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RESEARCH ARTICLE

Clinical Comparison of Medetomidine with Isoflurane or Sevoflurane for Anesthesia in Horses

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ABSTRACT

The effects of anesthesia using medetomidine combined with isoflurane or sevoflurane on hemodynamic parameters, blood biochemistry, and intraocular pressure was evaluated in horses. Healthy horses (n=12) with a mean body weight of 438±51kg were used. Premedication was provided by administering medetomidine (7 µg/kg) intravenously (IV), and general anesthesia was induced by administering ketamine (2.2 mg/kg) and midazolam (0.03 mg/kg) IV after which isoflurane (n=6) or sevoflurane (n=6) was administered for inhalation anesthesia. Blood gases, respiratory rate, heart rate, electrocardiogram, body temperature, and oxygen saturation, as well as systolic, diastolic, and mean arterial blood pressure were recorded at 0, 5, 15, 30, and 60 min after administering medetomidine. Statistically non-significant differences in the study variables were observed between the isoflurane and sevoflurane groups. Blood gases and electrolyte parameters in both groups were unchanged. Intraocular pressure and liver enzymes levels were similar to reference values. Anesthesia protocols of study using medetomidine combined with isoflurane or sevoflurane produced minimal complications in horses. Medetomidine with sevoflurane provided deep anesthesia, and had fewer cardiopulmonary effects than medetomidine with isoflurane.

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INTRODUCTION

The mortality rate for anesthesia among horses without systemic illness undergoing routine surgery is 1% (Hall *et al*., 2001). The inhalation anesthetics most commonly used in horses are sevoflurane and isoflurane (Taylor *et al*., 2001; Brosnan *et al*., 2012; Valente *et al*., 2015). Premedication for anesthesia is intended to ensure patient cooperation, provide analgesia, reduce anxiety, relax skeletal muscle, improve the induction of anesthesia, and reduce the dosages of anesthetics required for induction without causing excessive adverse cardiopulmonary effects. Alpha-2 adrenoreceptor agonists, such as xylazine, detomidine, medetomidine and romifidine, are widely used for anesthesia premedication (Hall *et al*., 2001). All these drugs have similar properties.

Medetomidine is a potent analgesic and a specific α-2 adrenoreceptor agonist (Ishizuka *et al*., 2013). Bettschart-Wolfensberger *et al*. (2003) demonstrated that the serum half-life of medetomidine is short, and that the renal clearance of medetomidine occurs rapidly. Therefore, an initial bolus of medetomidine must be followed by a continuous infusion of the drug to maintain therapeutic plasma levels for long periods. In horses, when medetomidine is administered as a bolus, therapeutic plasma levels are reached within 30 min. Afterward, a 2-hour constant-rate infusion of medetomidine maintains the plasma level of the drug, providing deep sedation. Heart rate and cardiac output decrease during the first 10 min of the infusion, but remain constant during the remainder of the 2-hour period (Kushiro *et al*., 2005; Kästner *et al*., 2006). Twenty minutes after terminating the infusion, the plasma level of medetomidine becomes undetectable, and the horse regains consciousness (Massoco and Neto, 2003).

The control of hemodynamic parameters, such as minimum heart rate, arterial blood pressure, cardiac output, and central venous pressure, is critical to survival during anesthesia and surgery (Massoco and Neto, 2003; Kalchofner *et al*., 2006). The aim of the current study was to compare the effects of medetomidine premedication combined with isoflurane or sevoflurane

inhalation anesthesia on hemodynamic parameters, blood biochemistry, and intraocular pressure in horses.

MATERIALS AND METHODS

Study Design: The current study was performed in the Department of Surgery, Faculty of Veterinary Medicine, University of Selcuk, Turkey, and was approved by the Ethics Committee of the Faculty of Veterinary Medicine. Twelve healthy male and female thoroughbred horses with a mean body weight of 438±51 kg were divided into two groups of six animals each. Medetomidine (Domitor; Pfizer, New York, NY, USA) was administered to premeditated horses, and general anesthesia was induced using ketamine (2.2 mg/kg, 10% Ketasol; Richterpharma, Wels, Austria) and midazolam (0.03 mg/kg, Demizolam CURAMED Pharma GmbH. Karlsruhe Germany). For inhalation anesthesia, one group of horses received isoflurane (Aerrane; Baxter Healthcare, Deerfield, IL, USA), and the other group received sevoflurane (Sevorane liquid; Abbott Laboratories, Abbott Park, IL, USA). The hemodynamic parameters, blood biochemistry, and intraocular pressure were recorded before and during anesthesia.

Anesthesia procedures: Animals were denied food for 12 h before being used in the experiments, whereas drinking water was provided *ad libitum*. A 20-gauge catheter was placed in the right external jugular vein of each animal for intravenous drug administration and blood collection. After premedication was provided. The horses were placed in right lateral recumbency and anesthesia was maintained by administering isoflurane or sevoflurane via a Surgivet large-animal, semiclosed anesthesia circuit system (Smiths Medical, Dublin, OH, USA) using intermittent positive-pressure ventilation. The initial vaporizer settings for the isoflurane group were 5% isoflurane and an oxygen flow rate of 4 L/min. Isoflurane was decreased to 4 and 2.5% at 10 and 15 min post induction, respectively. The initial vaporizer settings for the sevoflurane group were 8% sevoflurane and an oxygen flow rate of 4 L/min. Sevoflurane was decreased to 6, 4, and 3% at 10, 15, and 20 min post induction, respectively. Anesthesia was terminated at 60 min post induction in both groups, and the breathing circuit was disconnected from the tracheal tube.

Study variables: Heart rate (HR); electrocardiogram (ECG); body temperature (BT); oxygen saturation (SPO_2); and the systolic, diastolic, and mean arterial blood pressures were measured using a base-apex lead BM3 Vet monitor (Bionet, Seoul, Korea). Standard extremity derivations of aVL, aVR, and aVF were recorded. The hemodynamic parameters were recorded before (control) and 5, 15, 30, and 60 min after administering medetomidine. Spontaneous breathing, extubation, and stand up times were recorded. Blood was collected before anesthesia, 5^{th}, 15^{th} 30^{th} and 60^{th} minutes following the induction of anesthesia. WBC count; RBC count; hemoglobin level (Hg); hematocrit (Ht); blood pH; partial pressure of venous oxygen (PO_2); partial pressure of venous carbon dioxide (PCO_2); total carbon dioxide (tCO_2); and serum levels of bicarbonate, sodium, potassium, calcium, and glucose were measured using a Gem Premier 3000 (Biomerieux Diagnostics, Marcy l'Etoile, France) and a Medonic CA 530 hematology analyzer (PZ Cormay, Łomianki, Poland). Serum levels of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), α-glutamyl-transferase (GGT), total bilirubin (T-bil) were measured using a VetTest 8008 biochemical analyzer (Idexx Laboratories, Westbrook, ME, USA). Intraocular pressures were measured using a TonoVet Tonometer (Icare, Vantaa, Finland) before administering medetomidine (control) and at 5, 15, 30, and 60 min after inducing anesthesia. Animal behaviors, including quietness, anxiousness, excitement, aggression, and disobedience, were also recorded before and after anesthesia.

Statistical analysis: The values (mean±SE) of the study variables for the two groups were compared using followed by Tukey's test to evaluate the significance of deviations from the control values. The level of statistical significance was set at $P<0.05$.

RESULTS

Anesthesia maintenance and recovery: Anxiousness was observed in all of the horses in the isoflurane group and in two horses in the sevoflurane group. Appropriate and adequate sedation was observed in all of the animals after the induction of anesthesia. No significant differences were observed in the times for the loss and return of the palpebral reflex, the start of spontaneous breathing, extubation, or stand up time (Table 1).

Table 1: Clinical findings of isoflurane and sevoflurane groups during and after anesthesia of horses

Parameters	Isoflurane (min)	Sevoflurane (min)
Loss of palpebral reflex	16.2±3.47	9.38±0.66
Return of palpebral reflex	13.8±1.70	11.5±2.69
Spontaneous breathing	13.4±1.75	17.3±8.47
Extubation	18.7±1.63	19.4±1.83
Standing up	49.5±3.15	48.8±9.49

No significant differences were seen ($P>0.05$).

Cardiopulmonary findings: There were not any differences in the heart rate (HR), respiratory rate (RR), body temperature (BT), or systolic pressure were observed between the isoflurane and sevoflurane groups. The SPO_2 was significantly lower in the isoflurane group at 60 min post induction ($P<0.05$) than in the sevoflurane group (Table 2). The diastolic and mean arterial blood pressures were higher during anesthesia in the isoflurane group than in the sevoflurane group. No significant differences in the diastolic and mean arterial blood pressures were observed at 30 min post induction.

Hemato-biochemical parameters: The RBC count, Hg, and Ht of the two groups were significantly different at 0, 5, 15, 30, and 60 min after the induction of anesthesia. These results appeared within the reference values. Blood pH increased in the isoflurane group during anesthesia, whereas blood pH decreased in the sevoflurane group. Significant intra group differences in pH and PCO_2 were observed among the horses in the sevoflurane group at 15, 30, and 60 min after the induction of anesthesia, which also differed significantly from those of the isoflurane

Table 2: Cardiopulmonary findings of isoflurane (ISO) and sevoflurane (SEVO) groups during the anesthesia

VALUE	Groups	0 min	5 min	15 min	30 min	60 min
HR	ISO	113±32.2	85.0±17.8	65.2±14.3	52.8±8.30	51.4±10.5
	SEVO	52.2±8.32	67.2±13.5	51.8±13.3	46.2±8.53	40.8±3.75
SpO_2	ISO	97.8±0.17	97.2±0.54	97.7±0.33	94.7±1.23*	89.7±3.77*
	SEVO	89.7±3.41	94.0±2.32	90.0±5.57	89.8±5.71	95.2±1.11
RR	ISO	19.2±3.66	11.0±2.71	11.0±2.34	20.5±7.62	6.80±0.80
	SEVO	10.8±2.21	11.1±2.53	9.50±1.58	9.50±2.24	8.33±1.38
BT	ISO	36.2±0.36	36.1±0.36	36.3±0.33	36.1±0.37	36.1±0.33
	SEVO	36.6±0.32	36.5±0.29	36.5±0.41	36.4±0.33	36.4±0.22
Systolic Pressure	ISO	142±4.87	167±18.8	120±17.9	177±9.98	161±21.1
	SEVO	159±18.0	181±30.4	115±12.3	117±7.73	132±21.0
Diastolic Pressure	ISO	117±7.02	139±10.7	82.2±9.18	108±15.9**	105±25.1
	SEVO	89.2±18.7	110±25.4	66.2±8.97	56.4±6.61**	79.2±15.4
Mean Pressure	ISO	114±7.23	137±20.0	93.6±11.5	132±14.0**	123±12.5
	SEVO	115±17.8	137±28.4	89.8±10.9	90.6±7.42**	88.2±9.97

*(P<0.05), in groups evaluation; **(P<0.05), between two groups evaluation.

Table 3: Hematological, venous blood gas analysis and biochemical evaluations isoflurane (ISO) and sevoflurane (SEVO) groups during the anesthesia

Value	Group	0 min	5 min	15 min	30 min	60 min
RBC	ISO	10.1±0.42*	9.07±0.49*	7.52±0.42*	7.51±0.43*	7.12±0.40*
	SEVO	10.5±0.63*	8.95±0.36	8.36±0.32*	7.82±0.47*	7.26±0.51*
WBC	ISO	8.18±0.57	7.82±0.59	7.65±0.58	7.17±0.43	6.47±0.37
	SEVO	9.17±0.74	8.60±0.68	8.05±0.66	7.73±0.59	6.92±0.69
Hg	ISO	14.5±0.45*	12.8±0.87	11.4±0.43*	10.9±0.51*	10.5±0.46*
	SEVO	15.0±0.84*	12.9±0.45	12.1±0.46*	11.3±0.64*	10.6±0.72*
Ht	ISO	52.5±1.69*	45.3±3.21	40.4±1.71*	38.7±2.05*	36.6±1.89*
	SEVO	54.3±3.23*	45.7±1.68	42.6±1.61*	39.8±2.39*	36.9±2.66*
pH	ISO	7.44±0.02	7.41±0.02	7.43±0.03**	7.44±0.03**	7.46±0.04**
	SEVO	7.42±0.02*	7.39±0.01	7.36±0.01**,*	7.34±0.01**,*	7.34±0.01**,*
pCO_2	ISO	44.8±1.06	46.2±1.02	46.6±1.43	46.0±2.61**	46.8±5.42**
	SEVO	44.5±1.99*	46.0±1.51	52.1±2.93	56.7±2.84**,*	62.7±3.94**,*
HCO_3	ISO	30.2±1.34	29.2±1.04	30.9±1.20	31.1±0.73	32.5±1.47
	SEVO	28.9±0.43*	27.8±0.57*	29.3±1.03*	30.7±0.83	33.2±0.89*
tCO_2	ISO	31.6±1.37	30.6±1.01	32.4±1.17	32.5±0.68	33.9±1.57
	SEVO	30.4±0.47	29.2±0.60*	30.9±1.11	33.9±2.02	35.1±1.01*
PO_2	ISO	27.4±1.29*	33.8±2.03	42.8±3.49	48.2±5.21*	52.4±7.99*
	SEVO	28.0±1.86*	38.0±3.66*	51.2±2.53*	52.8±2.48*	55.5±3.01*
Glu	ISO	85.8±4.14*	94.4±1.47	111±4.91	127±8.98*	150±16.1
	SEVO	83.5±3.08	94.2±3.39	117±11.5	133±19.6	142±25.9
Na	ISO	138±1.93	138±1.81	138±2.35	138±1.58	137±1.31
	SEVO	138±1.19	139±1.47	138±0.79	138±1.31	137±1.20
K	ISO	3.42±0.16	3.26±0.09	3.32±0.13	3.36±0.02	3.40±0.07**
	SEVO	3.52±0.13	3.33±0.09	3.50±0.12	5.21±1.74	3.90±0.18**
Ca	ISO	1.25±0.07	1.26±0.06	1.29±0.08	1.26±0.03	1.31±0.04**
	SEVO	2.87±1.65	1.12±0.06	1.15±0.06	1.17±0.07	1.14±0.03**

*(P<0.05) in groups evaluation; **(P<0.05) between two groups evaluation.

Table 4: Biochemical values isoflurane (ISO) and sevoflurane (SEVO) groups before and after the anesthesia.

Values	Group	0 min	60 min
ALT	ISO	27.2±6.10	23.2±5.50
	SEVO	34.6±6.89	28.3±6.01
GGT	ISO	14.6±1.49	14.3±1.92
	SEVO	17.1±2.44	14.0±1.80
T-bil	ISO	3.03±0.42	2.45±0.43
	SEVO	4.28±0.98	2.98±0.74
AST	ISO	331±142	307±122
	SEVO	381±136	338±123
ALP	ISO	117±8.74	109±7.64
	SEVO	130±9.25	115±12.0

Table 5: Intraocular pressures isoflurane (ISO) and sevoflurane (SEVO) groups during the anesthesia

Time (minute)	ISO	SEVO
0	40.0±5.91	36.8±5.57
5	31.4±3.77	26.5±5.16
15	29.8±4.28	32.3±5.85
30	29.2±2.69	28.3±3.30
60	32.6±0.39	37.4±7.87

group. Significant intra group differences in the bicarbonate values were observed in the sevoflurane group at 0, 5, 15, and 60 min after inducing anesthesia (Table 3).

The tCO_2 were significantly different at 0, 30, and 60 min in the isoflurane group. The PO_2 values were statistically different in the isoflurane group at 0, 30, and 60 min post induction, and were statistically different in the sevoflurane group at 0, 5, 15, 30, and 60 min after the induction of anesthesia. No significant difference in the serum level of glucose was observed in the sevoflurane group, whereas significant differences were observed in the isoflurane group at 0 and 30 min post induction. The serum levels of potassium and calcium were significantly different between the isoflurane and sevoflurane groups at 60 min. No significant differences in the AST, ALT, ALP, GGT, or T-bil levels were observed between the two groups (Table 4).

Intraocular pressures: No significant difference in the intraocular pressure was observed between the groups (Table 5).

DISCUSSION

Numerous preanesthetic agents are used in horses, including phenothiazines, α-2 agonists, and opioids (Kempchen *et al*., 2012; Vilalba *et al*., 2014). In the present study, medetomidine was used for premeditated horses before inducing general anesthesia. Alpha-2 agonists provide better sedation, analgesia, and muscle relaxation than phenothiazine and opioids, and medetomidine is more effective than xylazine and detomidine (Yamashita *et al*., 2002). Previous studies of medetomidine in horses have used dosages of 7 and 10 µg/kg (Freeman and England, 2000; Johnston *et al*., 2004). In the study, 7 µg/kg of medetomidine intravenously as premedication for anesthesia in horses, achieving adequate sedation. The findings are consistent with those of a previous studies (Creighton *et al*., 2012; Vilalba *et al*., 2014).

The loss of the palpebral reflex occurred at 16.2±3.47 min in the isoflurane group and 9.38±0.66 min in sevoflurane group. The return of the palpebral reflex, spontaneous breathing, and standing up times were shorter in the sevoflurane than in the isoflurane group, but the differences were not statistically significant. These conditions were likely related to the low blood concentration and rapid elimination of sevoflurane from the blood (Yamashita *et al*., 2002).

General ECG assessments of the two groups revealed no significant atrial fibrillation or atrioventricular blockade. Cardiac activity was regular and rhythmic. However, arrhythmia and ventricular extrasystole were observed in some horses due to hypoxia, which may have been caused by respiratory depression during anesthesia. Peripheral vasodilatation caused by anesthetic agents can reduce arterial pressure and peripheral vascular resistance in a dose-dependent manner, which contribute to arrhythmia and ventricular extrasystole (Yamashita *et al*., 2002).

Previous studies have shown that sevoflurane depresses the cardiovascular system in a dose-dependent manner (Yamanaka *et al*., 2001). Wagner *et al*. (2012) reported that xylazine-ketamine or xylazine-propofol infusion significantly improved quality of recovery from sevoflurane anesthesia in horses. Xylazine-ketamine or xylazine-propofol infusions may be of benefit during recovery from sevoflurane anesthesia in horses for which a smooth recovery is particularly critical. However, oxygenation and ventilation should be monitored carefully. The risk of hypotension in horses receiving sevoflurane anesthesia increased with increasing dose of sevoflurane. By contrast, it was observed no hypotension in the horses in the sevoflurane group in the study. This may have been related to the maximum dosage used in study (8%), which was decreased at 5, 15, and 30 min after the induction of anesthesia.

The BT decreases during general anesthesia because of environmental factors, peripheral vasodilatation, and the depression of the cardiovascular system (Bednarski *et al*., 2011). In the study, the BT in both groups decreased during anesthesia, presumably for these reasons. During anesthesia, the mean BT ranged from 36.2 to 36.4°C.

Arterial and venous hematological parameters reflect the ventilation and fluid-electrolyte balance of animals. The partial pressures of arterial oxygen and carbon dioxide reflect lung function. Blood pH, SPO2, tCO2, and serum bicarbonate are also used to evaluate lung function. If the venous blood circulation is not impaired, these parameters can also be measured from the venous blood. However, the venous blood values are 5 to 10 mm Hg and 1 to 5 mEq/L higher, respectively, than those of the arterial blood, whereas the pH of venous blood is 0.03 to 0.05 units lower than that of the arterial blood (Steffey *et al*., 2005; Marcilla *et al*., 2012). In the study, the pCO_2, bicarbonate, and tCO_2 values increased during anesthesia, and these increases were greater in the sevoflurane than in the isoflurane group. Increases in pCO_2, bicarbonate, and tCO_2 were related to the compensatory response to respiratory acidosis and metabolic alkalosis.

Serum glucose increased during anesthesia in both groups in our study. General anesthesia may cause fear, excitement and hypoxia. Therefore, hyperglycemia could be caused by stress hormones, glucocorticoids and medetomidine. The decreases in Hg, Ht, and RBC count observed in both groups of horses in the study were likely the result of hypoxia during anesthesia (Grimsrud *et al*., 2015). Serum levels of calcium, potassium, and sodium are critical for maintaining homeostasis. Increases or decreases in the levels of these electrolytes influence ECG measurements during anesthesia. No statistically significant differences in serum levels of calcium, potassium, and sodium were observed within or between the two groups of horses in our study. These findings explain the absence of significant changes in the ECG traces of horses during anesthesia.

Monitoring hepatic function is also important before and during anesthesia because some anesthetic agents are detoxified in liver. Depending on the anesthetic agents used, anesthesia can exacerbate liver damage in animals with liver disorders. The eosinophil count and the levels of serum albumin, bilirubin, creatinine phosphokinase, sorbitol dehydrogenase, ALP, lactate dehydrogenase, AST, and serum cholinesterase are the most commonly analyzed hematological parameters (Peiris *et al*., 2012; Marcilla *et al*., 2012; Grimsrud *et al*., 2015). No statistically significant differences in the levels of liver enzymes or the hepatic profile were observed between the isoflurane and sevoflurane groups in the study. Although the amount of metabolism of sevoflurane by the liver is slightly greater than for isoflurane, the extent of metabolism is similar to isoflurane due to its insolubility

Intraocular pressure could be changed by animal's head positions. Therefore measurement should be taken in standing positions (Marzok *et al*., 2014). The mean intraocular pressure during anesthesia in the horses in our study did not differ significantly from the reference value. These results suggest that our anesthesia protocols can be used safely for eye surgeries in horses.

Conclusion: the light of clinical, cardiovascular, hematological and biochemical values were determined a situation of general anesthesia. Both anesthesic protocols could be used safely in horses. Both protocols appear to produce very similar degrees of depression in a dose-dependent manner. The only advantage sevoflurane may have over isoflurane is the ability to change depth of anesthesia slightly quicker.

Author's contribution: Authors will declare the contribution of MA, HE and EE conceived and designed

the review. MA, HE and EE executed the experiment and the sera analyzed in clinic laboratory of the Veterinary Faculty. The data were analyzed by statistician. All authors interpreted the data. Critically revised the manuscript for important intellectual contents and approved the final version.

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