**TITLE PAGE**

1. **Title**

An analysis of risk factors for a fracture or luxation in recovery from general anaesthesia in horses: a single centre study.

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1. **Author Statement**

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1. **Ethical animal research and informed owner consent**

The study was approved by the University of Liverpool Veterinary Ethics Committee (RETH000689). Owners of all the horses involved in the study provided written informed consent.

**Abstract**

Catastrophic fractures or luxations (FoL) sustained during recovery from general anaesthesia are a significant cause of mortality during equine anaesthesia. There is a lack of evidence regarding potential risk factors for a FoL occurring in the immediate anaesthetic recovery period. A single centre, retrospective, case-matched study was performed to identify risk factors for sustaining a catastrophic FoL during recovery from general anaesthesia. Clinical data were obtained for horses which sustained a catastrophic FoL when recovering from general anaesthesia from January 2011- June 2020 in a single centre referral population. Multivariable logistical regression analysis was performed to identify risk factors which were significant in horses where a FoL occurred. Statistically significant risk factors in our population of horses of sustaining a FoL in recovery included intra-operative administration of intra-tracheal salbutamol, intra-operative administration of ketamine and increasing age. Further research in this area, particularly with regards to salbutamol administration, is required.

**Keywords:** anesthesia, recovery, mortality, fracture, luxation

**Abbreviation glossary**

|  |  |
| --- | --- |
| **Abbreviation** | **Meaning** |
| ASA | American Society of Anesthesiologists |
| FoL | Fracture or luxation |
| GA | General anaesthesia |
| GGE | Glyceryl Guaiacolate Ether |
| MAP | Mean arterial pressure |
| PaO2 | Arterial oxygen tension |
| PaCO2 | Arterial carbon dioxide tension |
| SV | Spontaneous ventilation |

1. **Introduction**

Equine anaesthesia carries significant risk of fatal outcomes, with a documented perioperative mortality rate of 0.12% - 1% in healthy horses[1,2,3,4]  with risk increasing up to 11.7% when horses undergoing colic surgery are considered[2,4,5]. Fractures or other orthopaedic catastrophes, such as joint luxations, can occur during the recovery period, and are an important cause of peri-anaesthetic mortality. The risk of fracture in recovery from anaesthesia in horses is estimated to be approximately 0.2%[2]. When luxations are also included alongside fractures, they account for 71% of all anaesthesia related mortality[1,2,6,7]. Generally it is considered that horses undergoing fracture repair under general anaesthesia are at higher risk of a fracture in the recovery period; however, many fractures are sustained in horses with no reported underlying musculo-skeletal pathology.

The potential risk factors for a catastrophic orthopaedic event during recovery from general anaesthesia in horses are complex, and the aim of this study was to attempt to identify potential risk factors in the horse population attending a referral institution for emergency and elective anaesthesia and surgery in a case-matched population.

1. **Materials and methods**

**2.1 Retrospective study design and case acquisition**

Ethics approval was sought and gained from the University of Liverpool Ethics Committee (RETH000689). Case records from the University of Liverpool Philip Leverhulme Equine Hospital, between 2011 and 2018, were retrospectively reviewed. The total number of general anaesthetics performed in the hospital during this time period was approximately 3200. FoL cases were identified by reviewing the hospital clinical audit records. FoL cases were included if they could be successfully matched to the nearest 6 anaesthetics by date, the 3 previous and the 3 subsequent cases, each of which had successfully recovered from anaesthesia. Cases matches also needed to fit 2 other criteria: the type of surgery the horse had undergone (exploratory laparotomy, soft tissue or orthopaedic, grouped into elective or synovial sepsis/ wound repair) and whether recovery was assisted or unassisted.

All data were collected from the animal’s original anaesthetic record and the case records on the hospital management software.

**2.2 Inclusion criteria**

To be included in the study, all horses had to have a complete anaesthetic record. The FoL cases had a FoL diagnosed by clinical examination, diagnostic imaging (radiography) or on post mortem examination. The case-matches were included if complete anaesthetic records were available. Some control cases were a control for two FoL cases, due to the type of surgery and close timeframe between these cases.

**2.3 Exclusion criteria**

One FoL case was excluded, a horse undergoing a hindlimb splint bone removal (Metatarsal (MT) IV) which sustained a catastrophic MT III fracture in recovery. It was considered that due to the likelihood of pre-existing bone pathology in the case, suitable case-matches undergoing similar surgery with similar pre-existing pathology could not be identified. Horses weighing less than 200kgs were excluded as case matches, as many were manually assisted in recovery, which may have influenced recovery outcome. Manual assistance during recovery was rarely recorded in cases until a change in record keeping in 2018.

**2.4 Data analysis**

Data were collected, stored and initially processed in a Microsoft Excel spreadsheet (v.2010) and imported into IBM SPSS 25 (IBM, United States) for coding and analysis. Variables collected are shown in Table 1. Binary outcome variables were coded by their presence (1) or absence (0). Continuous variables included age (years), bodyweight (kilograms), duration of surgery and anaesthesia (minutes), lowest PaO2 (mmHg) and lowest PaCO2 (mmHg). Normality of the continuous data was assessed using both the Kolmogorov-Smirnov and Shapiro-Wilks tests.

Univariate logistic regression was used to investigate the effects of variables on the risk of FoL. Odds ratios (OR) with 95% confidence intervals (CI) and a p-value of <0.25 were considered for inclusion in the multivariable model. Variables were assessed for correlation using Spearman's rank correlation coefficients. Where Spearman's rank correlation coefficient was >0.8 the most statistically significant or biologically plausible variable was selected. The goodness-of-fit of the final models were assessed using a manual, stepwise, backward selection Hosmer-Lemeshow test.

**Table 1:**

**Variables included in the univariable analysis**

|  |  |  |
| --- | --- | --- |
| **Variable** | **Categories** | **Notes** |
| Breed | multiple | N/a |
| Sex | mare, gelding, stallion | N/a |
| ASA grade  | 1 - 5 +/- E (emergency) | N/a |
| Recumbency | right lateral, left lateral, dorsal | N/a |
| Alpha 2 agonist premedication | xylazine, romifidine, detomidinemedetomidine | N/a |
| Opioid premedication | methadone, morphine | N/a |
| Non-steroidal anti-inflammatory drug | flunixin, phenylbutazone, meloxicam | N/a |
| Induction agent | ketamine, thiopentone | N/a |
| Muscle relaxant  | diazepam, midazolam, GGE | N/a |
| Maintenance agent | halothane, isoflurane, sevoflurane, TIVA, desflurane | N/a |
| Recovery sedation | xylazine, romifidine, detomidine, medetomidine | N/a |
| Most senior anaesthetist | clinician, resident | N/a |
| Age | years | Age at time of surgery |
| Weight | kgs | Weighed or estimated |
| Duration of anaesthesia | minutes | From induction until placed in recovery |
| Duration of surgery | minutes | From drapes on until drapes off |
| Lowest PaO2 | mmHg | On blood gas analysis |
| Highest PaCO2 | mmHg | On blood gas analysis |
| Out of hours induction | yes or no | 5pm to 8am |
| Locoregional technique performed (local anaesthesia or opioid) | yes or no | Included epidural, intra-synovial, perineural or splash |
| Spontaneous ventilation | yes or no | N/a |
| Acepromazine premedication | yes or no | N/a |
| Partial intravenous anaesthesia used  | yes or no | Included lidocaine, alpha-2 agonists, ketamine |
| Intra-operative bicarbonate administration | yes or no | N/a |
| Intra-operative potassium chloride administration | yes or no | N/a |
| Intra-operative thiopentone top-up | yes or no | N/a |
| Intra-operative ketamine top-up | yes or no | N/a |
| Intra-operative vasopressor/ inotrope administration | yes or no | Included dobutamine and phenylephrine |
| Intra-operative colloid administration | yes or no | Included starches or gelatins |
| Peri-operative 7.2% saline administration | yes or no | Either pre-induction or intra-operative |
| Intra-tracheal salbutamol administration | yes or no | N/a |
| Presence of hypoxaemia | yes or no | <60mmHg |
| Presence of hypercapnia | yes or no | >70mmHg  |
| Presence of hypotension | yes or no | MAP <60mmHg for 15 minutes |
| Broodmare status | yes or no | In-foal or lactating |

1. **Results**

**3.1 Case details**

A total of 113 anaesthetic records were collected for the study, including 18 FoL cases. One FoL case was not included due to the likelihood of pre-existing significant bone pathology being present and the inability to find suitable case matches for the type of surgery or suspected pre-existing pathology. An overview of the FoL cases included in the analysis is available in Table 2. Of the 17 FoL cases, 12 had undergone a laparotomy, with 11 of these cases due to colic and the other case for a caesarean section.

**Table 2:**

**Comparative data for horses who sustained a FoL in the recovery period.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case number** | **OOH GA (induction between 5pm – 8am)** | **Surgery type** | **Age (years)** | **ASA****grade** | **GA duration (minutes)** | **Intra-operative inhaled salbutamol****administration**  | **Assisted recovery** | **Type of FoL****sustained** |
| 1 | Y | Exploratory laparotomy | 18 | 2E | 185 | N | N | L carpal dislocation |
| 2 | N | Soft tissue surgery: melanoma resection | 14 | 2 | 90 | N | N | # L tibia |
| 3 | N | Exploratory laparotomy | 20 | 3E | 150 | Y | N | # L tibia |
| 4 | N | Arthroscopy | 21 | 2 | 135 | N | N | # R tibia |
| 5 | N | Exploratory laparotomy | 19 | 4E | 166 | N | N | # R tibia |
| 6 | N | Tenoscopy | 14 | 2 | 150 | N | N | # R tibia |
| 7 | Y | Caesarean section | 18 | 4E | 105 | N | N | # L tibia |
| 8 | N | Exploratory laparotomy | 9 | 4E | 175 | Y | N | # R tibia |
| 9 | N | Exploratory laparotomy | 12 | 3E | 165 | Y | N | # R tibia |
| 10 | Y | Exploratory laparotomy | 16 | 3E | 203 | Y | N | R carpal dislocation |
| 11 | Y | Exploratory laparotomy | 8 | 5E | 140 | Y | N | # R femur |
| 12 | N | Exploratory laparotomy | 13 | 3E | 112 | Y | N | # L tibia |
| 13 | N | Exploratory laparotomy | 9 | 3E | 130 | Y | N | # R tibia |
| 14 | N | Tenoscopy | 7 | 2 | 225 | N | N | # R radius/ ulna |
| 15 | N | Exploratory laparotomy | 21 | 4E | 90 | N | Y | # RH MT |
| 16 | N | Tenoscopy and wound debridement | 17 | 2 | 140 | N | N | # R olecranon-articular  |
| 17 | Y | Exploratory laparotomy | 23 | 4E | 250 | N | N | C3 # and subluxation |

**ASA 1: A normal healthy patient; ASA 2: A patient with mild systemic disease; ASA 3: A patient with severe systemic disease, ASA 4: A patient with severe systemic disease that is a constant threat to life; ASA 5: A moribund patient who is not expected to survive without surgery; Addition of “E”: emergency surgery (defined as when a delay in treatment of the patient would lead to a significant increase in the threat to life or body part) ASA Physical Classification System[8]. Y = yes, N = no, # = fracture.**

**3.2 Variables**

Categorical, continuous and binary variables investigated are presented in Table 1.

**3.3 Descriptive statistics – FoL cases and controls**

A summary of descriptive statistics in included in table 3. Horses included ranged from 1-33 years of age (mean 11.6 years +/-5.6 SD). Recorded weight ranged from 207 to 784kgs (mean 544.2kgs +/- 95.7 SD). Duration of anaesthesia ranged from 40-390 minutes (median 130 minutes, IQR 48). Geldings (60.2%), mares (38.1%) and stallions (1.7%) were included in the case selection. Out of hours induction (classified as after 5pm) occurred in 41 cases (36.3%). Dobutamine was used in 95 horses (84.1%) for blood pressure support. Sixty-nine horses (61.1%) received intra-operative ketamine administration for analgesia or a light plane of anaesthesia and 49 horses (43.4%) received intra-operative thiopentone due to light plane of anaesthesia. Controlled mechanical ventilation was undertaken in 101 cases (89.4%) cases whereas 12 horses (10.6%) spontaneously ventilated. The incidence of hypoxaemia, defined as a PaO2 of <60mmHg, was 16.8% (n = 19), although in 8.8% (n = 10) of cases, no blood gas analysis had been performed. Salbutamol was administered to 25 horses (22.1%), although the correlation between hypoxaemia and salbutamol administration was 0.607 using a Spearman test. Of the horses that received salbutamol, 7 were FoL cases and 18 were controls. Hypotension (defined as a MAP of <60mmHg, for 15 minutes) was present in 66 horses (58.4%). Breeds included Thoroughbred including crosses (n=25, 21.2%), Cobs (n= 21, 17.8%), Warmblood/ Friesian (n= 20, 16.9%), Sports horses (n=18, 15.3%), Welsh/ Fell/ Connemara (n=18, 15.3%), Draught breeds (n=6, 5.1%) and Arabians (n=3, 2.5%).

Anaesthetic protocols within the hospital vary and are reflected by the frequencies of drug use in different cases. Alpha-2 agonist premedication was administered in 110 cases (97.3%) with xylazine being the most commonly chosen alpha-2 agonist used, being administered in 70 cases (61.9%). Romifidine was administered as alpha-2 agonist premedication in 31 horses (26.3%), detomidine in 8 horses (6.8%) and medetomidine in 1 horse (0.8%).

 In 109/113 cases (96.5%) general anaesthesia was induced with ketamine combined with either benzodiazepine, with the remaining 3.5% of cases having anaesthesia induced with thiopentone. Maintenance of anaesthesia was with isoflurane (52.2%), sevoflurane (39.8%), halothane (6.2%), TIVA (0.9%) or desflurane (0.9%), with the volatile agents being administered in 100% oxygen.

Sedation for recovery was infrequently administered, where 97 horses were not sedated (82.2%) and of the horses who were sedated (n=16), 3 horses received xylazine, 10 horses received romifidine, and 3 horses received detomidine.

Table 3: Summary of descriptive statistics and comparison between controls and FoL cases

|  |  |  |
| --- | --- | --- |
| **Variable** | **Control cases****n = 96** | **FoL cases****n = 17** |
| **Age (mean)** | 11.0 (+/- 5.5 SD) | 15.2 (+/- 4.9 SD) |
| **Weight (mean)** | 639.67 (+/- 97.6 SD) | 569.9 (+/- 81.5 SD) |
| **Duration of anaesthesia (mean)** | 136.5 (+/- 48.8 SD) | 153.6 (+/- 44.8 SD) |
| **Duration of surgery (mean)** | 101.3 (+/-45 SD) | 116.2 (+/- 42 SD) |
| **OOH induction** | 36 | 5 |
| **Dobutamine administration** | 81 | 14 |
| **Intra-operative ketamine administration** | 55 | 14 |
| **Intra-operative thiopentone administration** | 39 | 10 |
| **Hypoxaemia** | 17 | 2 |
| **Intra-tracheal salbutamol administration** | 18 | 7 |
| **Alpha-2 agonist premedication** | 93 | 17 |
| **Ketamine and benzodiazepine induction** | 93 | 16 |
| **Ketamine and GGE induction** | 1 | 0 |
| **Thiopentone induction (alone)** | 1 | 1 |
| **Thiopentone and GGE induction** | 1 | 0 |
| **Recovery sedation administered** | 13 | 3 |
| Breed | **TB and TB x** | 19 | 6 |
| **Cobs** | 17 | 4 |
| **WB/ Friesian** | 17 | 3 |
| **Sports horse** | 17 | 1 |
| **Welsh / Fell/ Connemara** | 17 | 1 |
| **Draught breeds** | 4 | 2 |
| **Arabians** | 3 | 0 |
| **Broodmare/ pregnant/ lactating** | 0 | 2 |

Table 3: Breed: 2 control cases missing data, Hypoxaemia: 9 controls and 1 FoL no data as no blood gas analysis performed. All other data complete.

**3.4 Statistical outcome**

**3.4.1 Univariable logistic regression**

The results of univariable logistical regression are in Table 4.

**Table 4: Binomial logistical regression evaluating potential risk factors for a fatal FoL in horses recovering from general anaesthesia**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **OR** | **CI (95%)** | **p-value** |
| **Age at surgery** | 1.142 | 1.036-1.258 | 0.007 |
| **Weight** | 1.004 | 0.998-1.010 | 0.231 |
| **Anaesthesia duration** | 1.006 | 0.997-1.016 | 0.189 |
| **Surgery duration** | 1.006 | 0.996-1.017 | 0.217 |
| **Ketamine top-up** | 3.479 | 0.938-12.904 | 0.062 |
| **Thiopentone top-up** | 2.088 | 0.732-5.956 | 0.169 |
| **PaCO2** | 1.038 | 0.993-1.085 | 0.099 |
| **Hypercapnia** | 2.240 | 0.759-6.608 | 0.144 |
| **Potassium chloride administration** | 2.440 | 0.744-8.00 | 0.141 |
| **Salbutamol administration** | 3.033 | 1.016- 9.053 | 0.047 |

**3.4.2 Multivariable logistic regression**

The results of multivariable logistical regression are in Table 5.

The following were found to be significant risk factors in sustaining a FoL in the immediate recovery period: the administration of intra-tracheal salbutamol during GA (OR 5.187, p = 0.01), the use of additional boluses of ketamine administered during the GA (OR 4.548, p = 0.05) and increasing age of the horse at the time of GA and surgery (OR 1.198, p = 0.002) compared to the matched control group.

**Table 5: Multivariable logistical regression results evaluating potential risk factors for a fatal FoL in horses recovering from general anaesthesia**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **Category** | **OR** | **95% CI** | **p-value** |
| **Age at surgery (years)** | Continuous | 1.198 | 1.07- 1.34 | 0.002 |
| **Salbutamol administration** | Yes  | 5.187 | 1.43-18.73 | 0.012 |
| **Ketamine top-up** | Yes  | 4.548 | 1.00-20.70 | 0.050 |

1. **Discussion**

Reducing morbidity and mortality remains a primary aim of the equine anaesthetist. To the authors’ knowledge, this is the first published retrospective study to attempt to identify risk factors for FoL in equine anaesthesia. In this study, three risk factors for sustaining a FoL in the immediate recovery period were identified; the administration of intra-tracheal salbutamol during anaesthesia, the administration of further ketamine boluses during general anaesthesia and increasing age.

Case-matching was chosen as the study design to assist in eliminating obvious confounding factors, with cases and controls having similar distributions across factors such as American Society of Anesthesiologists (ASA) grades[8] and the type of surgery with likely similar nociceptive stimuli. In our hospital, we see a variety of horses with various conditions and perform an array of surgeries ranging from quick, less invasive procedures to lengthy, highly invasive procedures with considerable risk to the patient and case matching allowed us to explore patient-related risk factors rather than procedure-related risk factors. Recovery option availability have varied over the study data-collection period, and we felt matching cases in terms of recovery support provided removed bias towards case outcome, for example, we may recover cases considered high risk for a FoL in recovery with rope-assistance.

Recovery in all but one of the FoL cases was unassisted. Within the hospital, there are the options to perform free recoveries, rope-assisted recoveries and manual restraint / assistance during recoveries. However, over the data collection period these options have changed, and rope-assisted options have not always been available to all cases, due to reconfiguration of the rope-system for improvements and varying numbers of the four recovery boxes having a rope-system in place. There is individual preference for methods of recovering horses, and this will vary depending on case and anaesthetist factors. In our hospital, we will often elect to avoid rope recoveries in very young horses, those who are minimally handled or in horses we suspect will not tolerate rope-assistance. The evidence regarding the benefits of assisted versus non-assisted recoveries is contradictory[9,10,11,12]but recovery support may be an important variable in the risk of a FoL occurring in the immediate post-operative period. Further research in this area is required to help provide evidence of the benefits of assisted versus unassisted recovery techniques[13]

Anaesthetic protocols within the hospital are highly variable and both anaesthesia specialists and sufficiently experienced anaesthesia residents perform in and out-of-hours anaesthesia for elective and emergency surgeries. Due to resident and undergraduate training, different protocols ensure trainees are exposed to and become comfortable with a wide range of drugs and techniques. In a recent study, the majority of 373 respondents (79%) routinely sedate horses for the recovery period[9] with only 4% of respondents never administering sedation for recovery. Evidence regarding the use of sedation in an aim to improve recovery quality is complex, with some studies showing sedation improves recovery quality[14,15].The complexity arises when interpreting the relationship between recovery quality and risk of injury during this period as many recovery quality scales exist, mainly aiming at appraising aesthetic quality or number of attempts taken to stand. This recovery data is often not directly associated with outcome of recovery i.e. actual risk of catastrophic injury in this period.

This study identified increasing age as a risk factor for FoL in recovery from anaesthesia. Ageing has significant effects on all body systems, most notably the musculoskeletal, cardiovascular and nervous system, and will also influence the pharmacodynamics of commonly used anaesthetic drugs. Many older horses also have significant co-morbidities, such as pars pituitary intermedia dysfunction, with 21.2% of equidae over 15 years of age being affected[16]. Sarcopenia, the loss of skeletal muscle and lean body mass which occurs with ageing, has long been recognised in human patients and is now being recognised in veterinary species[17]. This may predispose patients to hypothermia and decreased muscle mass may compromise ability to stand post-recumbency. Osteoarthritis is common in the UK equine population with 13.9% of horses estimated as being affected [18] including 33% racehorses of 3 years of age and under[19]. Osteoarthritis may also make standing after periods of recumbency more challenging and many horses with chronic lameness or musculo-skeletal pain anecdotally do not spend as much time recumbent, and may struggle to stand after recumbency, although the evidence for this is in the literature is lacking. Osteoporosis, a disease characterised by a decrease in bone mineral density and deterioration of the microarchitecture of bone tissue, which can lead to bone fragility an increase the risk of pathological fractures[20], is a well-recognised and economically important disease which poses a significant health problem in people. There is little evidence regarding this condition in veterinary literature, as most evidence on bone strength refers to the equine athlete. We can extrapolate human evidence to suggest that horses, as well as other veterinary species, may be affected by this condition, especially in older age. In humans, there is a steep increase in fracture incidence with age, and the frequency of osteoporosis is 52% in women over 80 years of age[20]. In one of the FoL cases, the fall which led to the fracture was subjectively not a high impact or high stress fall. This may suggest that a reduction in normal bone architecture was present, although a full post-mortem examination was not performed to confirm this. Other studies have also shown a relationship between increasing age and increasing risk associated with equine anaesthesia[2,3,4], although further studies in investigation this risk factor would be useful.

Hypoxaemia in horses undergoing general anaesthesia is common and can be problematic, although the incidence of hypoxaemia is rarely documented. In horses anaesthetised for exploratory laparotomy, the reported incidence of hypoxaemia (PaO2 under 80mmHg (10.7kPa)) has been reported at 13%[21]. Evidence that hypoxaemia, defined as PaO2 of <60mmHg (8.0kPa)[22], is detrimental to the outcome of horses undergoing anaesthesia is lacking, although the physiological effects have been well described[23] and there is evidence in people which shows that hypoxaemia is detrimental to normal myocardial function[24]. Hypoxaemia is challenging to treat, and in horses, methods of improving PaO2 include increasing the fraction of inspired oxygen, ventilation strategies, drug therapy and the use of inhaled nitric oxide[25], although the administration of nitric oxide is seldom performed in clinical practice[26]. Salbutamol, a short-acting β2-adrenergic agonist, administered via a pressurised metered dose inhaler (pMDI) via the endotracheal tube, has been described in the literature as helpful to treat hypoxaemia in horses under general anaesthesia[27,28,29]. Outcomes of treatment vary, and although it can increase PaO2[17,18] hypotension and tachycardia have also been described after is use[28]. It is hypothesised that salbutamol’s actions include improving pulmonary perfusion, due to its β2 effects on the pulmonary vasculature, rather than the direct effects on ventilation, which include bronchodilation[30]. The dose of salbutamol administered to horses to treat hypoxaemia under general anaesthesia is generally considered to be 2mcg/kg, and most pMDI’s administer 100mcg per actuation. Dosages administered in our hospital are often approximate, and not accurate, as violently painful colic patients are not always accurately weighed and instead undergo visual weight estimation. No horses were recorded as having signs of salbutamol overdose, which include sweating, sinus tachycardia and muscle tremors[31]. Salbutamol was identified as a risk factor for sustaining a FoL in recovery, although hypoxaemia was not. This result might be explained in that enough hypoxaemia cases did not have a FoL to achieve statistical significance, but enough hypoxaemic horses who received intra-tracheal salbutamol did, which made salbutamol administration a statistically significant risk factor. Although the presence of hypoxaemia is a precursor to the use of intratracheal salbutamol, methods for treating hypoxaemia in the hospital will vary with different case management approaches. To the authors’ knowledge, there is no evidence regarding the effect of salbutamol administration on recovery from general anaesthesia in horses. Anecdotally, clenbuterol administration, another β2-adrenoceptor agonist, can be associated with sweating and excitement in the recovery period, often leading to poor recovery qualities (M. Senior personal communication) although there is no evidence of this in the literature. One study[32] showed horses which had received intravenous clenbuterol had significantly quicker recovery times compared to control horses; however, recovery quality was not recorded. The effects of salbutamol on recovery quality and outcome warrants further investigation. Skeletal muscle also contains β2 adrenoceptors, and stimulation of these results in alterations of intracellular calcium[33]. Most research into the skeletal muscle effects of clenbuterol administration is directed towards longer-term administration in veterinary species and in humans where it can increase lean muscle mass[34]. A recent study[5] identified an association between intratracheal salbutamol administration and the presence of hypokalaemia, although there was no association with hypokalaemia and increased mortality. There is no current evidence to suggest salbutamol administration at clinically useful doses affects normal muscle function and physiology, which could influence recovery from anaesthesia, although further research in this area would be useful.

Ketamine, a commonly used drug in equine anaesthesia is also an efficacious analgesic drug in sub-anaesthetic doses. Ketamine, in combination with a muscle relaxant, was the most commonly chosen induction agent in the cases. This is likely due to licensing, cost, familiarity with the drug and the analgesic effects which helps provide multimodal analgesia during surgery. Ketamine top-ups were also administered in 61.1% of the cases (n= 69). The main reasons for intra-anaesthetic use of ketamine is either to provide deepening of an inadequate plane of anaesthesia, or to provide analgesia where it is considered that the patient is reacting to nociceptive stimuli, or to pre-empt anticipated nociceptive stimuli. Accordingly, intra-anaesthetic use of ketamine may reflect a potentially undulating plane of anaesthesia, the presence of intra-operative nociceptive stimuli or pain perception in recovery all of which may negatively impact recovery quality. Ketamine can cause ataxia during recovery, particularly when it has been used as an infusion intra-operatively[35]. In horses which received additional intra-operative ketamine boluses, administration in the last 20 minutes of anaesthesia is often avoided in an attempt to minimise any negative impact on recovery quality. The time from last ketamine top-up until recovery was not investigated. Thiopentone is another agent which is used to deepen the plane of anaesthesia, although there is evidence showing it can lead to poorer quality recoveries[12]. Other options for providing additional analgesia intra-operatively include lidocaine, alpha-2 agonists and opioids. The effect of these agents on recovery is variable with studies demonstrating poorer recovery qualities in horses receiving intra-operative lidocaine infusions[36,37], potentially improved recovery qualities in horses receiving intra-operative alpha-2 agonists infusions[38,39]However, the cardiovascular effects of these drugs also needs consideration. For example, alpha-2 agonists decrease cardiac output and an increase in systemic vascular resistance which has the potential to reduce perfusion, especially in already compromised patients[40,41].

Increasing body weight has previously been reported to be statistically significant in other studies considering anaesthetic risk[1,42], however there was no statistical significance relating to the risk of FoL in this study. Lighter horses (<200kgs) were excluded from the study due to different recovery techniques, which could not be accounted for when case-matching was performed. Out of hours anaesthesia is a significant in the general risk of the peri anaesthetic period[2] but no statistical significance of out of hours anaesthesia on the risk of FoL was found in our analysis.

Multiparous or lactating broodmares (2/113 cases) were not shown to have an increased risk of FoL, but as these numbers were very low, it is an area which warrants further investigation. In one study[43] it was demonstrated that equine bone strength during gestation and lactation will change throughout these periods, depending on dietary calcium intake, with a decrease in bone strength most notably during the first 12 weeks of lactation.

Of the FoL cases identified, 12 had abdominal surgery (11 due to colic and 1 caesarean section), with the remaining 5 undergoing orthopaedic or other soft tissue surgery. We recognise that surgery type may also be a risk factor for sustaining a FoL during recovery from general anaesthesia, although it was not statistically analysed due to the study design (case-matching for the type of surgery the horse had undergone). This area warrants future investigation as it may influence recovery outcomes.

Limitations of this study include a small sample size in a population seen at one referral teaching centre in the UK and was limited by the number of FoL which occurred in the study timescale. This could mean that certain variables identified in the univariable analysis may have been underpowered. Previous literature has also identified other risk factors in the equine perioperative period which increase morbidity and mortality, due to multiple causes, such as higher ASA grade [2,3,4,7], anaesthetic duration [2,4], colic surgeries [4], orthopaedic surgeries [4] and seniority of the surgeon [4]. In our study, we were specifically looking at risk factors for sustaining a FoL in recovery, and this was one of the reasons that case-matching was used. All anaesthetics are performed by either specialist anaesthetists (ECVAA or ACVAA diplomats) or specialists in training, which may not reflect the anaesthetic experience of many people in private practice who perform anaesthesia on horses. Other limitations are those inherent to retrospective data collection. The use of retrospective records relies on the individual anaesthetist completing them accurately. Being a teaching hospital, undergraduate clinical rotation students are also involved in filling in records and the quality of their record keeping is variable. Some records had missing data, and the digital scan quality of some of the records was poor, but no cases were excluded and all records were still legible and interpreted by one person (AB), to try to maintain consistency in reading parameters from a chart.

**Conclusion**

In conclusion, equine anaesthesia is still not without risk. Further evidence is required and would be beneficial with the aim of continuing to make equine anaesthesia as safe as possible. Age is an important factor when considering anaesthetic risk. The administration of intratracheal salbutamol can be beneficial in treating hypoxaemia, which itself can lead to challenges, although more evidence is required to help provide information on benefits and potential risks of salbutamol administration for the recovery period.

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**References**

[1]. Bidwell, L.A., Bramlage, L.R. and Rood, W.A. Equine perioperative fatalities associated with general anaesthesia at a private practice – a retrospective case series. Veterinary Anaesthesia and Analgesia. 2007; 34 (1): 23-30. <https://doi.org//10.1111/j.1467-2995.2005.00283.x>

[2]. Johnston, G.M., Eastment, J.K., Wood, J.L.N. and Taylor, P.M. The confidential enquiry into perioperative equine fatalities (CEPEF): Mortality results of Phases 1 and 2. Veterinary Anaesthesia and Analgesia. 2002; 29 (4): 159-70. <https://doi.org/10.1046/j.1467-2995.2002.00106.x>

[3] Dugdale, A.H.A., Obhrai, J., Cripps, P.J. Twenty years later: a single-centre, repeat retrospective analysis of equine perioperative mortality and investigation of recovery quality

Veterinary Anaesthesia and Analgesia. 2016; 43: 171-178. <https://doi.org/10.1111/vaa.12285>.

[4] Laurenza.C., Lea, A., Karine, P. Risk Factors of Anesthesia-Related Mortality and Morbidity in One Equine Hospital: A Retrospective Study on 1,161 Cases Undergoing Elective or Emergency Surgeries. Frontiers in Veterinary Science. 2020; 6. https://doi.org/10.3389/fvets.2019.00514

[5]. Adami, C., Westwood-Hearn, H., Bolt, D.M. and Monticelli, P. Prevalence of electrolyte Disturbances and Perianaesthetic Death Risk Factors in 120 Horses Undergoing Colic Surgery. Journal of Equine Veterinary Science 2020; 84. <https://doi.org/10.1016/j.jevs.2019.102843>

 [6]. Young, S.S. and Taylor, P.M. Factors influencing the outcome of equine anaesthesia: a review of 1,314 cases. Equine veterinary journal. 1993; 25 (2): 147-51. <https://doi.org/10.1111/j.2042-3306.1993.tb02926.x>

[7]. Dugdale, A.H.A. and Taylor, P.M. Equine anaesthesia-associated mortality: Where are we now? Veterinary Anaesthesia and Analgesia, 2016; 43 (3): 242-55. <https://doi.org/10.1111/vaa.12372>

[8]. ASA Physical Status Classification System. American Society of Anesthesiologists. [https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system. Accessed 10.8.2021](https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system.%20Accessed%2010.8.2021)

[9] de Miguel Garcia, C., Campoy, L. ,Parry, S., Miller, J.E., Martin-Flores, M. et al. Questionnaire on the process of recovering horses from general anesthesia and associated personnel injury in equine practice, Veterinary Anaesthesia and Analgesia. 2021; 48 (2): 223-9. <https://doi.org/10.1016/j.vaa.2020.12.005>

[10] Rüegg, M., Bettschart-Wolfensberger, R., Hartnack, S., Junge, H.K., Theiss, F. et al. Comparison of non-assisted versus head and tail rope assisted recovery after emergency abdominal surgery in horses. Pferdeheilkunde. 2016; 32: 469-78.

[11] Arndt, S., Hopster, K., Sill, V., Rohn, K., Kästner, S.B.R. Comparison between head-tail-rope assisted and unassisted recoveries in healthy horses undergoing general anesthesia for elective surgeries. Veterinary Surgery. 2020; 49: 329– 38.

[12] Louro, L.F., Robson, K., Hughes, J., Loomes, K., Senior, M. Head and tail rope-assisted recovery improves quality of recovery from general anaesthesia in horses undergoing emergency exploratory laparotomy. Equine Veterinary Journal. 2021; 00: 1– 10. <https://doi.org/10.1111/evj.13516>

[13] Kästner, S.B.R. How to manage recovery from anaesthesia in the horse- to assist or not to assist? Pferdeheilkunde. 2010; 26: 604-8.

[14] Woodhouse, K. J., Brosnan, R. J., Nguyen, K. Q., Moniz, G. W., Galuppo, L. D. Effects of postanesthetic sedation with romifidine or xylazine on quality of recovery from isoflurane anesthesia in horses, Journal of the American Veterinary Medical Association. 2013; 242 (4): 533-9. https://doi.org/[10.2460/javma.242.4.533](https://doi.org/10.2460/javma.242.4.533)

[15] Santos, M., Fuente, M., Garcia-Iturralde, P., Herran, R., Lopez-Sanroman, J. et al. Effects of alpha-2 adrenoceptor agonists during recovery from isoflurane anaesthesia in horses. Equine Veterinary Journal, 2013; 35: 170-5. https://doi.org/[10.2746/042516403776114117](https://doi.org/10.2746/042516403776114117)

[16]. Ireland, J.L and McGowan, C.M. Epidemiology of pituitary pars intermedia dysfunction: A systematic literature review of clinical presentation, disease prevalence and risk factors. The Veterinary Journal. 2018; 235: 22-33. <https://doi.org/10.1111/j.2042-3306.2012.00578.x>

[17]. Seddighi, R. and Doherty, T.J. Anesthesia of the geriatric equine. Veterinary Medicine: Research and Reports. 2012; 3: 53-64. [https://doi.org/10.2147/VMRR.S34162](https://dx.doi.org/10.2147/VMRR.S34162)

[18]. Ireland, J. L., Wylie, C. E., Collins, S. N., Verheyen, K.L.P. and Newton, J.R. **Preventative health care and owner-reported disease prevalence of horses and ponies in Great Britain.**Res Vet Sci.  2013; **95**(2): 418-24*.* https://doi.org/10.1016/j.rvsc.2013.05.00

[19]. Neundorf, R.H., Lowerison, M.B., Cruz, A.M., Thomason, J.J., McEwen, B.J. and Hurtig, M.B. Determination of the prevalence and severity of metacarpophalangeal joint osteoarthritis in Thoroughbred racehorses via quantitative macroscopic evaluation. American Journal of Veterinary Research. 2010; 71 (11): 1284-93. https://doi.org/[10.2460/ajvr.71.11.1284](http://doi.org/10.2460/ajvr.71.11.1284)

[20]. Christodoulou, C. and Cooper, C. What is osteoporosis? Postgrad Med J. 2003; 79: 133-8. <https://doi.org/10.1136/pmj.79.929.133>

[21]. Pascoe, P.J., McDonell, W.N., Trim, C.M., Van Gorder, J. Mortality rates and associated factors in equine colic operations - a retrospective study of 341 operations. Can Vet J. 1983; 24 (3): 76-85.

[22]. Hubbell, J.A.E. and Muir, W.W. Oxygenation, oxygen delivery and anaesthesia. Equine Veterinary Journal. 2015; 47: 25-35. <https://doi.org/10.1111/evj.12258>

[23]. Steffey, E.P., Willits, N. & Woliner, M. Hemodynamic and respiratory responses to variable arterial partial pressure of oxygen in halothane-anesthetized horses during spontaneous and controlled ventilation. American Journal of Veterinary Research. 1992; 53: 1850–8.

[24]. Allen, D.G. and Orchard, C.H. Myocardial contractile function during ischaemia and hypoxia. Circulation Research 1987; 60 (2): 153-68.

[25]. Wiklund, M., Kellgren, M., Wulcan, S., Grubb, T. and Nyman, G. Effects of pulsed inaled nitric oxide on arterial oxygenation during mechanical ventilation in anaesthetised horses undergoing elective arthroscopy or emergency colic surgery. Equine Veterinary Journal. 2020; 52: 76-82. <https://doi.org/10.1111/evj.13129>

[26]. Auckburally, A. and Nyman, G. Review of hypoxaemia in anaesthetised horses: predisposing factors, consequences and management. Vet Anaesthesia and Analgesia. 2017; 44 (3); 397-408. <https://doi.org/10.1016/j.vaa.2016.06.001>

[27]. Robertson, S.A. and Bailey, J.E. Aerosolized salbutamol (albuterol) improves PaO2 in hypoxaemic anaesthetized horses – a prospective clinical trial in 81 horses. Veterinary Anaesthesia and Analgesia. 2002; 29 (4); 212-8. <https://doi.org/10.1046/j.1467-2995.2002.00100.x>

[28]. Casoni, D., Spadavecchia, C. and Adami, C. Cardiovascular changes after administration of aerosolized salbutamol in horses: five cases. Acta Veterinaria Scandinavica. 2014; 56: 49.
<https://doi.org/10.1186/s13028-014-0049-z>

[29]. Patschova, M., Kabes, R. and Krisova, S. The effects of inhalation salbutamol administration on systemic and pulmonary haemodynamic, pulmonary mechanics and oxygen balance during general anaesthesia in the horse. Veterinarni Medicina. 2010; 55 (9): 445-56.

[30]. Bertin, F.R., Ivester, K.M. and Couëtil, L.L. Comparative efficacy of inhaled albuterol between two hand‐held delivery devices in horses with recurrent airway obstruction. Equine Veterinary Journal. 2011; 43: 393-8. <https://doi.org/10.1111/j.2042-3306.2010.00313.x>

[31]. Thompson, J.A., Mirza, M.H., Barker, S.A., Morgan, T.W., Bauer, R.W. and McConnico, R.S. Clenbuterol toxicosis in three Quarter Horse racehorses after administration of a compounded product. [Journal of the American Veterinary Medical Association](https://avmajournals.avma.org/loi/javma). 2011; 239, (6): 842-49. <https://doi.org/10.2460/javma.239.6.842>

[32]. Keegan, R.D., Gleed, R.D., Sanders, E.A., Seaman, G.C., Wertz, E.M. and Short, C.E. Treatment of Low Arterial Oxygen Tension in Anesthetised Horses with Clenbuterol. Veterinary Surgery. 1991; 20 (2): 145-52. <https://doi.org/10.1111/j.1532-950X.1991.tb00325.x>

[33]. Soppa, G.K.R., Smolenski, R.T., Latif, N., Yuen, A.H.Y., Mlik, A., Karbowska, J. et al. Effects of chronic administration of clenbuterol on function and metabolism of adult rat cardiac muscle. Am J Physiol Heart Circ Physiol 2005; 288 (3): 1468-76. [http://dx.doi.org/10.1152/ajpheart.00624.2004](https://doi.org/10.1152/ajpheart.00624.2004)

[34]. Thompson, J.A. Effects of clenbuterol on skeletal and cardiac muscle in horses. A Thesis. 2009. <https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.550.3964&rep=rep1&type=pdf>. Accessed 12.11.2020

[35]. Pöppel, N., Hopster, K., Geburek, F. and Kästner, S. Influence of ketamine or xylazine supplementation on isoflurane anaesthetized horses‐ a controlled clinical trial. Veterinary Anaesthesia and Analgesia, 2015; 42: 30-8. <https://doi.org/10.1111/vaa.12176>

[36] Ringer, S.K., Kalchofner, K., Boller, J. et al. A clinical comparison of two anaesthetic protocols using lidocaine or medetomidine in horses. Veterinary Anaesthesia and Analgesia. 2007; 34 (4): 257-68, <https://doi.org/10.1111/j.1467-2995.2006.00321.x>

[37] Valverde, A. Rickey, E., Sinclair, M. Rioja, E., Pedernera, J. et al. Comparison of cardiovascular function and quality of recovery in isoflurane-anaesthetised horses administered a constant rate infusion of lidocaine or lidocaine and medetomidine during elective surgery. Equine Veterinary Journal. 2010: 42; 192-9. <https://doi.org/10.1111/j.2042-3306.2010.00027.x>

[38] Risberg, A.I., Ranheim, B., Krontveit, R.I., Lervik, A., Haga, H.A. The cardiovascular status of isoflurane-anaesthetized horses with and without dexmedetomidine constant rate infusion evaluated at equivalent depths of anaesthesia. Veterinary Anaesthesia and Analgesia.2016; 43 (4): 412-23. <http://dx.doi.org/10.1111/vaa.12315>

[39] Simeonova, G.P., Dinev, D.N., Sleiman, M.U. Comparative Study on Sevoflurane Anesthesia Alone and Combined with Partial Intravenous Anesthesia using Dexmedetomidine in Healthy Horses. Pakistan Veterinary Journal. 2017; 37 (2), 155-9

[40] Gozalo-Marcilla, M., Gasthuys, F., Schauvliege, S. Partial intravenous anaesthesia in the horse: a review of intravenous agents used to supplement equine inhalation anaesthesia. Part 1: lidocaine and ketamine, Veterinary Anaesthesia and Analgesia. 2014; 41 (4): 335-45. <https://doi.org/10.1111/vaa.12179>

[41] Gozalo-Marcilla, M., Gasthuys, F., Schauvliege, S. Partial intravenous anaesthesia in the horse: a review of intravenous agents used to supplement equine inhalation anaesthesia. Part 2: opioids and alpha-2 adrenoceptor agonists, Veterinary Anaesthesia and Analgesia. 2015;

42 (1): 1-16, <https://doi.org/10.1111/vaa.12196>

[42]. Senior, J.M., Pinchbeck, G.L., Allister, R., Dugdale, A.H.A., Clark, L., Clutton, R.E. et al. Reported morbidities following 861 anaesthetics given at four equine hospitals. Veterinary Record. 2007; 160 (12): 407-8. <http://dx.doi.org/10.1136/vr.160.12.407>

[43]. Glade, M.J. Effects of gestation, lactation, and maternal calcium intake on mechanical strength of equine bone. Journal of the American College of Nutrition. 1993; 12 (4): 372-7. <https://doi.org/10.1111/j.1439-0396.2009.00946.x>

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