ACTA VET. BRNO 2024, 93: 145–157; https://doi.org/10.2754/avb202493020145

Comparison of two different doses of xylazine and ketamine versus medetomidine for partial intravenous anaesthesia in horses

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Received January 18, 2023
Accepted June 18, 2024

Abstract

Thirty horses were randomly divided into three groups and sedated with xylazine (1.1 mg/kg). General anaesthesia was induced with diazepam (0.03 mg/kg) and ketamine (2.5 mg/kg). Partial intravenous anaesthesia was maintained with isoflurane and constant rate infusion (CRI) consisting of xylazine 0.33 mg/kg/h and ketamine 1.5 mg/kg/h (X+K); or, higher dose of xylazine 1.2 mg/kg/h and ketamine 3.6 mg/kg/h (XX+KK); or, medetomidine 3.5 μg/kg/h (MED). Horses in each group breathed spontaneously. Heart rate, respiratory rate, peripheral oxygen saturation, palpebral and corneal reflexes, rescue doses with ketamine, invasive arterial blood pressure, inspired and expired gas compositions were measured. Anaesthesia, surgery, and recoveries were timed, and recovery was scored. The xylazine with ketamine groups showed a higher respiratory rate, a significant decrease in consumption of isoflurane, and a shorter time to standing in comparison with the medetomidine group. Recovery of the lowest quality was observed in group MED and a significantly improved recovery was observed in group X+K. The CRI consisting of xylazine with ketamine was shown to be a suitable alternative to CRI with medetomidine in horses undergoing arthroscopy.

Balanced equine anaesthesia, monitoring, elective surgery, recovery

Unlike inhalation anaesthetics, which are associated with the most serious side effects, injectable anaesthetics can better preserve cardiorespiratory functions (Luna et al. 1996; McMurphy et al. 2002). In equine anaesthesiology, it is essential to preserve cardiovascular functions, which ensure the perfusion of a large volume of muscle tissue and thus prevent possible fatal complications (Kälin et al. 2021). The correct use and combination of anaesthetics can reduce their negative effects. In addition to the cardiovascular benefits of partial intravenous anaesthesia (PIVA), there are possible benefits of injectable anaesthetics during the recovery phase; due to their sedative and analgesic effects, they may prevent untimed attempts to stand up and improve the quality of recovery (Valverde 2012). Aside from the fact that volatile agents can cause profound cardiovascular and respiratory depression, inhalation anaesthetics do not provide sufficient analgesia when used alone, and can therefore lead to postoperative hyperalgesia (Bettschart-Wolfensberger and Johnston 2012).

Constant rate infusion (CRI) was originally developed for standing sedation to help reduce the required minimum alveolar concentration (MAC) of inhalation anaesthetics (Valverde 2012). Doses of individual anaesthetics used in PIVA can be similar to those used for standing procedures, but are often lower than those used in total intravenous anaesthesia (TIVA) (Valverde 2012). The adjustment of the anaesthetic doses is based, among other factors, on the required length of anaesthesia, the expected degree of pain during the procedure, and also the anaesthesiologist's experience with the various drugs included in PIVA (Valverde 2012).

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Although PIVA preserves cardiovascular function, it has the potential to reduce the respiratory rate more than TIVA or inhalation anaesthesia alone. For that reason, in most studies describing PIVA techniques, mechanical ventilation is used; therefore, the effects of balanced anaesthesia (PIVA) on respiratory function are not well defined (Valverde 2012).

Because of their sedative and analgesic properties, α-2 agonists are part of most PIVA techniques. Alpha-2 agonists cause bradycardia, an initial increase followed by a decrease in blood pressure, an initial decrease in cardiac output, a decreased respiratory rate, and cause a transient decrease in peripheral oxygen saturation (Bettschart-Wolfensberger et al. 2005; Solano et al. 2009; Valverde 2010; Schauvliege et al. 2011). These side effects are potentiated by inhalational anaesthetics. However, lowering the MAC of inhaled anaesthetics with α-2 agonists results in similar or better cardiovascular function than when using inhalation anaesthesia alone (Valverde 2012).

It is reported that medetomidine (3.5–5 μg/kg/h) reduced the MAC of isoflurane by 28%, provided strong analgesia, and was associated with an increase in the quality of recovery (Bettschart-Wolfensberger et al. 2001; Neges et al. 2003; Doherty and Valverde 2006; Bettschart-Wolfensberger and Larenza 2007; Hubbell et al. 2010). Medetomidine is also one of the most used and well studied anaesthetics in balanced equine anaesthesia techniques.

Xylazine is generally a less commonly used anaesthetic for CRI during PIVA; however, like medetomidine, xylazine (0.5–1 mg/kg i.v.) has been reported to reduce the MAC of isoflurane by approximately 20% to 30% (Steffey et al. 2000; Bennet et al. 2004). Wiederkehr et al. (2021) published a study using 60 horses, which compared PIVA infusion of xylazine against medetomidine in combination with isoflurane. This study found that xylazine produced a 30% decrease in the use of dobutamine and recovery was faster with xylazine than with medetomidine.

Ketamine belongs to dissociative anaesthetics; it can induce analgesia, immobility, and loss of consciousness, without depression of cardiovascular functions, so it is an ideal candidate for balanced anaesthesia (Bettschart-Wolfensberger and Larenza 2007). Ketamine is the only drug used for balanced anaesthesia that might positively influence cardiovascular function (Bettschart-Wolfensberger and Larenza 2007). Ketamine can be used in anaesthetic or subanaesthetic doses; in subanaesthetic doses, it does not carry the side effects that are associated with anaesthetic doses, such as tonic spasticity, tremor, convulsions, etc. (Valverde 2012).

Although ketamine is associated with direct myocardial depression (S-ketamine, more so than R-ketamine), at clinical doses, either CRI or boli, ketamine is associated with better cardiovascular performance by increasing arterial blood pressure, cardiac output, and heart rate (Muir and Sams 1992; Bettschart-Wolfensberger and Larenza 2007).

The CRI of ketamine at low doses (0.4–1.5 mg/kg/h) is very well tolerated (Fielding et al. 2006; Lankveld et al. 2006; Larenza et al. 2009). The authors (NR, AP) have experience with analgesia in standing orthopaedic patients using 10 days of uninterrupted CRI analgesia with ketamine at a dose rate 0.8 mg/kg/h without adverse effects. In one study with TIVA, different doses of ketamine (5.4–9 mg/kg/h) were used in CRI in combination with xylazine (2.1–4.2 mg/kg/min). Prolonged (46–69 min) but improved recovery quality (4.4 –5 out of 5) was observed, compared to the group that received only CRI of ketamine (9 mg/kg/h). However, the ketamine group showed the shortest recovery time (33 min) compared to the xylazine + ketamine group, but slightly lower quality of recovery score (4.3 out of 5) (Mama et al. 2005; Valverde 2012).

Studies investigating the use of xylazine with ketamine as CRI in balanced anaesthesia techniques in equids are lacking. The purpose of our study was to evaluate and compare the cardiopulmonary effects and recovery in horses undergoing elective arthroscopy,

anaesthetized with isoflurane combined with two different regimes of xylazine plus ketamine or medetomidine.

Materials and Methods

Thirty client-owned horses were randomly divided into three groups consisting of 10 horses per group. The condition for inclusion in the study was the health status ASA (Physical Status American Society of Anesthesiologists) II and the need for elective arthroscopy.

All horses underwent cardiac auscultation, pulse measurement, and rectal temperature measurement prior to surgery. Every horse was fasted for 12 h prior to anaesthesia; water was not withheld. All horses were medicated with trimethoprim sulphate paste 30 mg/kg (Norodine Equine Paste 45 g; Norbrook Laboratories Limited, Monaghan, Ireland) p.o. and flunixin 1 mg/kg i.v. (Flunixin 50 mg/ml; Norbrook Laboratories Limited) 3 h before surgery. All anaesthetics were administered by the same anaesthesiologist.

One third of the initial dose of xylazine (1/3 of 1.1 mg/kg; Rometar 20 mg/ml; Bioveta, a.s., Ivanovice na Hane, Czech Republic) was applied i.v. to the horse in the stable, then the oral cavity was rinsed, the hooves were cleaned of dirt, and the horse was transported to the anaesthesia induction site. One jugular vein was shaved and aseptically prepared, subcutaneously infiltrated with lidocaine 2% (Lidocaine 2%; BIOPHARM, Jilove u Prahy, Czech Republic), a 14 gauge catheter (Equivet HiFlow catheter 14 × 3.5; Kruuse A/S, Denmark), and a three-way stopcock (Discofix C; Braun, Melsungen, Germany) was placed. Since young horses were often used in this study, in case the horse did not cooperate, the cannulation was performed in lateral recumbency immediately after the induction of general anaesthesia.

After cannulation, horses were sedated with the remaining 2/3 of xylazine. After 3 min, the quality of sedation was assessed by the main anaesthesiologist. Lowering of the head below the level of the withers, drooping eyelids, drooping lower lip, wide stance, penile prolapse in males and non-responsiveness to sound stimulus (fingers snapping) were indicative of effective sedation. The time from sedation to induction was recorded.

General anaesthesia was induced with diazepam 0.03 mg/kg i.v. (Apaurin 10 mg/2 ml; KRKA, d.d., Nove Mesto, Slovakia), immediately followed by ketamine 2.5 mg/kg i.v. (Ketamidor 100 mg/ml; Richter Pharma AG, Wels, Austria) in two separate syringes. Loss of the quadrupedal position was considered as t_0. Immediately after lying down, the horse was intubated in a lateral position with a silicone tracheal tube (22–26 mm, Kruuse A/S, Denmark) and hoisted to the surgical table. Promptly after placement in the desired position, the tracheal tube was connected to a closed circle system (Medical Developments Australia, Melbourne, Australia) with an anaesthesia monitor (Datex-Ohmeda S/5 Anesthesia Monitor system, GE Health Care Finland Oy, Helsinki, Finland). Lubricating ointment (Ophtalmo-azulen 1 × 5 g; Zentiva, k.s., Prague, Czech Republic) was applied into the conjunctival sacs, and gauzes were inserted into the external ear canals, in order to minimize acoustic irritation of the horse.

Isoflurane (Isoflurine 1000 mg/g; Vetpharma animal health, SL, Barcelona, Spain) was delivered from a vaporiser (Penlon Sigma Delta; Penlon, Abingdon, UK) in oxygen (> 95%) with a flow of 15 ml/kg. Spontaneous ventilation with the condition of at least two breaths per minute was performed with expired partial pressure of CO_2 tolerated up to 60 mmHg.

Intravenous CRIs were as follows; for the first group, xylazine 0.33 mg/kg/h with ketamine 1.5 mg/kg/h (X+K), for the second group, xylazine 1.2 mg/kg/h with ketamine 3.6 mg/kg/h (XX+KK), and for the third group, medetomidine 3.5 μg/kg/h (MED) (Cepetor 1 mg/ml; CP-Pharma Handelsges, Burgdorf, Germany). All horses were connected to the CRI immediately after being positioned on the surgical table, and CRI was administered using an infusion pump (Perfusor Compact S; Braun, Melsungen, Germany). At the same time an infusion of NaCl 0.9% was also started (B. Braun 0.9% NaCl 2000 ml; Braun, Melsungen, Germany) with a flow rate of 10 ml/kg/h. Horses were catheterized with urinary catheter, which was left in place utill the recovery phase. The amount of urine was not measured. For direct measurement of arterial blood pressure, a 22G catheter (Introcan Safety-Winged-PUR; Braun, Melsungen, Germany) was percutaneously inserted into the facial or transverse facial artery, immediately after the horse was connected to the inhalation circuit and CRI and fluid support infusion was started. The invasive arterial blood pressure monitoring system was zeroed at the level of the right atrium. The probe for peripheral oxygen saturation measurement was placed on the tongue.

Heart rate (HR), electrocardiography (ECG), respiratory rate (RR), peripheral oxygen saturation (SpO_2), mean arterial blood pressure (MAP), inspired concentration of isoflurane (FI-Iso), end-tidal concentration of isoflurane (Et-Iso), fraction of inspired oxygen (FI-O_2) and, end-tidal carbon dioxide concentration (Et-CO_2) were monitored continuously with a multiparameter monitor (GE Health Care Finland Oy, Helsinki, Finland) and recorded every 10 min into the patient's surgery protocol. The depth of anaesthesia was controlled continuously; if the anaesthesia was too superficial (rapid ocular reflexes, lacrimation, rapid spontaneous blinking, increased respiratory rate, nystagmus), the concentration of isoflurane was increased, and vice versa. If eye reflexes disappeared or there was a depression of breathing, the isoflurane concentration was reduced. In case of rapid nystagmus or movement, a bolus of 0.6 mg/kg ketamine i.v. was administered.

At the end of the surgery, the infusions and inhalation anaesthetic were stopped, the horses were hoisted from the table onto a trolley and then moved to the recovery box (located in the adjacent building). After termination

of anaesthesia, the first two groups (X+K, XX+KK) were given xylazine 0.25 mg/kg i.v. and the MED group was given medetomidine 2 μg/kg by i.v. injection. If, despite of the application of the α-2 agonist, the horse moved or showed rapid nystagmus, 0.15 mg/kg xylazine with 0.5 mg/kg ketamine mixed in one syringe was applied i.v., due to the prolonged transportation to the post-anaesthesia box and the need to ensure the safety of the staff and the horse. The time required for recovery was measured from the moment of the last prolongation of anaesthesia. The horse was placed in the recovery box in a lateral position, left or right depending on the operated limb or the location of the cannula. A tube with oxygen at a flow rate of 15 l/min was inserted into the endotracheal tube, or after extubation, into the nostril. Extubation was performed when the swallowing reflex reappeared. The horses were left in the box to stand spontaneously. Time needed for recovery, time spent in the sternal position, and quality of recovery (recovery score) were recorded. The recovery score was evaluated by the anaesthesiologist and two blinded observers experienced in equine medicine. For recovery quality assessment a 5-grade scoring system was used (Table 1), from 1 meaning 'excellent' to 5 meaning 'the poorest quality' recovery (Gozalo-Marcilla et al. 2013).

Table 1. Recovery score (Gozalo-Marcilla et al. 2013).

Score	Description of recovery
1	Very good, standing at the first attempt
2	Good, two attempts until standing
3	More than two attempts, horse remains calm, minimal ataxia when standing
4	Bad, several attempts to stand, horse becomes excited or in panic, risk of injury
5	Very bad, recovery resulting in injury of the horse

Statistical analysis

Statistical analysis was performed using one way ANOVA with Tukey's *post hoc* multiple comparisons test. All results presented in the Table 2 were tested by Kolmogorov-Smirnov, Sapiro-Wilk, D'Agostino and Pearson normality tests. All of the observed indices related to anesthesia were recorded at 10-min intervals (from t_{10} to t_{80}). All data were expressed as a mean ± SEM.

Results

No significant differences in age (X+K: 4.3 ± 0.62; XX+KK 6.3 ± 1.23; MED 5.3 ± 1.03 years; $P = 0.241$); body weight (X+K: 553.2 ± 29.30; XX+KK: 563.8 ± 16.54; MED: 540 ± 25.7 kg; $P = 0.765$), breed (different breeds of European warmblood, Haflinger [n = 1] in X+K; Thoroughbred [n = 1] in group XX+KK), BCS (X+K: 5 × 4/9, 5 × 5/9; XX+KK: 7 × 4/9, 1 × 3/9, 2 × 5/9; MED: 6 × 4/9, 4 × 5/9), sex (X+K: 3 stallions (st), 2 geldings (ge), 4 mares (ma); XX+KK: 2 st, 7 ge, 1 ma; MED: 6 ge, 4 ma), dorsal recumbency (X+K: n = 7; XX+KK: n = 7; MED: n = 7) or lateral recumbency (X+K: n = 1, XX+KK: n = 3; MED: n = 3) were observed in the total of 30 horses allocated into the three groups X+K, XX+KK, and MED. Two horses from group X+K and one from XX+KK were repositioned during the surgery, due to performing arthroscopy on different limbs. In the X+K and MED groups, four horses and in group XX+KK, three horses had more than one joint operated upon.

In all groups, sedation criteria were fulfilled, and no additive bolus of sedative was required. Induction of anaesthesia was performed 3 min after sedation in all patients.

In Table 2, the recorded measurements of RR, HR, MAP, SpO_2, $EtCO_2$, FI-Iso, Et-Iso in mean ± SEM for each group from time point t_{10} to t_{80} are shown.

Mean arterial pressure was within the target range (> 60 mmHg) in all groups, with no significant difference between groups. No inotropic substances were used.

The HR was within normal limits in all groups (26–40 beats/min), but significantly higher in group MED than in group XX+KK at time points t_{20}, t_{40} ($P < 0.05$) and

Table 2. Repeated evaluations in horses undergoing balanced isoflurane anaesthesia with different constant rate infusions.

Indicator	Group	Time point							
		t_{10}	t_{20}	t_{30}	t_{40}	t_{50}	t_{60}	t_{70}	t_{80}
	nX+K	10	10	10	9	7	5	5	4
	nXX+KK	10	10	10	10	9	8	8	6
	nMED	10	10	10	10	10	8	4	3
RR/min	X+K	6.90 ± 0.98	6.40 ± 1.18	6.00 ± 0.55*	5.55 ± 0.70	6.00 ± 0.69	6.40 ± 1.20	6.80 ± 0.96	6.25 ± 0.85
	XX+KK	4.60 ± 0.99	5.40 ± 0.40	4.80 ± 0.53	5.40 ± 0.61	5.11 ± 0.63	5.75 ± 0.94	4.87 ± 1.00	5.83 ± 1.22
	MED	4.30 ± 0.53	4.50 ± 0.60	3.50 ± 0.50*	4.40 ± 0.97	3.90 ± 0.48	3.62 ± 0.46	4.25 ± 0.94	4.66 ± 0.88
HR/min	X+K	31.1 ± 1.00	31.9 ± 1.11	31.6 ± 1.10	32.8 ± 1.14*	32.1 ± 1.05*	32.6 ± 2.04	33.0 ± 1.94	31.7 ± 2.09
	XX+KK	29.9 ± 0.88	29.0 ± 0.55*	29.8 ± 0.91	28.8 ± 0.69*€	28.3 ± 0.62*€	29.8 ± 0.54	30.5 ± 1.54	27.6 ± 0.33
	MED	32.2 ± 0.95	32.9 ± 0.84*	32.0 ± 1.15	32.2 ± 0.97€	32.6 ± 0.94€	33.1 ± 1.28	32.0 ± 2.04	32.0 ± 2.64
MAP (mmHg)	X+K	103.5 ± 6.97	99.99 ± 7.09	99.4 ± 6.87	100.3 ± 6.82	105.1 ± 6.46	108.2 ± 7.79	110.6 ± 5.66	106.6 ± 5.37
	XX+KK	101.9 ± 5.41	99.9 ± 5.58	101.1 ± 5.76	101.1 ± 6.43	105.3 ± 5.23	104.4 ± 4.21	105.3 ± 4.59	103.0 ± 4.96
	MED	99.5 ± 6.63	96.6 ± 6.18	91.8 ± 6.22	90.9 ± 5.88	90.6 ± 5.69	94.6 ± 6.12	107.5 ± 4.55	112.3 ± 6.48
SpO_2 (%)	X+K	97.2 ± 0.46	96.4 ± 0.40	96.4 ± 0.52	96.2 ± 0.49	95.0 ± 0.92*	97.2 ± 0.58	96.6 ± 0.60	96.0 ± 0.81
	XX+KK	95.7 ± 1.51	96.4 ± 0.68	95.5 ± 0.74	95.9 ± 0.52	96.2 ± 0.43	95.7 ± 0.67	94.8 ± 1.18	95.5 ± 1.17
	MED	97.7 ± 0.21[a]	97.6 ± 0.37[b]	97.4 ± 0.33	97.3 ± 0.15	97.2 ± 0.20*	97.2 ± 0.25	96.5 ± 0.28	95.6 ± 0.88[ab]
Et-CO_2 (mmHg)	X+K	48.2 ± 1.64	47.7 ± 1.68	47.6 ± 1.50	49.3 ± 1.69	51.7 ± 1.42	51.2 ± 1.45	47.4 ± 1.43	48.0 ± 1.08
	XX+KK	49.8 ± 1.20	50.0 ± 1.19	50.2 ± 0.97	51.3 ± 1.55	48.8 ± 1.37	50.62 ± 0.96*	50.7 ± 1.30	49.5 ± 0.67
	MED	48.7 ± 2.16	50.4 ± 2.15	52.9 ± 2.63	52.6 ± 2.35	54.7 ± 2.68	55.6 ± 1.78*	52.7 ± 2.39	51.0 ± 4.58
FI-Iso (%)	X+K	1.07 ± 0.08	1.03 ± 0.08	0.95 ± 0.08	0.90 ± 0.07	0.91 ± 0.09	0,92 ± 0.10	0.92 ± 0.10	0.79 ± 0.08
	XX+KK	1.38 ± 0.09[aBCDE]	1.29 ± 0.11[FGHI]	1.13 ± 0.10	0.96 ± 0.08[a]	0.81 ± 0.05[Bf]	0.78 ± 0.05[Cg]	0.79 ± 0.04[Dh]	0.80 ± 0.02[ei]
	MED	1.62 ± 0.08[jkLM]	1.48 ± 0.10	1.25 ± 0.09[j]	1.24 ± 0.04[k]	1.19 ± 0.07[l]	1.18 ± 0.03[m]	1.19 ± 0.11	1.16 ± 0.14
Et-Iso (%)	X+K	0.84 ± 0.07	0.80 ± 0.06	0.77 ± 0.06	0.71 ± 0.06	0.74 ± 0.07	0.73 ± 0.07	0.63 ± 0.12	0.73 ± 0.12
	XX+KK	0.99 ± 0.04[aBCDE]	0.94 ± 0.05[FGHi]	0.86 ± 0.05[j]	0.77 ± 0.05[a]	0.65 ± 0.03[Bf]	0.65 ± 0.03[Cg]	0.62 ± 0.03[DHj]	0.67 ± 0.02[ei]
	MED	1.20 ± 0.08	1.16 ± 0.08	1.00 ± 0.08	0.93 ± 0.04	0.95 ± 0.04	0.91 ± 0.04	0.93 ± 0.09	0.96 ± 0.14

Data are expressed as mean ± SEM. The same characters in the individual horizontal row are significantly different ($^{xx} = P < 0.05$, $^{Xx} = P < 0.01$, $^{XX} = P < 0.001$). The same indices in the individual vertical row are significantly different ($^{**}P < 0.05$, $^{**}P < 0.01$, $^{**}P < 0.001$).

X+K - xylazine with ketamine; XX+KK - increased dose of xylazine with ketamine; MED - medetomidin; n - number of horses in each group; RR - respiratory rate; HR - heart rate; MAP - mean arterial pressure; SpO_2 - oxygen saturation; Et-CO_2 - end-tidal carbon dioxide concentration; FI-Iso - inspired concentration of isoflurane; Et-Iso - end-tidal isoflurane concentration; t_{10}-t_{80} - timepoints of measurements expressed in minutes.

at t_{50} ($P < 0.01$). Significantly higher HR was also seen in group X+K compared to XX+KK at t_{40} ($P < 0.05$) and t_{50} ($P < 0.05$). Respiratory rate (RR) was significantly lower in group MED compared to X+K at time point t_{30} ($P < 0.01$). The lowest RR was observed in group MED compared to other groups.

SpO_2 values were significantly higher in group MED at t_{50} ($P < 0.05$). Peripheral oxygen saturation was within normal limits (≥ 95%) in all groups with a slight drop in group XX+KK at t_{70} (94.8 ± 1.18 %). In group MED alone, peripheral oxygen saturation was significantly higher at t_{20} than at t_{80} ($P < 0.05$).

Et-CO_2 in group MED was significantly higher than in group XX+KK at time point t_{60} ($P < 0.05$) and Et-CO_2 remained the highest in group MED throughout the surgery, but all groups were within normal range (< 60 mmHg) and no mechanical ventilation was required.

The vertical statistical analysis of FI-Iso and Et-Iso is presented in Figs 1 and 2. The FI-Iso was highest in group MED throughout the entire duration of anaesthesia compared to other groups. There was significantly lower FI-Iso at t_{30}, t_{40} ($P < 0.05$) and t_{50}, t_{60} ($P < 0.01$) compared to t_{10} in group MED. In group XX+KK, FI-Iso was significantly lower at t_{40}, t_{50}, t_{60}, t_{70}, t_{80} compared to t_{10}. A significant decrease of isoflurane concentration was also present at time points t_{40} ($P < 0.05$), t_{50}, t_{60}, t_{70} ($P < 0.001$) and t_{80} ($P < 0.01$) compared to t_{20} in group XX+KK. In group X+K, a gradual but non-significant decrease of FI-Iso in the timeline was also recorded. Significant differences were noted also between the groups. In group X+K at t_{10} ($P < 0.001$), t_{20} ($P < 0.05$), t_{40} ($P < 0.01$), t_{50} ($P < 0.05$), t_{60} ($P < 0.05$) and t_{80} ($P < 0.05$), FI-Iso was significantly lower compared to group MED.

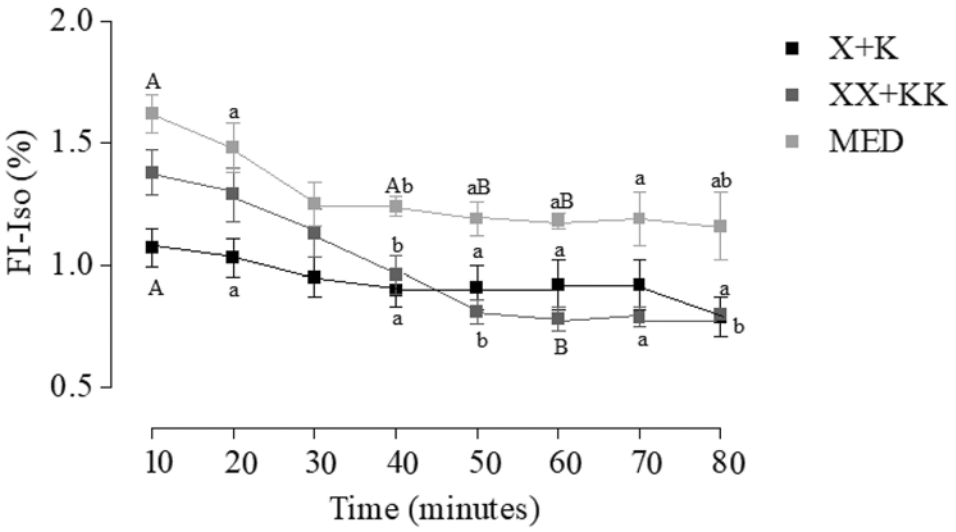

Fig. 1. Inspired concentrations of isoflurane in horses undergoing balanced anaesthesia with different constant rate infusions.

Results are presented as mean ± SEM. The same characters in the individual time points mark significant differences (aa = $P < 0.05$, Aa = $P < 0.01$, AA = $P < 0.001$, bb = $P < 0.05$, Bb = $P < 0.01$, BB = $P < 0.001$). FI-Iso - Inspired isoflurane concentration; X+K - xylazine with ketamine group; XX+KK - higher dose of xylazine with ketamine group; MED - medetomidine group.

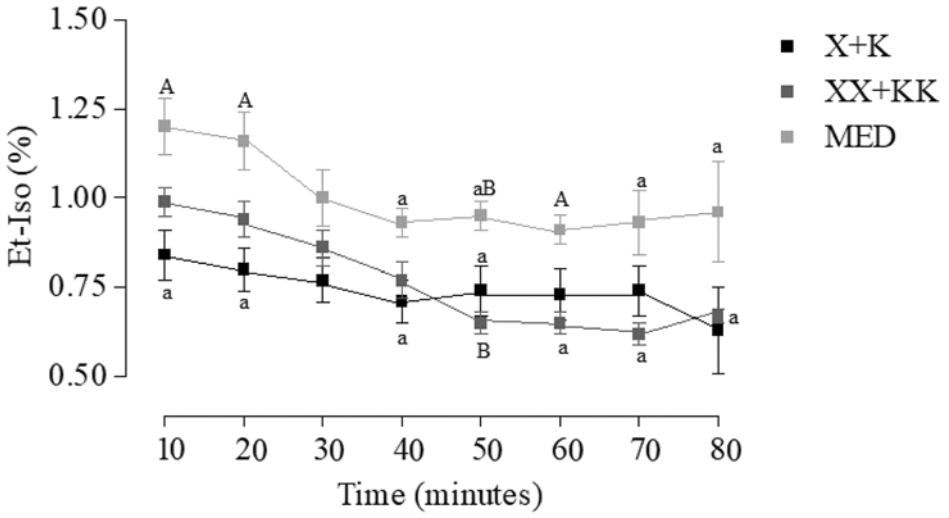

Fig. 2. Expired concentration of isoflurane in horses undergoing balanced anaesthesia with different constant rate infusions.

Results are presented as mean ± SEM. The same characters in the individual time points mark significant difference (aa = $P < 0.05$, Aa = $P < 0.01$, AA = $P < 0.001$, BB = $P < 0.001$). Et-Iso - End-tidal isoflurane concentration; X+K - xylazine with ketamine group; XX+KK - higher dose of xylazine with ketamine group; MED - medetomidine group.

Et-Iso was highest in group MED throughout the entire duration of anaesthesia compared to other groups. There was a significant decrease in Et-Iso at time points t_{10}, t_{20} ($P < 0.01$) and t_{40}, t_{50} ($P < 0.05$) in group X+K compared to group MED. A significant difference in the decrease of Et-Iso at t_{50} ($P < 0.001$) was also recorded in group XX+KK compared to group MED. Significant differences were also recorded within group XX+KK. At the time points t_{50}, t_{60}, t_{70} ($P < 0.001$) and t_{80} ($P < 0.01$), Et-Iso was significantly lower than at t_{10}. Also, at t_{50}, t_{60} ($P < 0.01$), t_{70} ($P < 0.001$) and t_{80} ($P < 0.05$) there was significantly lower Et-Iso compared to t_{20}. The last significance in linear statistics in group XX+KK was found at t_{70} ($P < 0.05$) where in comparison to t_{30}, there was also a significant drop in Et-Iso.

The total duration of anaesthesia (X+K: 87.9 ± 12.79; XX+KK: 89.3 ± 7.4; MED: 81.6 ± 5.96, $P = 0.821$) and the total duration of surgery (X +K: 55 ± 12.26; XX+KK: 56.1 ± 6.75; MED: 42 ± 7.38, $P = 0.488$) were identified between groups.

Two horses in groups X+K (n = 2) and MED (n = 2) required one bolus, and one horse in group MED required two boluses of ketamine due to nystagmus during surgery.

One horse from group X+K and one horse from group XX+KK received xylazine with ketamine mixture (0.15 mg/kg xylazine with 0.5 mg/kg ketamine in one syringe) during transportation to the recovery box because of nystagmus, tachypnoe, repeated ear movement and repeated swallowing reflex. Two horses from group X+K and seven horses from group XX+KK received an additive bolus of xylazine (0.25 mg/kg, i.v.) and in group MED, all 10 horses received medetomidine (2 µg/kg, i.v.) for the recovery phase.

The total recovery time was longest with medetomidine, but this was not significant (MED: 46 min [26–75 min]; X+K: 40.8 min [21–58 min]; XX+KK: 41.1 min [25–65 min]; $P = 0.652$; Fig. 3). The time spent in sternal position was not significantly different between

groups (P = 0.490), and only four horses from groups X+K and MED, and two horses from group XX+KK remained in the sternal position for at least one minute. Horses from group MED had the longest time in the sternal position (35 min; mean ± SEM 5.8 ± 3.492), followed by group X+K (20 min; mean ± SEM 3.1 ± 2.036); horses from group XX+KK spent the least amount of time in sternal recumbency (15 min; mean ± SEM 1.6 ± 1.492). Recovery was significantly better in group X + K compared to group MED (average score X+K: 1.3 ± 0.21; MED: 2.4 ± 0.34; P = 0.049).

When using the recovery scoring system (Gozalo-Marcilla et al. 2013), eight horses from group X+K, five horses from group XX+KK and two horses from group MED were classified as score 1. The worst recovery score was recorded in two horses in group MED with a score of 4 (Fig. 3).

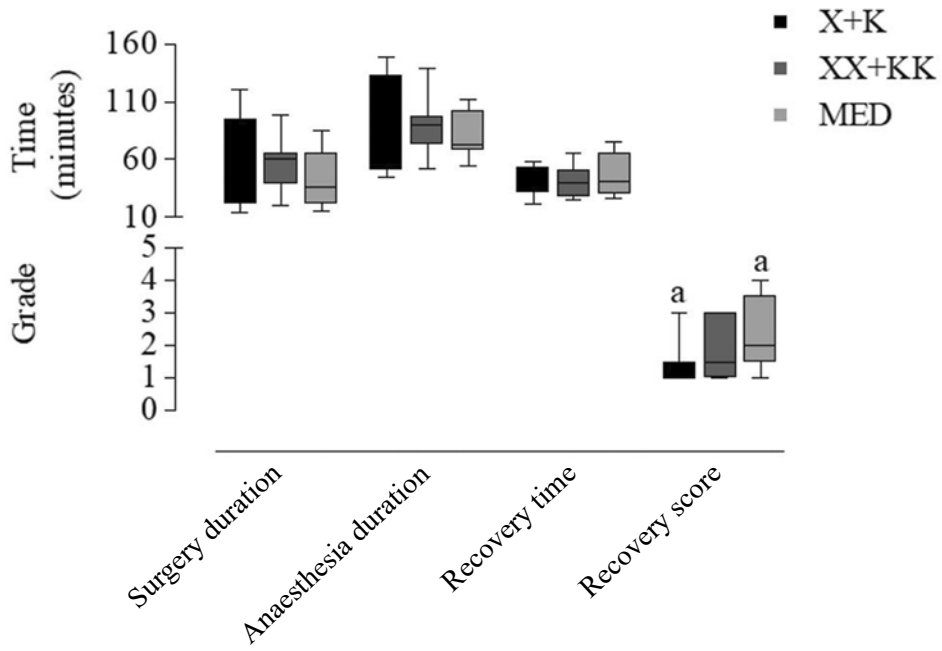

Fig. 3. Duration of anaesthesia, surgery, recovery and recovery scores for the different study groups

Results are presented as mean ± SEM. The same characters at the individual time points mark significant difference (aa = P < 0.05). X+K - Xylazine with ketamine group; XX+KK - higher dose of xylazine with ketamine group; MED - medetomidine group.

Discussion

This study compares the differences in selected cardiorespiratory indices and the duration and quality of the recovery period in horses undergoing PIVA with isoflurane as a volatile agent, with the addition of a CRI of xylazine with ketamine in two different concentrations, against medetomidine.

Only horses requiring elective arthroscopy were selected for this study due to similar length and certain presumed uniformity of the procedure. The length of the performed

surgery often depends on the surgeon's experience, the number of operated joints or the difficulty of the operation. Therefore, it was not possible to achieve complete uniformity in the length of the surgeries between individual horses. In order to achieve the highest possible statistical objectivity, anaesthetic indices were compared only in the time period from t_{10} to t_{80}, with the greatest emphasis from t_{10} to t_{60}; due to the larger number of horses in this particular period.

In our study, we used the same α-2 agonist (xylazine) for sedation in all observed groups, despite the fact that in group MED the CRI consisted of a different α-2 agonist. Some anaesthesiologists do not necessarily use the same α-2 agonist for both sedation and subsequent CRI. In previous studies, an initial dose of xylazine was followed by a CRI of medetomidine due to receptor occupancy (Valverde et al. 2010; Kempchen et al. 2012).

To the authors' knowledge, there is a lack of publications describing the combination of xylazine with ketamine as a CRI during PIVA, despite the fact that anaesthesiologists are of course familiar with this combination from TIVA techniques. However, studies describing the use of ketamine alone or in combination with lidocaine are available. Some studies report the use of ketamine as a CRI at a concentration of 1.9 mg/kg/h (Flaherty et al. 1998), but others up to 7–9 mg/kg (loading dose) and 5–6.7 mg/kg/h (maintenance dose) (Muir and Sams 1992; Knobloch et al. 2006), in order to achieve the necessary plasma concentration to reduce the MAC of an inhaled anaesthetic. The differences in these studies do not necessarily indicate fallacy, but may be due to the use of different drugs and differences between target plasma concentrations or delivering CRI (Valverde 2012).

Ketamine is recommended to be administered in combination with other anaesthetics in CRI with the aim of reducing the concentration of ketamine used (especially racemic). This is to minimise the described risks (such as tremor, muscle rigidity, ataxia, psychotic behaviour, etc.) related to the use of excessive doses, repetitive boluses (2 mg/kg total), or infusions of ketamine exceeding 1–2 h (Schatzmann and Girard 1984; Muir and Sams 1992; Bettschart-Wolfensberger et al. 1996; Hall et al. 2000). The risk is excessive norketamine formation and ketamine accumulation in muscle and fat tissues (Knobloch et al. 2006). These residues can be redistributed to the central compartment i.e. the brain, during recovery causing the aforementioned complications (Bettschart-Wolfensberger et al. 1996). The author (NR) uses doses of xylazine with ketamine presented in this study also in emergent patients (benefits from the positive inotropic effect of ketamine) and in surgical procedures that exceed 60 min without observing complications during the recovery phase, but she prefers a lower concentration (xylazine 0.33 mg/kg + ketamine 1.5 mg/kg) for procedures exceeding 90 min. To minimize the side effects of ketamine, it is recommended to interrupt its infusion 15 to 20 min before the end of the anaesthetic procedure (Spadavecchia et al. 2002); this method was not used in this study. It is also recommended to use additional post-anaesthetic sedation with α-2 agonists (Schatzmann and Girard 1984). However, in this study, due to the sufficient depth of anaesthesia, additive boluses of α-2 agonists in group X+K were not used in all patients; despite this, recovery in these horses was the best of the observed groups.

The HR was the lowest in group XX+KK during the entire anaesthesia, but stayed within normal limits. Despite the described positives that are associated with ketamine in terms of cardiorespiratory effects, it may provide direct negative inotropic effects on the myocardium leading to depression of myocardial contractility, especially when used as a single agent (Treese et al. 1973; Schwartz and Horwitz 1975; Diaz et al. 1976). However, athletic use of the horse can also have an effect on the HR, but the horses' athletic performance was not recorded in this study.

The RR was the lowest in group MED throughout the anaesthesia and the highest in group X+K. Alpha-2 agonists can produce hypoxaemia without a concomitant

hypercapnia (Celly et al. 1997) and are characterized by a decrease in respiratory rate, whereas ketamine is a respiratory stimulant and has been reported to cause bronchodilatation, reverse opiate-induced bradypnoea in humans, and also stimulate breathing during propofol anaesthesia (Eikermann et al. 2012; Algera et al. 2019). This finding could explain why the RR is higher in horses in the ketamine groups. Besides, CRIs with xylazine and ketamine significantly decreased isoflurane concentrations needed to maintain anaesthesia in comparison with group MED and as known, volatile anaesthetics cause respiratory depression.

SpO_2 was within normal limits in all groups. Significantly higher SpO_2 was observed at t_{10} and t_{20} compared to t_{80} in group MED. Significantly higher SpO_2 values were also observed in group MED at the time point t_{50} compared to group X+K. Interestingly, the RR was the lowest in group MED while $EtCO_2$ was the lowest in group XX+KK during this time period. $EtCO_2$ in general was the highest in group MED but stayed within normal limits. PaO_2 was not measured due to the clinic's limited equipment. All horses breathed spontaneously throughout anaesthesia and no mechanical support was used.

There were no significant differences in MAP between the groups and the values stayed within normal range (> 60 mmHg). Mean arterial pressure was the lowest in group MED during the first hour of the operation, but after t_{60} it started to increase. It is important to note that in the time period t_{70}–t_{80} only three horses were observed in group MED, while in the X+K group 5 (t_{70}) and 4 (t_{80}) and in XX+KK 8 (t_{70}) and 6 (t_{80}). Significance and differences in the time periods t_{70} and t_{80} should therefore be considered with caution as the group for comparison was relatively small. Although α2-agonists cause hypertension after initial vasoconstriction with compensatory bradycardia, followed by hypotension (Rowland 2013), MAP in group MED stayed at very satisfactory values. This could be a result of spontaneous ventilation and relatively short surgical times (Rowland 2013). In groups with ketamine, slightly higher MAP values were observed. This could be caused by the ability of ketamine to increase blood pressure through direct stimulation of the sympathetic nervous system, which increases heart rate, blood pressure, and cardiac output (McNally and Pablo 2009). In the ketamine with xylazine groups, concentrations of isoflurane were also lower than in group MED. Isoflurane causes vasodilation, a decrease in vascular tone and perfusion, and an increase in pulse pressure (Hubbel and Muir 2009). To decrease the isoflurane concentration needed for maintaining anaesthesia, it is ideal to use PIVA techniques. Horses in this study breathed spontaneously. Patients that are ventilated spontaneously during anaesthesia have a decreased intrathoracic pressure on inspiration. This pressure gradient increases blood flow to the thorax and the right atrium during inspiration, which in turn increases preload in the right ventricle and increases stroke volume in a normal heart (Kerr and McDonell 2009). Aside from decreasing the amount of isoflurane used, intravenous fluid therapy also supported the well-maintained MAP.

The cardiac index and peripheral vascular resistance were not evaluated in this study. In the xylazine plus ketamine groups, a significant reduction in the consumption of isoflurane in anaesthetized horses was evident compared to group MED. A combination of ketamine (3 mg/kg/h) with lidocaine (loading dose of 2 mg/kg) (Villalba et al. 2011) was described, in which MAC was reduced by 49% (1.25% vs 0.64%). At the same time, horses receiving CRI of ketamine with lidocaine had fewer superficial anaesthetic events, such as nystagmus and movement that required thiopental application, and required less inotropic support than horses receiving only isoflurane (Enderle et al. 2008). In group MED, the inspired and end-tidal concentrations of isoflurane were significantly higher, while being the lowest in group X+K. Logically, it would be expected that due to the higher dose of CRI, group XX+KK had the lowest isoflurane requirements; however, the lowest isoflurane concentrations were observed in group X+K. On the other hand, the higher concentrations of isoflurane in group XX+KK may be the reason why no light planes

of anaesthesia requiring an additive bolus of ketamine were observed in contrast to the other groups (X+K: n = 2, MED: n = 2).

The longest recovery was recorded in group MED. When comparing PIVA with xylazine vs medetomidine in 60 horses (Wiederkehr et al. 2021) and 490 horses (Hubbell et al. 2010), or 60 horses with dexmedetomidine vs medetomidine (Sacks et al. 2017), longer recovery was seen in all groups with medetomidine. This discrepancy could be based on faster metabolism or redistribution of xylazine or a superior sedative effect of medetomidine which has greater specificity for α-2 adrenoceptors (Wiederkehr et al. 2021).

In horses, untimed recovery is undesirable due to the need of exhalation of isoflurane and metabolization of injected anaesthetics. At the same time, prolonged recumbency is very dangerous due to atelectasis, hypoperfusion, post-anaesthesia myopathy, and neuropathy (Wiederkehr et al. 2021). Worsened recovery was recorded in group MED, being significantly inferior in quality compared to group X+K. This contradics previous studies that showed better recoveries using medetomidine compared to ketamine (Larenza et al. 2009). In one study (Bryant et al. 1991), xylazine was shown to cause less ataxia than medetomidine, assuming therefore that CRI using medetomidine could negatively affect recovery, but the authors used a much higher dose (10 μg/kg i.v.) of medetomidine than we did in our study.

The groups were similar as to the factors that might affect recovery quality, for example, weight, age, breed, sex, temperament, physical status, pre-surgical drug application, anaesthesia duration, position during surgery and invasiveness of the surgical procedure (Hubbell et al. 2010). Anaesthesia and surgery duration was the longest in group X+K and the shortest in group MED. Although it is not recommended to use ketamine for surgeries exceeding 90–120 min in order to avoid violent recoveries (Bettschart-Wolfensberger and Larenza 2007), in this study, recovery was worse particularly in horses administered a CRI of medetomidine. No complications associated with higher doses of ketamine (which were mentioned above) were observed during recoveries in groups X+K or XX+KK; however, only three horses that were from group X+K underwent anaesthesia exceeding 120 min.

In order to objectively evaluate the recovery, it needs to be stated that each group included young or temperamental horses and therefore, there is a potential individual influence of each horse on the recovery phase despite the use of the best anaesthetics. This is caused by the flight nature of the horse and we can only strive to find the best combinations of anaesthestics to achieve the lower morbidity and mortality rates seen in small animal anaesthesia (Laurenza et al. 2020).

A major limitation of this study is the small sample size and uniformity of the surgical procedure. A further weakness is that the anaesthesiologist was not blinded to the procedures and the depth of anaesthesia was judged subjectively though equally in all anaesthetized horses. Besides, acid-base indices, plasma concentrations of anaesthetics and the cardiac output were not examined.

In conclusion, the comparison of a CRI of lower dose of xylazine (0.33 mg/kg/h) with ketamine (1.5 mg/kg/h), a higher dose of xylazine (1.2 mg/kg/h) with ketamine (3.6 mg/kg/h), and medetomidine (3.5 μg/kg/h) resulted in a sufficient outcome in all groups, however, group X+K had the lowest requirements for isoflurane ($P \leq 0.05$) and group MED the highest ($P \leq 0.05$). The best recovery was observed in group X+K; the worst in group MED. Medetomidine CRI is currently believed to be the most widely used and published technique for PIVA in horses, but CRI consisting of xylazine with ketamine at reasonable concentrations should not be ruled out. The use of a xylazine and ketamine combination in the PIVA should be considered as a promising alternative of balanced isoflurane anaesthesia with positive cardiopulmonary influence, allowing spontaneous ventilation of the patient, a sufficient level of analgesia, and a smoother recovery.

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