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RESEARCH ARTICLE

Comparative Study on Sevoflurane Anesthesia Alone and Combined with Partial Intravenous Anesthesia using Dexmedetomidine in Healthy Horses

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ABSTRACT

Partial intravenous anesthesia (PIVA) seems to be a good alternative to either inhalational or total intravenous anesthesia regarding their adverse cardiopulmonary, respiratory, and other body systems effects. Many protocols have been recently investigated in order to find a safer, more effective one. The aim of the present study was to evaluate whether the addition of dexmedetomidine constant rate infusion (CRI) to sevoflurane anesthesia would have any beneficial influence on sevoflurane requirements, cardiorespiratory function, acid-base status, blood gases, hemocoagulation and recovery in healthy horses. Six horses were submitted to either sevoflurane anesthesia (group S) or PIVA using sevoflurane and dexmedetomidine (group SD). The main cardiovascular and respiratory parameters were recorded every 5 minutes throughout 3 hours. Acid-base and hemocoagulation variables, and blood gases were measured at the beginning and in the end of each anesthesia. Times to recovery and its quality were scored. Analysis of variance (ANOVA) for repeated measurements, t-test for normally distributed data or Mann-Whitney test for not normally distributed variables, one-way ANOVA, post-hoc Fisher test, and Wilcoxon signed rank test were used for statistical analysis. In conclusion, PIVA using dexmedetomidine CRI decreased slightly sevoflurane requirements in healthy horses. Sevoflurane anesthesia with or without dexmedetomidine CRI maintained stable cardiovascular status. Respiratory depression, increased blood lactate levels and unchanged coagulation parameters (except for APTT) were observed in the two anesthesia protocols. The recovery times were short and comparable in both groups but recovery quality was better in the SD group.

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INTRODUCTION

Anesthesia related mortality rate has been reported to be much higher in horses than in other domestic species of animals (Johnston *et al.*, 2002, 2004; Dugdale *et al.*, 2016). Lethality rate was 0.9% after elective procedures and 11.7% in emergency equine cases. Comparatively, the death rate of healthy dogs and cats (ASA 1 and 2) was 0.12% while for sick animals (ASA status 3 and over) the overall death rate was 4.77% (Bille *et al.*, 2012). Thus, it is appealing to seek safer anesthetic protocols in horses with minimum risk to life. Several factors have been associated to fatal outcomes occurring in the perianesthetic period, such as cardiovascular, respiratory, and coagulation disturbances, accidents during the recovery period, prolonged anesthesia, and high dose of inhalational anesthetics.

Different drugs and their combinations have been systemically administered in anaesthetized horses in order to reduce the amount of volatile agent whilst improving cardiopulmonary status and recovery quality. However, the results are often contradictory with insufficient information (Gonzalo-Marcilla *et al.*, 2014, 2015; Risberg *et al.*, 2016).

The aim of the study was to compare sevoflurane anesthesia to PIVA using sevoflurane and dexmedetomidine CRI regarding their effects on volatile agent requirements, cardiorespiratory function, acid-base status, blood gases, hemocoagulation and recovery in healthy horses.

MATERIALS AND METHODS

The study was performed with a permission given by the Ethical Committee of the Faculty of Veterinary Medicine at Trakia University in Stara Zagora.

Six healthy horses (three mares and three geldings), aged between 4 and 20 years, with body weight 272.67±27.04 kg were included in the trial. They were submitted to either sevoflurane anesthesia (group S) or PIVA using sevoflurane and dexmedetomidine (group SD) with two weeks washout period producing a cross-over design. Premedication and induction were the same in the two groups. Acepromazine maleate (Neurotranq®, Alfasan International, Holland) 0.03 $mg.kg^{-1}$ was applied intravenously and 30 min later, xylazine hydrochloride (Alfasan International, Holland) 0.8 $mg.kg^{-1}$ was injected IV. Induction was achieved with a mixture of diazepam (Diazepam, Sopharma, Bulgaria) 0.05 $mg.kg^{-1}$ and ketamine hydrochloride (Anaket®, Richter Pharma, Austria) 2.2 $mg.kg^{-1}$ IV.

Horses from group S were maintained in surgical plane of anesthesia only with sevoflurane (Sevorane®, Abbott Laboratories Ltd., United Kingdom) in 100% oxygen, whereas horses from the SD group received additionally dexmedetomidine hydrochloride (Dexdomitor®, Orion Pharma, Finland) CRI of 1.75 $\mu g.kg^{-1}.h^{-1}$ in saline solution at a concentration of 0.01 $mg.ml^{-1}$, applied by means of micro infusion pump WZ-50C6 (All Pro, China). A CRI of saline solution at the same rate and volume as in group SD was given to the S group. The syringes were prepared just before anesthesia and performing anesthetist was unaware of their content.

Intensive monitoring of anesthetic depth, cardiovascular and respiratory functions was performed throughout anesthesia duration which was three hours using a patient monitor PM-9000Vet (Mindray, China). Horses were allowed to breathe spontaneously. If the arterial partial pressure of CO_2 ($PaCO_2$) increased above 60 mmHg, the arterial partial pressure of O_2 (PaO_2) decreased bellow 100 mmHg, or respiratory rate (RR) was lower than 4 breaths $minute^{-1}$ for more than 3 minutes, an intermittent positive pressure ventilation (IPPV) was applied.

Ringer's solution (Actavis, Bulgaria) was administered in both groups at a minimum rate of 10 $ml.kg^{-1}.hour^{-1}$ with some corrections. The rate was adjusted to maintain mean arterial pressure above 60 mmHg. Nevertheless, if blood pressure continued to drop, dopamine hydrochloride (Warsaw Pharmaceutical Works Polfa SA, Poland) was infused starting at a rate of 0.5 $\mu g.kg^{-1}.min^{-1}$ and adjusted if required.

The surgical depth of anesthesia was maintained by adjusting vaporizer setting according to the classical parameters for anesthesia depth estimation and the response to electrical stimulation as previously described by Simeonova and Sleiman (2014).

Arterial and venous blood samples were collected before switching on the vaporizer and just before switching off the vaporizer for measurement of blood gases, acid-base and coagulation parameters.

After 3 hours of general anesthesia, the animals were moved to a quiet padded box and allowed to recover. The times for extubating, for assuming sternal position, and for standing were recorded. The quality of recovery was scored using the following grading system (Marcilla *et al.*, 2010):

Score	Description
1	One attempt to stand, no ataxia
2	One-two attempts to stand, some ataxia
3	More than two attempts to stand but quiet
4	More than two attempts to stand, excitement
5	Severe excitement, self-injuring

Statistical analysis: Data were analyzed by means of a commercially available software package (Statistica® 6-0 version, StatSoft Inc. USA). Analysis of variance (ANOVA) for repeated measurements was used to detect the influence of time and treatment upon each variable. Recovery times between two anesthetic protocols were compared using one-way ANOVA and post-hoc Fisher test. Recovery scores (median and interquartile range) were compared in the Wilcoxon signed rank test. The level of statistical significance was set at 0.05 for all analyses.

RESULTS

Dexmedetomidine supplementation decreased slightly sevoflurane requirements for maintenance of surgical anesthesia in healthy horses. This statement was made on the grounds of the results regarding EtSevo, MAC, and Sevo Vol %. All these parameters decreased with time and had lower values in the SD group than in the S group at all time periods (fig.1). A fifteen percent reduction of MAC was calculated in SD group (0.93±0.09) in comparison with the S group (1.09±0.11). EtSevo was by 12% lower in SD horses (2.0±0.31%) than in the S group (2.26±0.24%). The reduction of vaporizer setting was estimated to be 19% (3.48±0.56 in S group; 2.83±0.65 in SD group).

The main cardiovascular parameters heart rate, systolic, mean, and diastolic blood pressures remained stable throughout both anesthesia types and significant differences between groups were not observed. There were no arrhythmias in all anaesthetized animals. Horses from the SD group showed higher systolic and diastolic blood pressures vs the initial period but not in comparison with the S group.

Results regarding respiratory parameters saturation (SAT) and $EtCO_2$ did not differ between both anesthesia types. RR was a bit higher in the SD group, statistically significant only at 50^{th} min. Two out of six horses from the S group and three out of six animals from the SD group were periodically mechanically ventilated.

The 3-hour sevoflurane anesthesia in healthy horses led to respiratory acidosis with hypoxemia (Table 1). Respiratory acidosis developed at the end of both anesthesia protocols but slightly less significant changes were observed in horses submitted to PIVA with sevoflurane and dexmedetomidine while hypochromic anemia and hypoxemia were more obvious in this group. Hypoxemia developed in all animals despite high inspired oxygen concentrations in group S (mean FiO_2 of 88.96%) and group SD (mean FiO_2 of 87.27%). Values of blood electrolytes did not differ either vs the initial period or between groups.

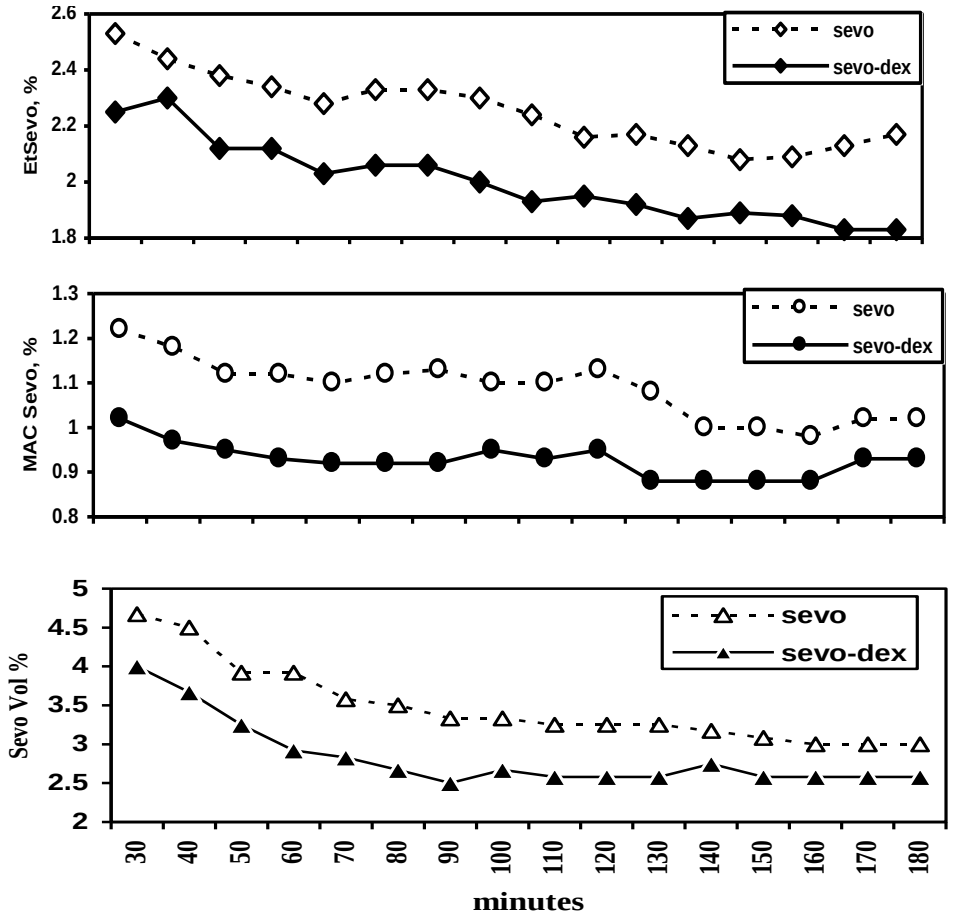

Fig. 1: Dynamics and differences of sevoflurane end tidal (EtSevo), minimal alveolar concentration (MAC Sevo), and vaporizer settings (Sevo Vol%) throughout the three hours of inhalation anesthesia (sevo) or PIVA using sevoflurane and dexmedetomidine CRI (sevo-dex) in healthy horses.

Table 1: Blood gases and acid-base parameters (mean±SD) of horses submitted to sevoflurane anesthesia (group S) or combined sevoflurane inhalational with CRI of dexmedetomidine (group SD)

Group	Period	n	pH	$PaCO_2$, mmHg	HCO_3, mmol/l	AG, mmol/l	tCO_2, mmol/l	BE, mmol/l	PaO_2, mmHg	tHb, g/l	Sat, %	Na^+, mmol/l	K^+, mmol/l	Cl^-, mmol/l
S	0 h	6	7.388	50.67	28.15	13.27	29.7	2.67	150.83	93.67	97.0	145.0	4.02	107.83
			±0.053	±5.57	±1.84	±1.01	±1.87	±2.22	±71.48	±14.71	±2.96	±3.35	±0.32	±2.48
S	3 h	6	7.261	71.50	29.67	11.60	31.88	1.5	85.33	76.67	89.0	145.5	3.78	108.17
			±0.065**	±10.29**	±2.93	±3.56	±3.04	±3.42	±34.11	±10.80	±6.45	±1.38	±0.25	±1.6
SD	0 h	6	7.395	52.0	29.48	11.85	31.1	3.85	144.0	97.5	96.5	145.17	4.08	108.17
			±0.052	±3.95	±1.89	±2.12	±1.85	±2.61	±86.25	±11.15	±3.08	± 3.66	±0.29	±2.79
SD	3 h	6	7.318	69.0	31.48	9.3	33.58	3.88	90.0	66.03	81.83	142.67	4.15	106.33
			±0.095	±21.65*	±3.89	±3.45	±4.51	±2.63	±32.73	±32.89*	±19.53*	±4.68	±0.36	±3.08

*P<0.05; **P<0.01; ***P<0.001 – level of significance of differences between 0 h and 3 h. $PaCO_2$ – arteria partial pressure of carbon dioxide; HCO_3 – actual bicarbonate content; AG – anion gap; tCO_2 – total carbon dioxide content; BE – base excess; PaO_2 – arterial partial pressure of oxygen; tHb – total hemoglobin content; Sat – saturation.

Table 2: Blood coagulation parameters of horses (mean±SD) submitted to sevoflurane anesthesia (group S) or combined sevoflurane inhalation with CRI of dexmedetomidine (group SD)

Group	Period	n	D-dimer, µg/ml	Fibrinogen, g/l	APTT, s	PT, s	TT, s	Lactate, mmol/l
S	0 h	6	2.19±1.1	2.91±0.85	57.82±8.86	12.02±1.84	19.72±2.55	1.51±0.47
S	3 h	6	2.18±0.92	2.36±1.17	65.75±9.75	13.37±2.5	19.92±2.27	3.94±2.23**
SD	0 h	6	2.18±0.96	3.57±1.01	58.08±14.31	13.17±0.47	18.47±3.32	0.92±0.22
SD	3 h	6	2.92±1.12	3.3±1.07	49.47±9.11▲	12.78±0.91	18.63±2.6	1.56±0.43▲▲

* P<0.05; **P<0.01 – level of significance of differences between 0 h and 3 h; ▲P<0.05; ▲▲P<0.01 – level of significance of differences between two anesthesia types for the respective period; PT - prothrombin time, APTT - activated partial thomboplastin time, TT - thrombin time.

Table 3: Recovery score (median and IQR) and recovery times (mean±SD) in sevoflurane anaesthetized horses with (group SD) and without (group S) a CRI of dexmedetomidine.

Group	n	Score	Extubation Time (min)	Time to Sternal (min)	Time to Standing(min)
S	6	3 (3-3)	5.83±2.04	12.33±3.56	26.17±6.46
SD	6	2 (1-3)*	7.17±3.37	14.5±7.37	24.67±12.01

*Differences between two anesthesia types (P<0.05).

Sevoflurane anesthesia did not influence any of the investigated coagulation variables. The addition of dexmedetomidine to sevoflurane anesthesia caused only a shortening of APTT, whereas other coagulation parameters did not change (Table 2). Both anesthesia types increased blood lactate levels. We found out a difference in values between groups by the 3rd hour of

anesthesia. D-dimer showed similar results in all time periods for the two groups.

Extubating times, times to sternal, and times to standing did not differ between S and SD groups (Table 3). Recovery score of horses submitted to CRI of dexmedetomidine with sevoflurane anesthesia was lower, meaning better recovery quality than that of horses anaesthetized with sevoflurane alone.

DISCUSSION

We found out that dexmedetomidine administration in horses as a constant-rate infusion (CRI) during sevoflurane inhalational anesthesia preserved optimal cardiopulmonary function with fast, calm and coordinated recoveries. Limited inhalational anesthetic sparing effects have been demonstrated in horses.

A recent similar study of Gozalo-Marcilla *et al.* (2013) demonstrated that dexmedetomidine CRI decreased mean sevoflurane MAC from 2.42 to 1.07% with mean MAC reduction of 53%. Their experimental design was similar to ours but we found out only 15% reduction of MAC and 12% reduction in EtSevo. This difference might be due to the lack of a loading dose of dexmedetomidine in our PIVA protocol. In the study of Patel *et al.* (2013) the use of dexmedetomidine with sevoflurane was associated with a statistical significant 21.5% decrease in EtSevo when dexmedetomidine loading dose was given as compared to the group where fentanyl was applied before CRI of dexmedetomidine.

In humans high concentrations of dexmedetomidine have been reported to decrease MAC of sevoflurane by 17%, whereas there was no difference between the placebo and the low dose dexmedetomidine group (Fragen and Fitzgerald, 1999).

In dogs the effects of lidocaine and dexmedetomidine or their combination, administered by CRI, on the MAC of sevoflurane was determined by Moran-Munõz *et al.* (2014). According to their results the CRI administration of lidocaine, dexmedetomidine and their combination produced a significant reduction in the MAC of sevoflurane by 26.1±9.0, 43.7±11.8 and 54.4±9.8%, respectively. They used an intravenous loading dose of 2µg/kg dexmedetomidine, followed by 2µg.kg^{-1}.hr^{-1} CRI.

The probable explanation of unsatisfactory sevoflurane-sparing effect of dexmedetomidine could also be the low dose used in our experiment. A calculated CRI of 7µg.kg^{-1}.h^{-1} dexmedetomidine after a bolus of 3.5 µg.kg^{-1} was equisedative to a CRI of 1mg.kg^{-1}.h^{-1} xylazine after a bolus of 0.5 mg.kg^{-1} (Müller *et al.*, 2012). In their study on isoflurane-sparing effect of dexmedetomidine Marcilla *et al.* (2012) used the same low dose of 1.75µg.kg^{-1}.h^{-1} as in our experiment after initial loading dose of 3.5.µg.kg^{-1} and concluded that dexmedetomidine did not reduce significantly isoflurane requirements in horses submitted to elective surgeries. MAC-reducing action of dexmedetomidine requires a central noradrenaline turnover suppressive effect >20%, antinociceptive effect >40% and hypnotic effect >80% of the available alpha-2-adrenoceptors occupation in locus coeruleus (Rabin *et al.*, 1996).

Regarding the influence of the used alpha-2 agonist on cardiovascular and respiratory functions our results showed that sevoflurane anesthesia with or without dexmedetomidine supplementation maintained stable cardiovascular parameters and the low dexmedetomidine dose did not intensify cardiovascular depression caused by volatile anesthetics. These data were in concordance with other investigations (Marcilla *et al.*, 2010; 2012). All volatile agents cause dose-dependent hypotension (Grosenbaugh and Muir, 1998). The modern anaesthetics are potent vasodilators; reductions in blood pressure above 1 MAC are largely due to dose-dependent decreases in stroke volume and cardiac output. Mode of ventilation further impacts the magnitude of this depression. When ventilated to maintain isocapnea, cardiac output is much better preserved between 1.0 to 1.5 times MAC of sevoflurane than over 1.5 times MAC (Steffey *et al.*, 2005). We also used IPPV for maintenance of adequate respiration but cardiovascular parameters remained stable with MAC around 1 and with the help of dopamine.

All inhalational agents cause dose-dependent hypoventilation. As a species, horses are much more sensitive to the respiratory-depressant effects of volatile anesthetics than dogs, cats, or humans. Lightly-anaesthetized horses at concentrations around MAC commonly have arterial CO_2 tensions >65 mmHg and may require ventilatory support. We also observed a hypercarbia causing acidemia as was reported by Matthews *et al.* (1999) which required periodical mechanical ventilation in both S and SD groups. According to our results the addition of dexmedetomidine to sevoflurane anesthesia seemed to deepen these respiratory effects which are not unfavorable effects, as maintaining intraoperative $EtCO_2$ at 60 mmHg in mechanically ventilated horses resulted in more rapid RSV compared with when $EtCO_2$ was maintained at 40 mmHg (Thompson and Bardell, 2016).

Ventilation-perfusion (V/Q) mismatch and physiologic right-to-left shunts commonly occur in recumbent anaesthetized horses, resulting in an increased alveolar-to-arterial oxygen gradient that reflects impaired pulmonary gas exchange function (Brosnan, 2013; Hubbell and Muir, 2015). We found out profound hypoxemia in both groups which corresponded to elevation in blood lactate levels. This was opposite to the data of Serpa *et al.* (2012) who reported no significant increase in blood lactate caused by detomidine CRI in sevoflurane anaesthetized horses. With low levels of serum insulin, the effect typical for alpha-2 agonists, body tissues are unable to capture glucose. The observed lactate serum concentrations below the normal range suggest that all lactate produced by the tissues is being utilized in the energy metabolism. This was not the case in our study.

The investigations regarding the influence of general anesthesia on blood coagulation in horses are very limited. In humans halothane has been shown to suppress platelet aggregation in vitro and ex vivo. Sevoflurane had a stronger suppressive effect on platelet aggregation than halothane and isoflurane with increased bleeding time at 1-1.5 times MAC (Yokubol *et al.*, 1999). In the present in vivo study sevoflurane anesthesia did not alter coagulation parameters while a combination with dexmedetomidine slightly shortened APTT. In our previous works (Simeonova, 2012; Simeonova and Sleiman, 2014) we found out that in contrast to inhalational anesthesia alone,

the combination of halothane or isoflurane with dexmedetomidine caused an activation of coagulation system detected by elevation in plasma D-dimer levels that corresponded to an elevation of blood lactate levels. These data suggest that minor changes in coagulation system in horses receiving a CRI of dexmedetomidine in addition to volatile anesthesia were more likely due to combined effects of PIVA on body systems such as hypoxia, acidosis, hypotension, and low body temperature, rather than to pharmacological properties of the drug itself.

Recovery of horses was fast and uneventful in both S and SD groups with better quality when dexmedetomidine was supplemented to sevoflurane. Matthews *et al.* (1999) also reported a satisfactory recovery in sevoflurane anaesthetized horses submitted to various surgical procedures. Mean time to sternal recumbency was 27 min, average time to standing was 33 min and time to adequate coordination was 44 min. These times were longer than those in our study, probably because most horses received xylazine during recovery or because of higher body weight of animals. We found out that a combination of sevoflurane with dexmedetomidine CRI could improve recovery quality in healthy horses.

Conclusions: PIVA using dexmedetomidine CRI decreased slightly sevoflurane requirements in healthy horses. Sevoflurane anesthesia with or without dexmedetomidine CRI maintained stable cardiovascular status, whereas respiration was depressed as a result of respiratory acidosis and hypoxemia which were more obvious in SD group. Both anesthesia types increased blood lactate levels. Coagulation parameters did not change in sevoflurane anesthesia and little APTT shortening was detected when dexmedetomidine was added. The recovery times were short and comparable in both groups but recovery quality score was better in the SD group.

Authors contribution: DD and GS conceived and designed the project. MS gave financial support. GS and MS executed the experiment and analyzed the venous and arterial blood samples. DD and GS interpreted the data, critically revised the manuscript for important intellectual contents. All authors approved the final version.

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