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Research article
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The investigation of xylazine, detomidine, isoflurane and sevoflurane anaesthetic combinations on clinical, laboratory and cardiovascular parameters and on intraocular pressure in horses

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ABSTRACT. The aim of this study was to investigate the effects of anaesthetic combinations of xylazine, detomidine, sevoflurane and isoflurane on clinical, laboratory, and cardiovascular parameters as well as their effects on intraocular pressure in horses. Twenty-four mixed-breed horses (twelve male and twelve female) were used for this study. The horses were allocated into four groups (six horses in each group): XS (xylazine-sevoflurane), XI (xylazine-isoflurane), DS (detomidine-sevoflurane) and DI (detomidine-isoflurane). Clinical evaluations, hematological, biochemical tests and measurement of intraocular pressure were done before (0th), during (5th, 15th and 30th min) and at the end of anaesthesia (60th min). The detected differences were statistically evaluated. In conclusion, this study shows that the anaesthetic combinations of sevoflurane and isoflurane with xylazine and detomidine provided safe and suitable anaesthesia in horses. Our study did not reveal any statistical differences in intraocular pressure measurements. However, it should be noted that intraocular pressures were measured with the animals lying down and our results do not rule out changes in intraocular pressures in a standing position. We concluded that these anaesthesia protocols are suitable for ophthalmic surgery.

Keywords: anaesthesia, equine, eye.

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INTRODUCTION

Alpha-2 (α-2) agonists are the greatest improvements in modern equine practice. For treatments and diagnostic procedures, α-2 agonists are widely used in equine medicine and anaesthesia (Mutoh et al., 1997; Guedes et al., 2017). Administration of α-2 agonists also reduces the amount of inhalational anaesthetic needed to maintain general anaesthesia in horses (Nyman et al., 2009; Rohrbach et al., 2009). α-2 Agonists such as detomidine, xylazine, medetomidine and romifidine are used for premedication in horses, and they have similar properties (Arıcan et al., 2015).

The inhalation anaesthetic agents such as isoflurane and sevoflurane are used for procedures requiring long-term anaesthesia in horses. Unlike injectable anesthetics, they enter the body through the lungs and move into systemic circulation from the respiratory tract (Hall et al., 2000; Del Barrio et al., 2017).

Isoflurane is an inhalant anesthetic agent with a low blood/gas solubility (1.4 in horses) coefficient. The lower blood/gas solubility causes rapid induction and short recovery time from general anaesthesia (Kalchofner et al., 2009; Ida et al., 2013). It leads to dose-dependent cardiac and respiratory depression. The α-adrenergic stimulation associated with isoflurane increases blood flow in skeletal muscles and reduces systemic vascular resistance and arterial blood pressure (Yamashita et al., 2006; Steffey, 2009). Sevoflurane is structurally similar to isoflurane but has lower blood/gas solubility (0.6 in horses). Its effects on the central nervous system (CNS) are fewer than those of isoflurane, but there is still a dose-dependent depression. CNS depression is greater at increasing doses when compared to the other inhalation agents. It also reduces cerebral vascular resistance and metabolism at high doses (Yamanaka et al., 2001; Kronen, 2003).

Intraocular pressure (IOP) is defined as the equilibrium between production and drainage of humor aqueous in the ciliary processes of the eye. The anaesthetic agents may cause changes in IOP (Komáromy et al., 2006; Monk et al., 2017). The aim of this study was to investigate the effects of xylazine, detomidine, isoflurane and sevoflurane anesthetic combinations on clinical, laboratory, and cardiovascular parameters as well as their effects on IOP in horses.

MATERIALS AND METHODS

The current study was performed in the Surgery Department of the Faculty of Veterinary Medicine, University of Selcuk, Turkey and was approved by the Ethics Committee of the Faculty of Veterinary Medicine. Twenty-four mixed-breed horses (twelve male and twelve female) weighing 450 ± 51 kg, 7.6 ± 5 years old were used for this study. The clinical examination and hematological tests were done before starting the study. The horses were allocated into four groups (six horses in each group): XS (xylazine-sevoflurane), XI (xylazine-isoflurane), DS (detomidine-sevoflurane) and DI (detomidine-isoflurane). All horses were fasted for 12 h before premedication; water intake was not restricted. Before premedication, the body weight, respiratory rate, body temperature, and heart rate of the horses were recorded.

Before premedication, a 20-gauge intravenous catheter was placed in the right jugular vein for blood sample collection and administration of anaesthetic drugs. Electrocardiography (ECG) leads (aVL, aVR, aVF) and oxyhaemoglobin saturation (SpO2) were monitored by a BM3 Vet monitor (Bionet, Seoul, Korea) before premedication and during anaesthesia. Intravenous xylazine (1.1 mg/kg b.w., Rompun 2%, Bayer, Mississauga, Canada) was used for premedication in XS and XI groups, and intravenous detomidine (6 µg/kg b.w., Domosedan, Pfizer, New York, NY, USA) was used for premedication in DS and DI groups. Ketamine hydrochloride (2 mg/kg b.w., Ketasol 10%, Richterpharma, Wels, Austria) and midazolam (0.03 mg/kg b.w., Demizolam, Curamed Pharma GmbH. Karlsruhe Germany) were mixed in the same syringe and intravenously administered to induce anesthesia for assisted fall. After induction of anaesthesia, horses were placed in left lateral recumbency and the trachea was intubated with a cuffed endotracheal tube with an internal diameter of 30 mm. The endotracheal tube was attached to a large animal circle breathing system anaesthesia machine (Large animal LSD 3000 anaesthetic machine, Dublin, OH, USA, 12 breath/min), and anaesthesia was maintained with either sevoflurane (Sevorane liquid, Abbott Laboratories, Abbott Park, IL, USA) or isoflurane (Aerrane, Baxter Healthcare, Deerfield, IL,USA) for 60 min. The initial concentration of

sevoflurane was 8% + 4 l O_2/min and was reduced to 4%. After 30 min of anaesthesia, the sevoflurane dose was changed to 2% + 4 l O_2/min, which was maintained until the end of anaesthesia (60 min). The initial dosage of isoflurane was 5% + 4 l O_2/min, which was reduced to 4% after 15 min. At 30 min of anaesthesia, the isoflurane dose was changed to 2.5 % + 4 l O_2/min, which was maintained until the end of anaesthesia (60 min). After 60 min, the administration of inhalation anaesthetics was discontinued, and all animals were supported with O_2 for 10 min.

Clinical evaluations

Before pre-anaesthetic administration and during anesthesia (5th, 15th, 30th and 60th min) heart rate (HR), ECG, body temperature (BT), SPO_2, respiratory rate (RR), systolic, diastolic and mean arterial pressure were measured and recorded.

After initiation of inhalation anaesthesia, palpebral reflex was controlled during and at the end of anesthesia in all groups. Palpebral reflex (sluggish) time (PRs), corneal reflex (strong) (PRS), palpebral reflex (normal) (PRn), spontaneous respiration return time (SRRT) and standing up time (SUT) were recorded on examination papers.

Haematologic evaluations

Before (control) and during anaesthesia (5th, 15th, 30th and 60th min) a 15-ml blood sample was collected from the right jugular vein for hematologic, blood gas, and biochemical evaluations. Red blood count (RBC), white blood count (WBC), blood pH, venous partial carbon dioxide pressure ($PvCO_2$), venous partial oxygen pressure (PvO_2), total carbon dioxide (tCO_2), hemoglobin level (Hb), hematocrit (Ht), bicarbonate (HCO_3-), electrolytes (Na^+, K^+) and lactic acid were measured using a Gem Premier 3000 (Biomerieux Diagnostics, Marcy l'Etoile, France) and a Medonic CA 530 hematology analyzer (PZ Cormay, Łomianki, Poland).

Biochemical evaluations

The serum levels of total protein (TP), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), α-glutamyl transferase (γGT), total bilirubin (T-bil) and glucose (Glu) were measured before and at the end of anaesthesia (60th min) using a VetTest 8008 biochemical analyzer (Idexx Laboratories, Westbrook, ME, USA).

Intraocular pressures measurements

Before pre-anaesthetic administration, eyes examination (palpebral, corneal and pupillary reflexes, conjunctiva) were done in all horses and intraocular pressures were measured using a TonoVet tonometer (Icare, Vantaa, Finland) before administering xylazine and detomidine (control) and at the 5th, 15th, 30th, and 60th min after inducing anaesthesia. The same eyes (right) were evaluated in all horses.

Data and statistical analysis

IBM SPSS 21 statistics programs were used to analyze the data. The Shapiro-Wilk test was used for normality then the one and two-way repeated measure (ANOVA) followed Tukey significance tests to compare intra-group and inter-group values. The level of statistical significance was set at $P < 0.05$. Results were presented as Mean ± SE (Standard Error).

RESULTS

Clinical evaluation results

In the current study, suitable and adequate sedation was provided in all groups. The clinical evaluations are shown in Table 1. There were significant differences seen in PRsT and SUT values between groups. The PRsT values of sevoflurane groups were shorter than those of the isoflurane groups ($P < 0.05$). The SUT values were higher in group DS than in the others ($P < 0.05$).

The cardiopulmonary findings are shown in Table 2. Increases and decreases were seen in HR, SpO_2

Table 1. Clinical Evaluation of groups (Mean ± SE) PRsT; Palpebral reflex sluggish time, PRST; palpebral reflex strong time, SRRT; spontaneous respiration return time, SUT; standing up time, a,b,c; P < 0,05 between groups.

Group	PRsT	PRST	SRRT	SUT
XS	5.98±0.57[a]	14.28±3.31	10.42±4.47	39.83±8.63[a]
XI	17.66±2.61[b]	14.54±0.80	18.55±1.21	32.00±4.41[a]
DS	5.80±0.71[a,c]	17.23±1.05	9.81±3.83	79.50±14.39[b]
DI	18.00±4.06[b]	14.50±3.13	23.66±6.29	26.83±1.72[a]

Table 2. Cardiopulmonary evaluation of groups (M±SE)

Values	Groups	0th	5 th	15th	30th	60th	Reference ranges
HR	XS	57±8.42	47.6±12.04	62.8±13.33	52.1±10.99	51.3±9.24	28-45
	XI	54±8.42	68±12.04	55.8±13.33	55±10.09	55.5±9.24	28-45
	DS	46.8±8.42	51.6±12.04	56±13.33	34.8±10.99	31.8±9.24	28-45
	DI	34.3±8.42	35.6±12.04	49.8±13.33	60.5±10.99	54.3±9.24	28-45
SpO_2 %	XS	92.3±1.77	95.5±0.77	96.5±0.62	95.3±1.30	95±1.34	85-100
	XI	95.6±1.37	97.8±0.77	97.1±0.62	94.6±1.30	94.6±1.34	85-100
	DS	96.5±1.77	96.5±0.77	96.1±0.62	95.1±1.30	94.1±1.38	85-100
	DI	94.3±1.77	96±0.77	96.5±0.62	95.5±1.30	96±1.34	85-100
RR	XS	15.5±4.01	16.6±4.54	19.4±5.74	14.4±3.17	11.4±1.43	8-20
	XI	13.1±2.61^{ab}	27.3±9.38^{a}	11.6±2.04^{ab}	7.2±1.20^{b}	7.6±0.98^{b}	8-20
	DS	13.1±2.92	9±1.26	10.8±1.55	11.5±1.38	12.8±2.70	8-20
	DI	10.4±2.56	8.75±2.78	13.5±4.99	18±7.18	7.6±1.60	8-20
BT	XS	36.8±0.09^{a}	36.7±0.08^{a}	35.9±0.12^{b}	35.7±0.18^{b}	35.7±0.2^{b}	37.5-38
	XI	37.1±0.21	37±0.22	36.5±0.42	36.3±0.41	36.1±0.30	37.5-38
	DS	37±0.26	36.6±0.31	36.5±0.46	36.5±0.40	36.3±0.37	37.5-38
	DI	37.1±0.34	36.8±0.34	37.1±0.27	36.9±0.35	36.9±0.40	37.5-38
SP	XS	153.3±7.81	105.3±5.57	151.5±10.14	107.8±10.17	87.8±6.22	112±14
	XI	161.8±7.8	158.5±5.57	125.6±10.14	118.3±10.17	103.3±6.22	112±14
	DS	153.6±7.81	153.6±5.57	122.5±10.14	118.3±10.17	103.3±6.22	112±14
	DI	160.1±7.81	155.5±5.57	122.8±10.14	106.6±10.17	94.6±6.22	112±14
DP	XS	59.6±10.64^{*,a}	58.3±8.57^{*,a}	121.6±7.3^{*,b}	104.1±5.82^{*,b}	70.8±7.50^{a}	70±14
	XI	117±10.64^{a}	107±8.57^{*,a}	80.3±7.36^{a}	61.5±5.82^{b}	47±7.50^{b}	70±14
	DS	119.3±10.64^{a}	83±8.57^{*,b,c}	80.3±7.36^{a,c}	61.5±5.82^{b,c}	56.6±7.50^{b,c}	70±14
	DI	124.1±10.64^{a}	95.5±8.57^{*,b}	80.3±7.36^{b}	61.5±5.82^{b}	60.6±7.50^{b}	70±14
MP	XS	99.5±19.86	77±12.5	132.8±8.14	106.1±6.57*	80.3±4.31	90±14
	XI	109.4±21.76^{a,c}	114.4±13.73^{a}	97.2±8.92^{a}	74.6±7.20^{b,c}	68.6±4.72^{b,c}	90±14
	DS	98.6±19.86^{a}	111.5±12.54^{a}	91.6±8.14^{a}	72.8±6.57^{b}	67.1±4.31^{b}	90±14
	DI	96±19.80^{a}	111.5±12.50^{a}	91.6±8.12^{a}	72.8±6.55^{b}	67.1±4.28^{b}	90±14

HR; heart rate, SpO_2; oxygen saturation, RR; respiratory rate, BT; body temperature, SP; systolic pressure, DP; diastolic pressure, MP; mean pressure, *,**; $P < 0.05$ between groups evaluation, a,b,c ; $P < 0.05$ in groups evaluations. References: Arıcan et al. 2015.

and SP (systolic pressure) values before and during anaesthesia in all groups. The changes detected in these values were not statistically significant. Respiratory rate (RR) increased at 5 min and decreased from 15 min until the end of anaesthesia in XI ($P < 0.05$). Significant differences were seen in diastolic (DP) and mean pressures (MP) between and within groups ($P < 0.05$). Decreases of DP were recorded at 5th, 15th, 30th, 60th min of anaesthesia in XI, DS and DI. Increases of DP were detected at 15,

Table 3. Hematological evaluation of groups (Mean ± SE).

30, 60 min of anaesthesia in XS. In XI, DS and DI the MP increased at 5 min of anaesthesia and decreased until the end of anesthesia. In XS the MP decreased at 5 min and increased at 30 min of anaesthesia. BT decreased from 15 min until the end of anaesthesia in XS. The decrease of BT was statistically significant ($P < 0.05$).

Haematologic results

The measured hematologic and blood gas parameters are shown in Table 3. In hematologic evaluations, RBC, WBC, Hb, Ht and lactic acid values showed changes. The changes of RBC, WBC, Hb and Ht values were in reference intervals in all groups. The lactic acid levels were lower than reference range before and during anaesthesia in all groups. In DS, there was significant difference recorded in lactic acid levels between 0th min and the other times.

The pH values decreased at 15th min of anaesthesia in DS. This reduction was below the reference range and it was significant ($P < 0.05$) (Table 3). At 0th, 5th, 15th, 30th, 60th min of anaesthesia, the $PvCO_2$ values were higher in sevoflurane groups (XS and DS) than in isoflurane groups (XI and DI). The $PvCO_2$ values increased during anaesthesia in sevoflurane groups. After 5 min of anaesthesia, the $PvCO_2$ values started to decrease in isoflurane groups, and the reductions were significantly different ($P < 0.05$). There were no significant differences seen in PvO_2 values between groups at the 0th, 5th, 15th, 30th and 60th min of anaesthesia. Before and during anaesthesia the PvO_2 values were lower than reference range in DI ($P < 0.05$) (Table 3). Differences in tCO_2 values were seen in all groups. The tCO_2 values were higher than reference range at 15th, 30th and 60th min of anaesthesia in XS and DS ($P < 0.05$). The other differences were in reference interval (Table 3). The HCO_3 levels of XS and DS were significantly different from XI and DI ($P < 0.05$).

Biochemical results

Biochemical parameters are shown in Table 4. There were significant differences detected in TP, AST, ALT and ALP values among and within groups. All of the values were within the normal range (Table 4). T-bil values were higher at 0 and 60th min of anesthesia than the reference range in XS. At the end of the anaesthesia Glu values in XS, XI and DI were higher than XS and reference values (Table 4).

Intraocular pressures results

Intraocular pressures (IOP) were measured before and during anesthesia (5th, 15th, 30th and 60th min) (Table 5). There were no significant differences observed between and within groups (reference range: 13-37 mmHg).

DISCUSSION

Arıcan et al. (2015) compared the clinical effects of sevoflurane, isoflurane, and medetomidine anaesthetic combinations in horses. They found the loss of palpebral reflex, return of palpebral reflex and standing up times to be shorter in a sevoflurane group than in an isoflurane group. They attribute this to the low blood concentration of sevoflurane at a plane of anaesthesia and its relatively rapid elimination from the body. In our study, there were significant differences observed in PRsT and SUT ($P < 0.05$). Palpebral reflex sluggish time of sevoflurane groups was shorter than those of isoflurane groups which may be supported by the previous finding of low blood concentration and rapid elimination of sevoflurane from the blood. Detomidine binds α-2 adrenoreceptors in the locus coeruleus and medulla spinalis to provide sedative and analgesic effects. It suppresses norepinephrine and dopamine release in CNS. Because of this, detomidine is more potent and has fewer side effects than xylazine. It has been reported that detomidine produces deeper and longer sedation than xylazine (Steffey and Pascoe, 2002; Rochbrach et al., 2009). In this study, SUT was longer in XS and DS than XI and DI. The longest and shortest times were detected in DS and DI. This condition suggested that anaesthetic combinations, anaesthetic doses and animal related factors (age, sex and weight) could influence the post anaesthetic parameters.

Generally cardiac arrhythmias which occur during anaesthesia can cause serious problems, and

Values	Groups	0th	5th	15th	30th	60th	Reference ranges
RBC (x10^6/mm^3)	XS	9.8±0.12	8.8±0.63	8.6±0.81	7.7±0.53	7.9±0.48	7-13
	XI	10.3±0.43	8.1 ±0.34	7.5±0.28	7.3±0.33	7±0.19	7-13
	DS	10.6±0.38	10.8±0.28	10.7±0.18	10.1±0.32	9.3±0.37	7-13
	DI	9.7±1.07	10.9±0.87	11.4±0.48	11±0.32	10.6±0.43	7-13
WBC (x10^3/mm^3)	XS	9±1.06	8.34±0.93	7.64±0.84	8±1.01	6.96±0.75	6-12.5
	XI	10.6±0.74	9.4±0.63	9.2±0.59	8.6±0.66	8.3±0.63	6-12.5
	DS	7.8±0.42	8.9±1.23	8.6±1.42	8.65±0.95	7,6±0.60	6.12.5
	DI	8±1.20	9.1±1.26	9.2±1.07	9.6±0.95	9.5±0.95	6-12.5
pH	XS	7.3±0.02	7.3±0.02	7.3±0.02	7.3±0.02	7.3±0.02	7.36-7.43
	XI	7.4±0.001	7.3±0,001	7.4±0.01*	7.4±0.08	7.4±0.03	7.36-7.43
	DS	7.4±0.001^{a}	7.3±0.02^{ab}	7.2±0.02^{*,b}	7.2±0.02^{b}	7.2±0.02^{b}	7.36-7.43
	DI	7.4±0.01	7.3±0.02	7.3±0.01	7.4±0.03	7.4±0.01	7.36-7.43
$PvCO_2$ (mm/Hg)	XS	47.2±1.06^{*,c}	52.6±1.6^{*,bc}	55.8±1.74^{*,b}	59.2±1.24^{*,ab}	63.4±1.99^{*,a}	38-48
	XI	36.9±1.44**	38.2±1.33**	32.9±0.95**	29.6±4.60**	33.3±2.19**	38-48
	DS	45.4±0.92^{*,c}	52.8±3.15^{*,bc}	59.4±3.77^{*,abc}	64.5±5.43^{*,ab}	70.2±5.89^{*,a}	38-48
	DI	36±0.45^{**,ab}	38.6±1.87^{**,a}	36.4±0.88^{**,ab}	33.8±1.30^{**,ab}	32.8±1.52^{**,b}	38-48
PvO_2 (mm/Hg)	XS	30.6±1.32	42.8±2.92	48.8±8.5	52.6±7.28	48.2±8.16	37-56
	XI	29.6±1.09^{c}	37.5±1.72^{bc}	42.4±1.79^{ab}	43.9±3.21^{ab}	48.7±2.3^{a}	37-56
	DS	31.2±2.03^{bc}	28.8±1.35^{c}	42.8±1.80^{ab}	47.5±4.17^{a}	55.2±6.2^{a}	37-56
	DI	33.5±3.19^{ab}	29.2±1.56^{b}	33.1±0.90^{ab}	34.3±1.56^{ab}	31.6±2.0^{b}	37-56
tCO_2	XS	32.9±0.73*	33.8±1.37	34.1±1.49*,**	35.9±1.04	37.3±0.95*	24-32
	XI	27.2±0.83*	26.5±1.20	25.1±1.10*	21.1±4.31	26.6±0.77**	24-32
	DS	33.4±0.73^{**b}	33.2±1.16^{b}	34.1±1.08^{*,**,ab}	35.9±1.28^{ab}	39.2±2^{*,a}	24-32
	DI	25.9±0.59*	26±1.48	25.4±0.83	24.8±0.54	25.1±1.07**	24-32
Hb (g/dL)	XS	14.6±0.30	13.22±1.03	12.56±1.02	11.66±0.94	11.8±0.83	11-19
	XI	15.5±0.55^{a}	12.3±0.51^{b}	11.5±0.41^{b}	11±0.46^{b}	10.7±0.2^{b}	11-19
	DS	15.3±0.27	15.4±0.51	15.3±0.54	14.4±0.70	13.4±0.39	11-19
	DI	13.5±1.18	15.8±0.63	16.2±0.53	15.4±0.36	14.8±0.33	11-19
Ht (%)	XS	50.22±1.60	45.16±3.42	44±3.66	39.74±3.21	40.2±2.60	35-52
	XI	52.3±1.93	40.5±1.66	37.8±1.39	36.3±1.57	34.8±0.75	35-52
	DS	54.8±1.87	55.94±1.88	55.3±1.71	51.4±3.05	47.6±2.30	35-52
	DI	44.6±4.61	51.4±2.50	53.6±1	53.1±1.51	51.1±1.40	35-52
HCO_3 (mm/L)	XS	31.4±0.73*	32.1±1.37	32.4±1.46*,**	34.1±1.04*	35.4±0.94*	22-29
	XI	26±0.79**	25.4±1.18	24±1.08*	24.3±1.12**	25.5±0.74**	22-29
	DS	32±0.70^{*,ab}	31.6±1.07^{b}	32.3±1^{**,ab}	33.9±1.10^{*,ab}	37±1.83^{*,b}	22-29
	DI	24.8±0.59**	24.8±1.43	24.3±0.83*	23.8±0.54**	24±1.04**	22-29
Na (mEq/L)	XS	136.4±0.87	136±0.54	137±1.04	136.2±1.06	135.2±0.96	136-142
	XI	142.8±0.30	142±1.26	142.6±1.35	127.4±16.46	140.6±1.99	136-142
	DS	138±0.83	138.6±0.87	137.2±0.96	137.7±1.25	136.5±0.47	136-142
	DI	140±1.06	138±2.25	135±1.92	137±1.44	137.6±1.08	136-142
K (mEq/L)	XS	3.5±0.17	3.3±0.20	3.4±0.26	3.6±0.30	3.7±0.28	2.2-4.6
	XI	2.9±0.06	2.8±0.11	2.7±0.11	26.4±23.27	2.8±0.16	2.2-4.6
	DS	3.5±0.19	3.8±0.23	3.4±0.23	3.7±0.29	3.8±0.36	2.2-4.6
	DI	3.2±0.07	3.5±0.09	3.4±0.05	3.4±0.05	3.5±0.08	2.2-4.6
Lactic acid (mg/dL)	XS	0.6±0.12	1.1±0.26	1±0.20	0.7±0.04	1±0.16	4-12
	XI	0.6±0.25	1.1±0.30	1±0.18	08±0.05	1±0.15	4-12
	DS	0.5±0.05^{b}	1.6±0.10^{a}	1.6±0.15^{a}	1.5±0.20^{a}	1.2±0.50^{a}	4-12
	DI	0.6±0.25	1.1±0.35	1±0.15	0.8±0.15	1±0.15	4-12

RBC; red blood count, WBC; white blood count, PH; blood PvH, $PvCO_2$; venous partial carbon dioxide, PvO_2; venous partial oxygen pressure, tCO_2; total carbon dioxide, Hb; hemoglobin level, Ht; hematocrit, HCO_3; bicarbonate, *,**; P < 0.05 between groups evaluation, a,b,c; P < 0.05 in groups evaluations. References: Kawamura 2011, Aros et al. 2017, http://cal.vet.upenn.edu/projects/fieldservice/Equine/EQCLPATH.htm

Table 4. Biochemical evaluations of groups (Mean ± SE)

Values	Groups	0th	60th	Reference ranges
TP (g/dL)	XS	7.4±0.27	6.9±0.18	5.6-7.9
	XI	7.05±0.18 [a]	6.2±0.10 [b]	5.6-7.9
	DS	7.07±0.25 [a]	6.47±0.26 [b]	5.6-7.9
	DI	7.4±0.25	6.9±0.20	5.6-7.9
AST (g/dL)	XS	337.66±30.98	320.16±34.3	100-600
	XI	591±213.50	345.25±160.08	100-600
	DS	410.75±171.55	356.25±146.08	100-600
	DI	450±52.23	345±122.05	100-600
ALT (IU/L)	XS	25±3.52	28±5.97	5-50
	XI	28±8.71	40.75±9.97	5-50
	DS	18.50±6.38	30.50±10.41	5-50
	DI	25.2±7.28	42.3±6.65	5-50
ALP (IU/L)	XS	3.2±0.20	2.86±0.12	1.9-3.2
	XI	3.07±0.23	2.65±0.11	1.9-3.2
	DS	3.40±0.12 [a]	2.87±0.08 [b]	1.9-3.2
	DI	3.05±0.23	2.58±0.15	1.9-3.2
T-bil (mg/dl)	XS	4.96±0.98	4.26±0.65	0-3.5
	XI	4.15±0.21	3.40±0.44	0-3.5
	DS	3.40±0.83	2.95±0.68	0-3.5
	DI	4.1±0.65	3.2±0.78	0-3.5
γGT (U/L)	XS	15±2.8	15±2.7	0-87
	XI	11.25±3.03	18.25±8.08	0-87
	DS	14.75±2.46	12.50±3.17	0-87
	DI	16±3.05	19±2.18	0-87
Glu (IU/L)	XS	105.16±7.53	169.66±2.80	64-150
	XI	92.25±1.49[a]	130.50±5.7[b]	64-150
	DS	88±2.16[a]	186.75±17.01[b]	64-150
	DI	104.2±8.57	165.6±3.33	64-150

TP; total protein, AST; aspartate transaminase, ALT; alanine transaminase, ALP; alkaline phosphatase, T-bil; total bilirubin, γGT; α-glutamyl transferase, Glu; glucose, a,b,c; P < 0.05 in groups evaluations. References: Kawamura 2011, Takasu et al., 2013, Aros et al., 2017, http://cal.vet.upenn.edu/projects/fieldservice/Equine/EQCLPATH.htm

monitoring is required (Muir and Hubbell, 2009; Erol and Arıcan, 2017). Anaesthetic agents cause dose-dependent reductions in arterial blood pressure with myocardial depression and peripheral vasodilatation. Many investigators (Ebert et al., 1995; Aida et al., 1996; Röding et al., 1996; Duke-Novakovski et al., 2015) have reported this dose-dependent suppression of the cardiovascular system. Sevoflurane and isoflurane have been reported to be equally arrhythmogenic in animals (Matthews and Hartsfield, 2004). In this study HR, SpO_2, BT, RR, SP, DP and MP values were recorded at the beginning of the anaesthesia and SP and MP values were higher than the reference ranges in all groups (Table 2). In this study HR, SpO_2, BT, RR, SP, DP and MP values were recorded at the beginning and during of the anaesthesia. DP and MP values showed significant decreases and increases during anesthesia in all groups (P < 0.05). DP values were higher than reference range at 0th 5th and 15th min of anaesthesia in XI, DS and DI. The statistically differences were detected between groups at 0th, 5th and 30th min of anaesthesia in DP values. Intra-groups evaluation of DP values, there were statistically differences recorded at 0th and other times in all groups. In XS, MP value was statistically different at 30th min of anaesthesia than others. Intra-groups evaluation of MP values, the statistically differences were detected between 0th, 5th, 15th and 30th, 60th min of anaesthesia in XI, DS and DI.

However, evaluations of ECG traces from all groups did not show atrioventricular blockade, atrial fibrillation, hypoxia-related extra systoles or dysrhythmias. The electrolyte parameters correlated well with our ECG evaluations as there were no significant differences detected in Na and K values.

Taylor and Clerk (2007) reported that reduction of BT can occur secondary to variations in skin thickness and environmental temperature in horses. In our study, BT showed decreases during anaesthesia in all groups. However, the decrease was significantly different only in XS.

The horse's hematologic profile is affected by different factors which are nutritional, environmental, age, sex, performance, and genetics (Padalino et al., 2014). At the same time stress, excitement, fear and the associated catecholamine exchange in blood circulation, as well as

Table 5. IOP evaluation of groups (Mean ± SE)

	Groups	0th	5th	15th	30th	60th	Reference range
IOP (mm/Hg)	XS	24±0.6	27.8±3.81	38.7±2.95	34.7±2.58	35.4±1.15	13-37
	XI	32±1	34.2±0.50	34.2±1.15	33.9±0.57	34.4±0.50	13-37
	DS	52.3±4.45	32.7±3.73	50.3±2.71	42.3±2.59	41.5±3.33	13-37
	DI	34.4±2.58	25.7±1.78	20.2±0.34	21.1±0.22	20.1±0.48	13-37

IOP; intraocular pressure, Reference; Komáromy et al., 2006; Monk et al., 2017

hyperglycemia and hypoxia can all cause changes in venous blood parameters (Robinson, 2009). These are potential reasons for the changes of RBC, WBC, Hb, Ht and lactic acid at the beginning of and during anaesthesia in the present study.

Analysis of blood gas samples from arterial and venous blood give information about ventilation and fluid-electrolyte balance (Hartsfield et al., 2006; Erol and Arıcan, 2017).In venous blood gas parameters, the significant differences were detected in pH, $PvCO_2$, PvO_2, tCO_2 and HCO_3 values ($P < 0.05$). The changes in pH values were noted during anesthesia in all groups. Depending on the changes of pH values, effected in $PvCO_2$, PvO_2, tCO_2 and HCO_3- values. These changes were more evident in sevoflurane groups and related to the compensatory response to respiratory acidosis and metabolic alkalosis. Venous blood values (pH, $PvCO_2$, PvO_2, tCO_2 and HCO_3) are 5-10 mmHg and 1-5 mEq/l higher than arterial values (Steffey et al., 2005; Marcilla et al., 2012).

The α-2 agonists cause cardiac depression and hypoxemia. The resulting cardiac depression and hypoxemia decrease PO_2 and increase PCO_2 values. In addition, inhalation anaesthetic agents cause respiratory depression and increase in PCO2 values. The level of depression depends on doses of inhalation agents (Kronen, 2003). Detomidine is 10 times more potent and produces deeper and longer sedation than xylazine (Yamashita et al., 2000; Steffey et al., 2005; Padalino et al., 2014). The effects of sevoflurane on CNS are lower than isoflurane and compared to other inhalation anesthetics the suppression effect is greater at increasing doses. Sevoflurane reduces systemic vascular resistance, arterial blood pressure and mean pulmonary arterial pressure during anaesthesia. However, these conditions are not fully observed during anesthesia and may vary depending on the anaesthetic duration (Mutoh et al., 1997; Muir and Hubbell, 2009). The decreases of anaesthetic agent doses during the anaesthetic period and the concurrent ECG and venous blood parameters evaluations support the literature findings (Mutoh et al., 1997; Kronen, 2003; Padalino et al., 2014). Yamashita et al. (2006) emphasized that α-2 agonists and ketamine-midazolam combinations cause to decrease PO_2 values but do not significantly change PCO_2 and cardiovascular findings. They have also been associated with intrapulmonary shunts and ventilation-perfusion mismatch. Intermittent positive pressure ventilation (IPPV) suppresses the cardiovascular functions during general anaesthesia in horses because the mechanical ventilation increases thoracic pressure and retards venous blood circulation (Taylor and Clerk, 2007). Kushiro et al. (2005) reported that cardiovascular functions are more suppressed than during normal spontaneous breathing during anesthesia in horses due to the increased amount of catecholamine in circulation. There were statistically differences recorded in $PvCO_2$, PvO_2, tCO_2 and HCO_3 values between and among groups. In XS and DS, $PvCO_2$ values were higher than XI and DI at 5, 15, 30 and 60th min of anesthesia. PvO_2, tCO_2 and HCO_3 values of DI were lower than the others at same times. The highest values of $PvCO_2$, PvO_2, tCO_2 and HCO_3 were detected in DS at 60th min of anesthesia. In the current study, the observed decreases and increases in $PvCO_2$, PvO_2, tCO_2 and HCO_3 values in groups were thought to be due to the changes in the amount of circulating catecholamine and ventilation support, and varied

depending on the anesthetic agents' doses.

The biochemical values may be different in the pre-anaesthetic, anaesthetic and post-anaesthetic periods due to differences in anaesthetic agents. It is important to have information about liver function before and after anaesthesia. The differences in these values because of detoxification of anaesthetic agents in liver balance the anaesthetic agents' effects on liver (Steffey, 2009; Hubbell et al., 2011). In the present study, the biochemical parameters' levels changed after anaesthesia. However, the TP, AST, ALT and ALP values detected, although significantly different, were still within the reference interval (Table 4). T-bil values were higher at 0 and 60th min of anesthesia than reference range in XS. At the end of anaesthesia Glu values in XS, DS and DI were higher than in XI and the reference values. The use of α-2 agonists in horses cause to decrease in TP value and hyperglycaemia (Muir and Hubbell, 2009). In our study TP values decreased in all groups at 60th min. This condition supported the literature information. The changes of AST, ALT and ALP values between 0th and 60th min in all groups were thought due to detoxification of anaesthetic agents in liver. The significant difference of ALP value in DS was more evident than others. However, it was within reference interval. The higher T-bil values reason was thought to be due to age, sex and gender of horses. The increases of Glu values in all groups supported the anaesthetic agents' effects on liver.

Ketamine is the most commonly used dissociative anaesthetic agent in horses. It has been reported that it increases renal blood flow, mucous secretions of the respiratory tract and the amount of catecholamine in circulation. The fact that ketamine is metabolized in the liver was reported in previous studies (Hall et al., 2000; Rosetti et al., 2008; Levionnois et al., 2010; Oku et al., 2011). Liver function during anaesthesia depends on liver blood flow, metabolites of anaesthetic agents and other drugs. Isoflurane and sevoflurane are less hepatotoxic than other inhalation anaesthetics (Topal et al., 2003). Our study supported the literature's previously reported information (Hall et al., 2000; Topal et al., 2003; Rosetti et al., 2008; Levionnois et al., 2010; Oku et al., 2011).

In general anaesthesia, anaerobic metabolism begins to produce lactate due to decreased perfusion in tissues and an increase in the amount of lactate during anaesthesia. Along with anaerobic metabolism Glu levels increase due to sympathetic stimulation and lipolysis (Edner et al., 2005). Steffey and Pascoe (2002) emphasized that α-2 agonists increase the serum Glu levels in a dose-dependent manner. In XS, DS and DI the Glu values were greater than reference limits at the end of the anesthesia (Table 4). The increase of Glu values were significant in XI and DS. However, DS Glu values were higher than reference interval. The changes of Lac values were detected in groups but they were in reference limits. The measured Glu values in our study showed changes due to anaerobic metabolism during the anaesthesia.

The IOP measurement is part of the routine eye examination in horses with tonometry and has become more widely used in recent years. The reference range for horses using tonometry is reported as 15-37 mmHg (Komáromy et al., 2006; Monk et al., 2017). Several factors such as the time of day, sedation, anesthetic agents and head position influence the IOP (Hall et al., 2000; Stine et al., 2014; Arıcan et al., 2015; Monk et al., 2017). In the present study, there were no statistical differences seen in IOP values at the 0th, 5th, 15th, 30th and 60th minutes of anaesthesia between and within groups. The IOP values of DS were higher at the 0th (Control), 15th, 30th and 60th min of anesthesia. No statistical differences were detected between and within groups. These differences were thought to be related to the anaesthetic agents' effects on the intracranial and cerebral perfusion pressures. On the other hand, these results suggest that the anaesthetic combinations used in our study can be used safely for eye surgeries in horses.

CONCLUSION

In conclusion, this study shows that the anaesthetic combinations of sevoflurane and isoflurane with xylazine and detomidine provided safe and suitable anaesthesia in horses. It is a comprehensive study on the evaluation of anaesthesia combinations in horses and the transfer of our experience to clinicians. There were statistical differences

in hematologic, biochemical and cardiovascular parameters even when these values were found within normal physiological limits. It was determined that both inhalation anaesthetic drugs studied could depress the respiratory system due to dose-dependent effects, and similar effects were observed between sevoflurane and isoflurane anaesthesia on the respiratory and circulatory systems. It has been clinically determined that the choosing of α-2 agonist and their action times are very important in general anaesthesia. The cardiopulmonary changes were more prominent in sevoflurane groups. Our study did not reveal any statistical differences in IOP measurements. However, it should be noted that intraocular pressures were measured with the animals lying down and our results do not rule out changes in IOP in a standing position. We concluded that these anaesthesia protocols are suitable for ophthalmic surgery.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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