414–420.

33. Lloyd, A.S., Martin, J.E., Bornett-Gauci, H.L.I. and Wilkinson, R.G. (2008) Horse personality: Variation between breeds. *Appl. Anim. Behav. Sci.* **112**, 369–383.

34. Leece, E.A., Corletto, F. and Brearley, J.C. (2008) A comparison of recovery times and characteristics with sevoflurane and isoflurane anaesthesia in horses undergoing magnetic resonance imaging. *Vet. Anaesth. Analg.* **35**, 383–391.

35. Muir, W.W., Skarda, R.T. and Milne, D.W. (1977) Evaluation of Xylazine and ketamine hydrochloride for anesthesia in horses. *Am. J. Vet. Res.* **38**, 195–201.

36. Taylor, P.F. (1963) Thiopentone Anaesthesia in Horses. *Aust. Vet. J.* **39**, 356–357.

37. Waterman, A.E., Robertson, S.A. and Lane, J.G. (1987) Pharmacokinetics of intravenously administered ketamine in the horse. *Res. Vet. Sci.* **42**, 162–166.

38. Abass, B.T., Weaver, B.M.Q., Staddon, G.E. and Waterman, A.W. (1994) Pharmacokinetics of thiopentone in the horse. *J. Vet. Pharmacol. Ther.* **17**, 331–338.

39. Lankveld, D.P.K., Driessen, B., Soma, L.R., Moate, P.J., Rudy, J., Uboh, C.E., Dijk, P. Van and Hellebrekers, L.J. (2006) Pharmacodynamic effects and pharmacokinetic profile of a long-term continuous rate infusion of racemic ketamine in healthy conscious horses. *J. Vet. Pharmacol. Ther.* **29**, 477–488.

40. Ringer, S.K., Kalchofner, K., Boller, J., Fürst, A. and Bettschart-Wolfensberger, R. (2007) A clinical comparison of two anaesthetic protocols using lidocaine or medetomidine in horses. *Vet. Anaesth. Analg.* **34**, 257–268.

41. Enderle, A.K., Levionnois, O.L., Kuhn, M. and Schatzmann, U. (2008) Clinical evaluation of ketamine and lidocaine intravenous infusions to reduce isoflurane requirements in horses under general anaesthesia. *Vet. Anaesth. Analg.* **35**, 297–305.

42. Menzies, M.P.L., Ringer, S.K., Conrot, A., Theurillat, R., Kluge, K., Kutter, A.P., Jackson, M., Thormann, W. and Bettschart‐Wolfensberger, R. (2016) Cardiopulmonary effects and anaesthesia recovery quality in horses anaesthetized with isoflurane and low‐dose S‐ketamine or medetomidine infusions. *Vet. Anaesth. Analg.* **43**, 623–634.

43. Lindegaard, C., Thomsen, M.H., Larsen, S. and Andersen, P.H. (2010) Analgesic efficacy of intra-articular morphine in experimentally induced radiocarpal synovitis in horses. *Vet. Anaesth. Analg.* **37**, 171–185.

44. Sysel, A.M., Pleasant, R.S., Jacobson, J.D., Moll, H.D., Modransky, P.D., Warnick, L.D., Sponenberg, D.P. and Eyre, P. (1996) Efficacy of an epidural combination of morphine and detomidine in alleviating experimentally induced hindlimb lameness in horses. *Vet. Surg.* **25**, 511–518.

45. Loon, J.P.A.M. van, Grauw, J.C. de, Dierendonck, M. van, L’ami, J.J., Back, W. and Weeren, P.R. van (2010) Intra-articular opioid analgesia is effective in reducing pain and inflammation in an equine LPS induced synovitis model. *Equine Vet. J.* **42**, 412–419.

46. Tulamo, R. ‐M, Bramlage, L.R. and Gabel, A.A. (1989) Sequential clinical and synovial fluid changes associated with acute infectious arthritis in the horse. *Equine Vet. J.* **21**, 325–331.

47. Sheehy, J.G., Hellyer, P.W., Sammonds, G.E., Mama, K.R., Powers, B.E., Hendrickson, D.A. and Magnusson, K.R. (2001) Evaluation of opioid receptors in synovial membranes of horses. *Am. J. Vet. Res.* **62**, 1408–1412.