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EFFECTS OF LONG LASTING ANAESTHESIA AND EXPERIMENTAL ABDOMINAL SURGERY UPON SOME VITAL PARAMETERS IN HORSES

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Abstract

The aim of the experiment was to study changes in blood gases, electrolytes, acid-base and some coagulation parameters occurring during long lasting anaesthesia and strangulation obstruction of the small intestine in horses.
Five healthy ponies were used for that purpose. They were submitted to 9 hours isoflurane anaesthesia with CRI of dexmedetomidine and ketamine. Strangulation obstruction of the small intestine was performed for 6 hours for histomorphometric investigations and was restored with enteroanastomosis afterward. Arterial and venous blood samples were taken in three periods and investigated parameters were measured.
Instead of periodic IPPV oxygenation progressively decreased judged from lowered PaO_2 and saturation with time. Moreover, a respiratory acidosis developed at 3rd hour and went deep at 9th hour. With regard to coagulation system alterations affected only D-dimer. Increase in D-dimer values corresponded with elevation of blood lactate level.
Long lasting anaesthesia and abdominal surgery does not impaired significantly oxygenation and coagulation in healthy horses but could contribute to further worsening of already compromised functions in colic horses.

Key words: *blood gases, haemocoagulation, horses, isoflurane anaesthesia, strangulation obstruction.*

INTRODUCTION

An anaesthetic-related death has been reported to be 10 times higher in colic horses undergoing emergency abdominal surgery in comparison with healthy horses undergoing elective anaesthetic procedures (Johnston et al., 2002). Each of strangulation obstruction (McClure et al., 1979), general anaesthesia (Day et al., 1995) or abdominal surgery instigates respiratory and coagulation systems of horses. Colic horses enter anaesthesia with already compromised functions that could result in intensification of respiratory depression and coagulation disorders. We tested the combined effects of the intestinal damage, anaesthesia and surgery upon some parameters of respiration and coagulation.

The adaptive mechanisms against hypoxemia such as increases in ventilation, cardiac output, and contraction of the spleen are obtunded during inhalation anaesthesia in contrast to the awake horses (McDonell and Kerr, 2007). Moreover, oxygenation is disturbed in anaesthetized horses due to ventilation-perfusion mismatching within lung parenchyma because of compression and absorption atelectasis (Nyman et al., 1990). Dorsally recumbent horses are more prone to compression atelectasis than other species as they have long slope diaphragm (Nyman and Hedenstierna, 1989). These effects are enhanced in colic horses because of the pressure applied to the diaphragm by exaggerated abdominal organs.

Coagulopathies are common in horses with colic and have been associated with increased morbidity and mortality (Schaer and Epstein, 2009). According to the results of Imaz et al. (2002) all tested parameters of haemostatic profile such as PT, APPT, fibrinogen, AT III, FDP and platelet count changed with the severity of colic horses.

The aim of the experiment was to study changes in blood gases, electrolytes, acid-base and some coagulation parameters occurring during long lasting anaesthesia and strangulation obstruction of small intestine in horses.

MATERIALS AND METHODS

The study was approved by the Institutional Ethical Committee on Animal Experiments in Stara Zagora, Bulgaria. It was part of another research relating to histomorphometrical

changes in the intestine during strangulation obstruction. Five healthy ponies aged between 2 and 7 years, weighing 213.2 ± 71.2kg (mean ± SD) were donated for the experiment. Horses were allowed to adapt for a month and were fed and bred in one and the same conditions. Deworming was performed using mebendazole 7.5mg/kg PO (Telmin® paste, Janssen Animal Health, Belgium).

Animals were submitted to 9 hours anaesthesia using isoflurane and continuous rate infusion (CRI) of dexmedetomidine and ketamine. Meanwhile, 6 hours lasting strangulation obstruction was induced, biopsy tissue samples were taken in two-hour periods, whereupon an enteroectomy and enteroanastomose were performed.

Food but not water was withdrawn 12 hours before anaesthesia. Premedication was performed with xylazine hydrochloride (Alfasan International, Holland) 0.8mg/kg given IV 15 minutes before induction. Both jugular veins were cannulated with 14G venous catheters (Venocan plus®, Kruuse, Denmark). Induction was did with a mixture of diazepam (Sopharma, Bulgaria) 0.05mg/kg and ketamine hydrochloride (Anaket®, Richter Pharma, Austria) 2.2mg/kg IV. After tracheal intubation using silicone tube 20-22 OD (Cook, USA) horses were hoisted and placed on the padded surgical table in dorsal recumbence.

Anaesthesia was maintained with isoflurane (Aerane®, Baxter, Slovenia) in 100% oxygen given by Penlon Sigma Delta vaporizer mounted on large animal anaesthesia machine LDS 3000 equipped with mechanical ventilator DHV 1000 (Surgivet, USA). A continued rate infusion (CRI) of 1.75μg kg^{-1} h^{-1} dexmedetomidine (Dexdomitor®, Orion Pharma, Finland) plus ketamine 1mg kg^{-1} h^{-1} diluted in saline solution was applied using microinfusion pump WZ-50C6, All Pro, China). Ringer solution (Actavis, Bulgaria) was given at rate of 10ml kg^{-1} h^{-1} through the second venous jugular catheter. The required surgical anaesthetic depth was maintained by adjusting the vaporizer setting.

Left or right facial artery was used for arterial access by cannulating it with 22 G catheter (Venocan plus®, Kruuse, Denmark). Arterial blood samples were withdrawn in heparinized syringes immediately after catheter placement, 3 hours and 9 hours later for blood gases, electrolytes and acid-base status and lactate measurements. Repiratory/Blood gases VetStat® cassettes and VetStat® electrolyte and blood gas analyzer (IDEXX Laboratories, Inc., USA) were used for that purpose. Lactate levels were determined by colorimetric method using enzymatic Roche/Hitachi lactate reagent (Roche Diagnostica, Germany). The mean alveolar arterial oxygen gradient (P (A-a) O_2) was calculated for every period using the following equation:

P (A-a) O_2=PAO_2-PaO_2= (FiO_2 x (BP-PH_2O))-$PaCO_2$/RQ, where

BP means barometric pressure in the alveolus at see level and is equal to 760mmHg; PH_2O – water vapor pressure in alveolar air at 37°C is equal to 48mmHg; RQ – respiratory quotient assumed 0.8.

The arterial access was necessary also for invasive measurement of blood pressures.

Intensive monitoring of the animals was made in 5-minute intervals all the time by means of multi-parameter patient monitor PM-9000Vet (Mindray, China). The following main parameters were traced: heart rate (HR), respiratory rate (RR), saturation (Sat), one-waveform electrocardiography (ECG) using three lead wires placed in sternal-withers configuration, invasive systolic (SYS), mean (MEAN), and diastolic (DIA) blood pressures, capnography, inspired and expired concentrations of oxygen (FiO_2, EtO_2 respectively), carbon dioxide ($FiCO_2$, $EtCO_2$ respectively), and isoflurane (FiIso, EtIso respectively), minimal alveolar concentration (MAC) of isoflurane.

Horses were allowed to breathe spontaneously. If the arterial partial pressure of CO_2 ($PaCO_2$) increased above 60mmHg, the arterial partial pressure of O_2 (PaO_2) decreased bellow 100mmHg, or RR was lower than 4 breaths $minute^{-1}$ for more than 3 minutes, an intermittent positive pressure ventilation (IPPV) was applied. Tidal volume of 20ml kg^{-1}, peak inspiratory pressure (PIP) no more 30cm H_2O, RR 8 breaths $minute^{-1}$, and inspiratory time 2.5 seconds were set in assisted-controlled mode of respiration.

Mean arterial blood pressure was maintained above 60mmHg by speeding up the rate of Ringer solution or by infusion of dopamine

hydrochloride (Warsaw Pharmaceutical Works, Polfa SA, Poland) at rate of 0.5-1 μg kg^{-1} min^{-1}. Ventral abdominal wall was aseptically prepared and covered with surgical drapes. A 20 cm long ventral midline skin incision was followed by white line incision starting from the umbilical mark forward. Caudal jejunum was exteriorized and 2 meter long segment was isolated. Double ligatures from Polyglactin 910 (DemeCRYL®, USP1, Demeteck Corporation, USA) were placed on blood vessels going to it and obstruction of both ends of segment was made with the same absorbable but heavier sutures (Sutupak®, USP 2, Ethicon, Germany). Tissue biopsy samples were taken from intestine in 2-hour intervals for histomorphometrical investigations. After 6 hours of strangulation obstruction had passed damaged intestinal segment was removed, the two ends sutured with polydioxanone 2-0 (PDS®II, Ethicon, Germany) by one-layer Lembert continuous pattern and abdominal incision closed routinely using polydioxanone USP 2 (Suturak®, Ethicon, Germany).

Coagulation parameters fibrinogen, prothrombin time (PT), activated partial protrombin time (APPT), thrombin time (TT), and D-dimer were measured in blood samples taken in citrated tubes during three periods − before premedication, at the 3rd hour of anaesthesia and operation, and at the 9th hour. The first four parameters were measured by mean of coagulometer Amelung KC 1A, Germany and tests of Human Diagnostica, Germany. For D-dimer measurement latex-aglutination colorimetric method and test was used (Spinreact, Spain).

After the end of the procedure animals were allowed to recover in padded stall. A standard postoperative intensive therapy was performed on the next days.

Statistical analysis was performed by means of Statistica® 6-0 version computer program (StatSoft Inc. USA). Kolmogorov-Smirnov test was used to test the distribution of data. Mann-Whytney U test was used afterward to calculate the differences of respiratory, acid-base and coagulation parameters between the three investigated time periods. P-value < 0.05 was considered as statistically significant.

RESULTS AND DISCUSSIONS

Surgical plane of anaesthesia was keep with comparatively low concentrations of isoflurane (fig. 1). Vaporizer setting, EtIso and MAC were adjusted in narrow ranges of 1.23/0.96/1.8%; 0.98/0.84/1.16%; 0.92/0.78/1.04% respectively (mean/minimal/and maximal values) decreasing with time after the first hour.

The main clinical parameters were in acceptable limits (fig. 2 and 3) and unexpected life threatening events were not observed. All horses were administered dopamine for maintenance of adequate blood pressure. Not anyone of them developed whatever type of arrhythmia throughout anaesthesia and surgery.

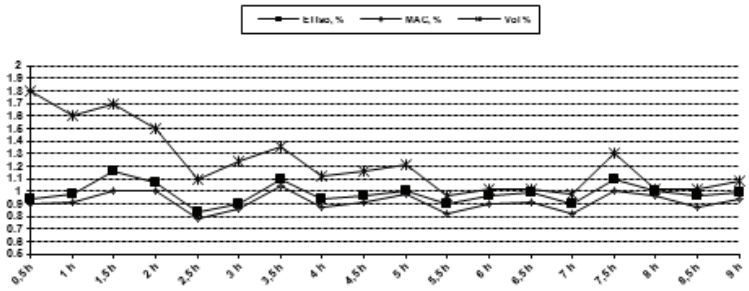

Figure 1. Changes in anaesthesiological parameters during anaesthesia and abdominal surgery in horses. EtIso − end tidal of isoflurane; MAC − minimal alveolar concentration; Vol%-volume percentage

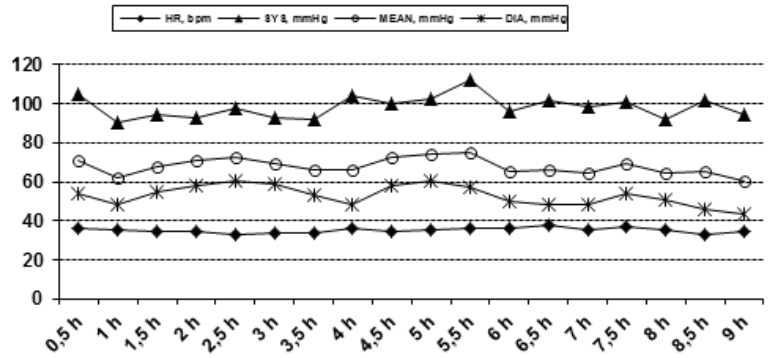

Figure 2. Changes in the main cardiovascular parameters during abdominal surgery under isoflurane anaesthesia. HR – heart rate; bpm – beat per minute; SYS – systolic blood pressure; MEAN – mean blood pressure; DIA – diastolic blood pressure

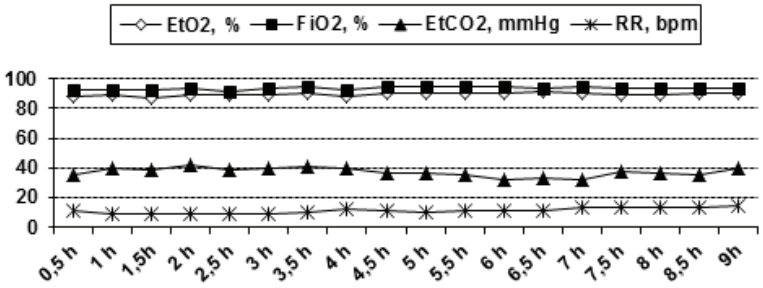

Figure 3. Changes in the main respiratory parameters during abdominal surgery under isoflurane anaesthesia. EtO2 – end tidal of oxygen; FiO2 – fraction of inspired oxygen; EtCO2 – end tidal of carbon dioxide; RR – respiratory rate; bpm-breath per minute;

Most of the time horses breathed spontaneously with IPPV applied periodically. Instead of periodic IPPV oxygenation progressively decreased with time judged from lowered PaO_2 and saturation (table 1).

Table 1. Changes in haemocoagulation parameters and blood lactate during experimental 6 hours lasting strangulation obstruction upon isoflurane anaesthesia in horses. Mann-Whitney nonparametric analysis was used to test the differences in parameters between investigated periods. Data are presented as mean ± standard deviation.

Parameter	n	0 hour	3rd hours	9th hour
pH	5	7.44 ± 0.05	7.33 ± 0.04 *	7.23 ± 0.09 *
$PaCO_2$, mmHg	5	43.2 ± 4.87	56.2 ± 9.52	65.2 ± 4.87 *
HCO_3, mmol/l	5	26.92 ± 1.94	27.46 ± 9.52	28.38 ± 5.04
Anion gap, mmol/l	5	12.0 ± 1.93	12.24 ± 1.3	9.9 ± 8.67
tCO_2, mmol/l	5	28.26 ± 1.99	29.2 ± 2.52	31.0 ± 6.85
BE, mmol/l	5	2.9 ± 2.19	0.5 ± 1.46	-1.2 ± 2.77 *
PaO_2, mmHg	5	195.4 ± 30.96	88.4 ± 27.19 *	90.6 ± 38.2 *
Hb, g/l	5	99.2 ± 29.88	115.0 ± 35.9	102.6 ± 24.71
Sat,%	5	99.2 ± 0.84	93.2 ± 5.36	88.2 ± 5.39 *
P (A-a) O_2, mmHg	5	419.88 ± 15.03	510.63 ± 29.4*	497.18 ± 20.25*
Sodium, mmol/l	5	140.4 ± 3.85	141.6 ± 8.41	141.6 ± 11.44
Potassium, mmol/l	5	4.58 ± 0.82	3.44 ± 0.51	4.0 ± 1.49
Clorides, mmol/l	5	106.2 ± 2.17	105.2 ± 7.46	108.0 ± 5.18

-$p < 0.05$ with regard to the "0 hour" period

* -$p < 0.05$ between "3rd hour" and "9th hour" periods

General anaesthesia using isoflurane was connected with high perioperative morbidity rate due to the high concentration of inhalation anaesthetics (Johnston et al., 1995) as well as to their dose-dependant cardiopulmonary depression (Steffey et al., 1980). Several methods had been tried to reduce the concentrations required for surgery since then. Partial intravenous anaesthesia (PIVA) combines volatile anaesthesia with continuous intravenously administration of analgesic and anaesthetic agents in low doses, with the aim of stabilizing physiological parameters.

Surgical anaestesia usually requires 1.2-1.4 times the MAC of inhalation agent. This means that for isoflurane EtIso commonly should be 1.6%. The addition of lidocaine by CRI to isoflurane anaesthesia in horses decreased the need for maintainance of surgical anaesthesia by 25% (Schunbeck et al., 2012).

When CRI of medetomidine, the forerunner of dexmedetomidine, was given to horses which were also receiving CRI of ketamin and lidocain a reduction the concentration of isoflurane necessary to maintain satisfactory anaesthesia for surgery was achieved, and reduced the dobutamine required to maintain mean arterial pressure (Kempchen et al., 2012). The reported values of EtIso (0.65%) were very similar to our results. We chose the newest alpha-2 agonist in our PIVA in order to decrease isoflurane requirements and to improve cardiopulmonary function, and to counteract to the pain.

The results of Pascoe et al. (2005; 2006) showed that dexmedetomidine infusions decrease the intra-operative requirements of isoflurane in dogs undergoing surgery in a dose dependant manner and low doses (0.5 μg kg^{-1} h^{-1}) appeared to have minimal effect on cardiopulmonary values, whereas the high doses (3 μg kg^{-1} h^{-1}) caused typical changes expected with an alpha-2 agonist.

Hubbell et al. (2011) observed atrial fibrillation in one of five horses submitted to 3 hours isoflurane anaesthesia without surgery but no changes in cardiovascular function was detected with the exception of blood pressure which had to be maintained with dobutamine. We did not find any arrhythmia in our experimental protocol but as in the before mentioned work we had to counteract to hypotension with dopamine infusion. The lack of arrhythmias could be explained with low concentrations of all used anaesthetics.

It is well known that volatile anaesthetics decrease ventilation dose-dependently suppressing directly the medullary and aortic and carotic body chemoreceptors' stimulation. In contrast, alpha-2 agonists are known to have the least effects on respiration in comparison to other sedatives. Intravenous administration of low dose dexmedetomidine did not alter arterial pH, PaO_2 and $PaCO_2$ in horses (Bettschart-Wolfensberger et al., 2005).

The same as our protocol of isoflurane anaesthesia but without CRI and surgery caused respiratory disturbances in both 50% and > 95% inspired oxygen (Hubbell et al., 2011). The reason for that was the increase of shunt fractions and alveolar dead space ventilation during 3 hours of anaesthesia. Our results showed development of hypoxemia and hypercarbia as was reported by many other investigators (Day et al., 1995; Kazuto, 2001). In contrast to previous report, IPPV did not ameliorate significantly oxygenation in our study. This may be due to the longer anaesthesia applied in our experiment, to the combined effects of anaesthesia and surgery, or because of the fact that improvement only occurs when PEEP values that compromise cardiac output are employed (Wettstein et al., 2006). Administration of 100% oxygen will usually improve hypoxemia in patients with ventilation-perfusion mismatch, but not in patients with significant right to left shunt (Muir and Morais, 2007). This might have been happened in our experimental animals as we calculated an elevation of A-a gradients with time provided animals inspired over 90% oxygen during the whole procedure.

Isoflurane anaesthesia without surgery resulted in increased venous lactate concentrations independent on inspired oxygen concentrations (Hubbell et al., 2011). In our study the increase lactate levels could be due not only to increased production during hypoxemia but also to decreased venous drainage causing an accumulation of produced lactate within the muscles during long lasting anaesthesia. Similar increased plasma lactate levels were

reported in isoflurane anaesthetized healthy horses which were much more pronounced during anaesthesia in colic horses (Edner et al., 2007). This finding implies that during anesthesia there is a demand for energy through anaerobic metabolism even in the healthy horse because of inadequate muscle oxygenation and metabolism.

Major surgery is associated with a hypercoagulable and proinflammatory state that persists into the postoperative period. Perioperative inflammatory responses to trauma can trigger hypercoagulability, especially in patients undergoing colic surgery.

Inflamation affects coagulation and fibrinolysis, and horses with inflammatory and ischemic disease are at risk of coagulopathies (Cesarini et al., 2010; Mendez-Angulo et al., 2010). Early stages of these diseases are characterized by hypercoagulability. Conventional coagulation testing supported the presence of hypercoagulation (decreased AT and increased D-Dimer concentrations), thrombelastography and coagulation abnormalities were rarely found in the same horses and the methods were not statistically related (Dunkel et al., 2010). Epstein et al. (2012) found out that the odds ratio of nonsurvival horses with gastrointestinal diseases and SIRS were 23.75 times higher if APTT was greater than 85.6 sec on the second day of admission.

Pablo et al. (1983) induced strangulation obstruction of distal jejunum just like in our experiment and found out that 6 hours, but not 2 or 4 hours, lasting strangulation resulted in severe ischemic damage to the intestines that was associated with significant coagulopathy consistent with disseminated intravascular coagulation (DIC). We did not observe notably prolonged clothing times and changes in fibrinogen levels but found out a significantly increase D-dimer concentrations with time that corresponded to the elevations in lactate levels.

In clinical studied horses with different types of colics, especially those with enteritis or peritonitis, was found significantly higher plasma D-Dimer concentrations and more severe coagulopathies on admission than in horses with other diagnoses (Cesarini et al., 2010). Moreover, a potential cut-off value for nonsurvival was found at approximately 4 ng/mL with odds ratio 8.8 for nonsurvival. D-dimer proved to be an early and more reliable parameter than FDP in predicting DIC development in colic horses (Stokol et al., 2005). Moreover, it turned out to have a predictive value for survival (Sandholm et al., 1995).

In the present study was tested if anaesthesia could contribute to coagulation disorders related to intestinal strangulation and surgery. Generally, anaesthesia alone was not reported to change coagulation parameters in healthy patients. Aydilek et al. (2007) studied the effects of xylazine-diazepam-ketamine, our induction anaesthetics, on the APTT, PT and platelet count in horses and did not find any significant alterations outside normal reference values. Several studies of the effects of inhalation anaesthetic agents on coagulation system reported that halothane (Kohro and Yamakage, 1996) and sevoflurane but not isoflurane had an inhibitory action on platelet function (Elrashidy et al., 2007). Dinev and Andonova found out increased concentrations of thromboxane B_2 between 1 and 2.5 hours of halothane anesthesia and during the corresponding stages of the surgical intervention which suggested that the anesthetic technique and surgery caused similarly a significant increase in thromboxane B_2.

CONCLUSIONS

Therefore, we could conclude that minor changes in coagulation during our experiment probably were due rather to the bowel ischemia and inflammation than to anaesthesia itself.

Finally, with regard to clinical relevance long lasting anaesthesia and abdominal surgery does not impaired significantly oxygenation and coagulation in healthy horses but could contribute to further worsening of already compromised functions in colic horses.

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