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## Evaluation of a Mixture of Thiopental-Guafinesine-Metedomidine and Sevoflurane Anesthesia in Horses

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**Abstract:** The anesthetic and cardiopulmonary effects of a combination of continuous intravenous infusion using a mixture of 6 g L<sup>-1</sup> thiopental-75 g L<sup>-1</sup> guafinesine-3 mg L<sup>-1</sup> metedomidine (0.30 mL/kg/h) and Oxygen-Sevoflurane (OS) anesthesia (TGM-OS anesthesia) in horses were evaluated. The concentration of sevoflurane (Sevo) required maintaining surgical anesthesia was around 1.5% in TGM-OS and 3.3% in OS anesthesia. Mean Arterial Blood Pressure (MABP) was maintained at around 77 mm Hg under TGM-OS anesthesia, while dobutamine (0.43±0.13 µg kg<sup>-1</sup>) infusion was necessary to maintain MABP at 60 mmHg under OS anesthesia. No apparent complication was observed during and after anesthesia in all cases. Recovery from anesthesia under TGM-OS anesthesia was very calm and smooth. The times required for the horse to return both sternal and standing position in group under TGM-OS anesthesia tended to be shorter than group under OS anesthesia which statistical differences were p<0.05 and p<0.01, respectively. Thiopental Guafinesine-Metedomidine and Oxygen-Sevoflurane anesthesia (TGM-OS anesthesia) may be useful for prolonged equine anesthesia because of its minimal cardiopulmonary effects and good recovery from anesthesia.

**Key words:** Equine, thiopental, guafinesine, metedomidine, sevoflurane

## INTRODUCTION

Sevoflurane (Sevo) is a halogenated inhalant anesthetic with favourable chemical and pharmacodynamic properties. Its low blood solubility facilitates rapid induction and recovery from anesthesia and better control of anesthesia depth during maintenance when compared to other common used volatile anesthetic agent (Eger, 1994; Behne *et al.*, 1999). Mean values for the Minimal Alveolar Concentration (MAC) of Sevo in horses have been reported by some researchers i.e., 2.3% by Aiada *et al.* (1994), 2.31% by Natalini, (2001) and 2.6-2.9% by Mizuno *et al.* (1996). For these reasons the new inhalant agent has gained increasing interest in horse anesthesia. However, Sevo causes dose dependent cardiopulmonary depression as well as hypoventilation and hypotension at the stage of surgical anesthesia (Aida *et al.*, 1996; Grosenbaur and Muir, 1998). Assisted or controlled ventilation and administration of vasopressin should be considered during Sevo-O<sub>2</sub> (OS) anesthesia in horses and

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intermittent positive ventilation has been used to improve hypoventilation during anesthesia in horses but this also leads to further cardiac depression (Yamashita *et al.*, 2000). A low dose dobutamine infusion has been recommended to prevent or treat hypotension that develop in horses anesthetized with a volatile anesthetic agents (Donaldson, 1988; Lee *et al.*, 1998; Swanson *et al.*, 1985). The infusion of dobutamine in horses anesthetized with halothane, sometimes leads to the development of cardiac arrhythmias and tachycardia (Donaldson, 1988; Lee *et al.*, 1998; Young *et al.*, 1998). It has been suggested that intravenous anesthesia may be associated with lower incidence of perioperative cardiovascular emergencies and lower anesthetic risk (Johnston *et al.*, 2002). Total Intravenous Anesthesia (TIVA) has been investigated as an alternative to inhalation anesthesia (Bettschart-Wolfansberger *et al.*, 1996; Nolan *et al.*, 1996; Flaherty *et al.*, 1997; Taylor *et al.*, 1995, 1998). This involves different drugs combination administered either as repeated injection or as infusion. One of the most studied and familiar TIVA technique in horses is using a combination of ketamine,  $\alpha_2$  agonist and guaifenesine (Greene *et al.*, 1986; McCarty *et al.*, 1990; Taylor *et al.*, 1992, 1998; Young *et al.*, 1993). It has been reported that combination of continuous intravenous infusion using a mixture of guaifenesine-ketamine-xylazine and OS and guaifenesine - ketamine - medetomidine could minimize cardiovascular effects by reducing requirement of Sevo for the maintenance of surgical anesthesia in horses and at this anesthesia MAPB was maintained at an appropriate level without administration of vasopressor (Yamashita *et al.*, 2000).

Medetomidine is more specific  $\alpha_2$  adrenoceptor agonist compared to detomidine and xylazine and it is more potent than xylazine in both behavioral and neurochemical effects (Bryant *et al.*, 1991; Yamashita *et al.*, 2002). It is emphasized that a mixture of GKM would be more potent than that GKX (Yamashita *et al.*, 2000).

The purpose of this study was to evaluate the anesthetic and cardiopulmonary effects of a combination of continuous intravenous infusion using mixture of Thiopental-Guaifenesine-Medetomidine and OS (low dose) anesthesia (TGM-OS anesthesia) in horses.

## MATERIALS AND METHODS

This study protocol was approved by Atatürk University's Animal Care and Use Committee. This study was conducted between 2005-2008, at the Ataturk University, Veterinary Faculty, Clinic of Surgery, Erzurum, Turkey.

### Animals

In this study, two group horses were used. Group A consisted of eight local breed aged  $6.5 \pm 1.3$  years and weighing  $457 \pm 28$  kg. Group B consisted of eight local breed aged  $7.8 \pm 2.4$  years and weighing  $430 \pm 30$  kg.

### Study Design

Animals were fasted for 12 h before experiments but water were given *ad libitum*. In addition to physical examination, venous blood samples for standard clinical haematology and serum chemistry profiles were taken from each horse one day prior to the experiment. All horses in groups A and B were premedicated by using  $0.010 \text{ mg kg}^{-1}$  of medetomidine (Domitor, Orion Pharma) intravenously and anesthetized with  $6 \text{ mg kg}^{-1}$  thiopental (Veterinary Pentothal, Rhone-Merieux). After orotracheal intubation, the horses were positioned in left lateral recumbency and the right fascial artery was raised surgically in to a subcutaneous position under Sevo (Sevorane, Abbot Laboratories)+O<sub>2</sub> (OS) anesthesia in groups A and B. Anesthesia were maintained under thiopental-guaifenesine (Guailaxin, Ford-Dodge)-medetomidine (TGM)+OS (TGM-OS) anesthesia in group A and under OS anesthesia in group B for 180 min. TGM mixture containing  $75 \text{ g L}^{-1}$  of guaifenesine,  $3 \text{ mg L}^{-1}$  of medetomidine

and 6 g L<sup>-1</sup> thiopental in serum physiologic was injected at 0.30 mL/kg/h through infusion pump (Flo-Dard RMC 9611) and a 16 inch gouge catheter (Happycath, Medikit) placed in the right jugular vein and surgical anesthesia was maintained by controlling the concentration of inhaled Sevo+O<sub>2</sub> in group A. In group B surgical anesthesia was maintained by Sevo+O<sub>2</sub> anesthesia. When ABP decreased around 50 mmHg, dobutamine 0.43±13 µg/kg/min (Dobutrex, Shionogi) was administered intravenously to maintain Arterial Blood Pressure (ABP) around 60 mmHg. All horses in group A and B were anesthetized for 3 h with TGM+OS anesthesia and OS anesthesia, respectively.

### Sample Collection and Analysis

Heart Rate (HR) Mean Arterial Blood Pressure (MABP) and Body Temperature (BT) were recorded by an anesthetic monitoring system (Bionet, Br3). Arterial blood pressure was measured by connecting an 14 gauge catheter placed into the right fascial artery to a pressure transducer. Arterial blood samples were taken from the same catheter into a heparinized syringe and analyzed by a blood gas analyzer (Technicon RA-TX).

All samples and data were collected each 30 min during anesthesia. Statistical analysis were made using one way ANOVA test.

## RESULTS

In group A, spontaneous blinking and nystagmus were observed at the beginning of the anesthesia and they also showed a dull palpebral reflex and strong corneal reflex. In the horses of group B, corneal reflex and palpebral reflexes were observed but spontaneous nystagmus and tearing were not seen during anesthesia. Total anesthesia time, the time required for the horse to return the sternal position, the number of attempts to stand and to the standing position after the anesthesia period in group A and B are given in Table 1.

The time required for the horse to return both sternal and standing position in group A tended to be shorter than group B and statistical differences were p<0.05 and p<0.01, respectively. The attempts to stand in all group was almost equal. In group B, hypotension developed after an hour anesthesia. Six horses in group B required infusion of dobutamine (0.45±0.15 µg/kg/min) to maintain ABP during OS anesthesia.

Changes in Sevo dose, Body Temperature (BT), Heart Rate (HR), Respiratory Rate (RR), Mean Arterial Blood Pressure (MABP), partial pressure of CO<sub>2</sub> (PaCO<sub>2</sub>), partial pressure of O<sub>2</sub> (PaO<sub>2</sub>) and dobutamine during anesthesia in group A and B are summarised in Table 2.

The percentage Sevo required for the anesthesia in group A (approximately 1.5%) was lower than group B (approximately 3.3%) which was different statistically (p<0.01). Mean Arterial Blood Pressure (MABP) was high at the beginning of the anesthesia in both groups. In group A, MABP was maintained at an appropriate level and was higher than that in group B (p<0.01). When ABP decreased in group B, dobutamine was administered intravenously to maintain the mean ABP at approximately 63 mmHg. BT decreased during anesthesia in both groups. HR was at about 35 beats min<sup>-1</sup>. in group A but it increased in group B which was different statistically (p<0.05). RR were also different statistically between two groups as seen in Table 2. Oxygenation was excellent in all horses of both groups and the PaO<sub>2</sub> levels were about 400 mmHg and above it.

Table 1: Mean values (±SD) of sternal position, attempts to stand and standing position.

Conditions (min)	Group A (Mixture+SevoO <sub>2</sub> )	Group B (SevoO <sub>2</sub> )
Anesthesia time	180.0	180
Sternal position	25.0±13	34.0±8*
Attempts to stand	2.6±1	3.2±2
Standing position	38.0±14	53.0±17**

\*p<0.05, \*\*p<0.01

Table 2: Mean values ( $\pm$ SD) of sevoflurane (Sevo), Body Temperature (BT), Heart Rate (HR), Respiratory Rate (RR), Arterial Blood Pressure (ABP), partial pressure of CO<sub>2</sub> (PaCO<sub>2</sub>), partial pressure of O<sub>2</sub> (PaO<sub>2</sub>) and dobutamin during anesthesia period

Variables	Groups	Time after intubation (min)						
		0	30	60	90	120	150	180
Sevo (%)	A	2.30 $\pm$ 0.6*	1.5 $\pm$ 0.3**	1.5 $\pm$ 0.2**	1.4 $\pm$ 0.3**	1.3 $\pm$ 0.4**	1.5 $\pm$ 0.1**	1.5 $\pm$ 0.2**
	B	2.80 $\pm$ 0.2	3.1 $\pm$ 0.3	3.3 $\pm$ 0.3	3.2 $\pm$ 0.3	3.3 $\pm$ 0.2	3.3 $\pm$ 0.4	3.4 $\pm$ 0.3
BT (Co)	A	37.60 $\pm$ 0.3	37.1 $\pm$ 0.4	36.3 $\pm$ 0.6	35.9 $\pm$ 0.5	35.3 $\pm$ 0.3	35.8 $\pm$ 0.3	35.6 $\pm$ 0.5
	B	37.40 $\pm$ 0.3	37.2 $\pm$ 0.3	36.4 $\pm$ 0.7	35.1 $\pm$ 0.3	35.4 $\pm$ 0.6	35.4 $\pm$ 0.2	36.6 $\pm$ 0.5
HR (breats min <sup>-1</sup> )	A	35.40 $\pm$ 3	36.9 $\pm$ 3*	35.4 $\pm$ 3**	34.5 $\pm$ 2**	35.4 $\pm$ 4**	35.1 $\pm$ 3**	35.4 $\pm$ 6**
	B	35.60 $\pm$ 4	37.4 $\pm$ 5	38.4 $\pm$ 3	37.4 $\pm$ 4	38.4 $\pm$ 5	38.3 $\pm$ 2	39.4 $\pm$ 3
RR (breaths min <sup>-1</sup> )	A	7.00 $\pm$ 4	7.0 $\pm$ 2*	7.0 $\pm$ 4*	7.0 $\pm$ 4**	7.0 $\pm$ 4**	8.0 $\pm$ 1	8.0 $\pm$ 2
	B	7.00 $\pm$ 2	8.0 $\pm$ 3	8.0 $\pm$ 4	9.0 $\pm$ 3	9.0 $\pm$ 2	8.0 $\pm$ 2	8.0 $\pm$ 4
MABP (mmHg)	A	86.00 $\pm$ 13	83.0 $\pm$ 10	79.0 $\pm$ 10**	77.0 $\pm$ 13**	76.0 $\pm$ 8*	76.0 $\pm$ 7*	77.0 $\pm$ 8*
	B	78.00 $\pm$ 10	74.0 $\pm$ 5	47.0 $\pm$ 4	53.0 $\pm$ 11	63.0 $\pm$ 9	66.0 $\pm$ 5	69.0 $\pm$ 9
PaCO <sub>2</sub> (mmHg)	A	42.00 $\pm$ 3	37.0 $\pm$ 4	38.0 $\pm$ 1	39.0 $\pm$ 2	41.0 $\pm$ 3	40.0 $\pm$ 4	41.0 $\pm$ 2
	B	42.00 $\pm$ 4	42.0 $\pm$ 2	41.0 $\pm$ 2	42.0 $\pm$ 3	42.0 $\pm$ 1	42.0 $\pm$ 1	42.0 $\pm$ 2
PaO <sub>2</sub> (mmHg)	A	412.00 $\pm$ 75	452.0 $\pm$ 56	424.0 $\pm$ 41	413.0 $\pm$ 63	435.0 $\pm$ 41	437.0 $\pm$ 53	412.0 $\pm$ 46
	B	450.00 $\pm$ 76	384.0 $\pm$ 43	412.0 $\pm$ 35	404.0 $\pm$ 42	425.0 $\pm$ 55	432.0 $\pm$ 57	434.0 $\pm$ 54
Dobutamin	A	0.0**						
	B	0.43 $\pm$ 0.13						

\*p<0.05, \*\*p<0.01

## DISCUSSION

Volatile anesthetic agents are widely used in various species for their hypnotic properties. For prolonged procedures, horses are commonly anesthetized with volatile anesthetic agents and these agents produce dose related cardiopulmonary depression (Steffy and Howland, 1978) and provide poor analgesia. Cardiovascular problems contribute greatly to the high mortality rate in horses (Jonston *et al.*, 2002). In order to optimize anesthesia, the amount of inhalation agents should be minimized and additional analgesia provided. TIVA can be used as an alternative to inhalation anesthesia to maintain better cardiopulmonary performance (McMurphy *et al.*, 2002).  $\alpha$ 2 adrenoreceptor agonist are potent analgesics and reduce Minimal Alveolar Concentration (MAC) of inhalation agent (Steffey and Pascoe, 2002).

Intravenous agents commonly used in horses, such as ketamine, which has known analgesic properties (Wright, 1982). TIVA is commonly used for short anesthetic procedures because of potential drug accumulation in the body. The combination of inhalation and injectable agents allows benefits from both forms of anesthesia, reducing such undesirable effects as cardiopulmonary depression and prolonged recovery because of surgical anesthesia over a long time (Spadavecchia *et al.*, 2002; Kushiro *et al.*, 2005). In this method, sedative, analgesic and injectable anesthetic drugs were combined and used either as repeated injection or as infusion. The most commonly used TIVA combination is ketamine-any  $\alpha$ 2 agonist and guaifenesine (Bettschart-Wolfansberger *et al.*, 1996; Nolan *et al.*, 1996; Flaherty *et al.*, 1997; Taylor *et al.*, 1998). Ketamine is widely used for intravenous induction and maintenance of general anesthesia in horses (Muir and Sams, 1992). Because recovery from ketamine is not smooth and muscle rigidity occurs, this drug is not recommended as the sole intravenous agent (Muir *et al.*, 1977), even during inhalation anesthesia (Serteyn *et al.*, 1987; Muir and Sams, 1992). Therefore, ketamine is commonly combined with guaifenesine, any  $\alpha$ 2 agonist, which all having good myorelaxant properties (Greene *et al.*, 1986). In the present study, induction of anesthesia (in groups A and B) and during maintenance of anesthesia in group A medetomidine which has more  $\alpha$ 2 agonist effect than xylazine (England and Clarke, 1996) and thiopental which has better effect on muscle relaxation than ketamine, were preferred as anesthetic mixture. When earlier studies examined 2.3% by Aiada *et al.* (1994), 2.31% by Natalini (2001) and 2.6-2.9% by Mizuno *et al.* (1996) the amount of Sevo used were between 2.31 and 2.9%. But in the present study, the amount

of Sevo used were in between 2.9-3.7% in group B except first 30 min of the anesthesia period. This situation occurred due to reduction in the preanesthetic effects which was used in group B. As a matter of fact this is confirmed with the result obtained from group A. Young *et al.* (1993) reported their experiences with guaifenesine ( $100 \text{ g L}^{-1}$ ), ketamine ( $2 \text{ g L}^{-1}$ ) and xylazine ( $1 \text{ g L}^{-1}$ ) anesthesia in horses undergoing various types of surgery and they found that the average infusion rate to maintain anesthesia was  $1.1 \text{ mL/kg/h}$ . In GKX-OS anesthesia, the dose rates of guaifenesine, ketamine and xylazine were  $30 \text{ mg/kg/h}$ ,  $1.2 \text{ mg/kg/h}$  and  $0.3 \text{ mg/kg/h}$ , respectively (Yamashita *et al.*, 1997). The dose rates of guaifenesine, ketamine and medetomidine were  $25 \text{ mg/kg/h}$ ,  $1.0 \text{ mg/kg/h}$  and  $0.00125 \text{ mg/kg/h}$ , respectively in GKM-OS anesthesia (Yamashita *et al.*, 2000). Anesthesia was maintained by Taylor *et al.* (2001) with IV infusion of detomidine ( $0.04 \text{ mg mL}^{-1}$ ), ketamine ( $4 \text{ mg mL}^{-1}$ ) and guaifenesine ( $100 \text{ mg mL}^{-1}$ ) (DKG) for 140 min.

In the present study, the dose rates of guaifenesine and medetomidine were 22.5 and 0.0009 mg/kg/h, respectively.

Induction of anesthesia with xylazine (Mama *et al.*, 1995) and xylazine premedicated horses (Mama *et al.*, 1996) were associated with spontaneous uncoordinated and coordinated muscle activity immediately after recumbency of some horses. This behavior is in contrast to the smooth quiet induction of anesthesia recorded in ponies (Nolan and Hall, 1985). In the present study, in both groups, medetomidine ( $0.010 \text{ mg kg}^{-1}$ ) and thiopental ( $6 \text{ mg kg}^{-1}$ ) were used induction period. Induction of anesthesia was smooth and uneventful and satisfactory conditions for tracheal intubation were present in both groups. But in both groups, apnea occurred after thiopental administration in a total of 7 horses, in this situation, mechanical ventilation were applied to these 7 horses. Apnea was expected complication after thiopental infusion (Alon *et al.*, 1993; Murison, 2001).

In the present study, heart rate increased at the beginning of the anesthesia in both groups (first 30 min). An increase in heart rate after thiopental injection (Taylor, 1990) and sevoflurane in horses (Aida *et al.*, 2000; Grosenbaugh and Muir, 1998) has also been reported. The results observed in the present study could also be due to the usage of both thiopental and sevoflurane but this situation could also be the results of reflex tachycardia occurred response to hypotension. In present study, ABP decreased including in the induction period in both groups. However, differences between group A and B with regard to ABP were different statistically ( $p < 0.05$ ). This situation could be due to thiopental used during anesthesia period in group A and high dose sevoflurane used during anesthesia period in group B. Higher ABP obtained in group A compared to group B could be due to mixture of TGM used in group A which provoked reduction of the amount of sevoflurane concentration. In group B, increased heart rate was observed in a whole anesthesia period. This finding corresponds with above mentioned studies (Aida *et al.*, 2000; Grosenbaugh and Muir, 1998). During general anesthesia, movement reported to occur in horses and this controlled with thiopental (Bettschart-Wolfensberger *et al.*, 2005; Ringer *et al.*, 2007). In the present study, movement were not seen in both groups. This situation could be due to continuously usage of thiopental in group A and usage of a high dose sevoflurane in group B. Due to cardiovascular depression, postanesthetic myopathy, colitis and lameness reported to occur in horses and this can be impeded through holding ABP about 65-70 mmHg or above level (Grandy *et al.*, 1987; Lindsay *et al.*, 1989). For this purpose, dobutamine reported to be used at  $1-5 \text{ } \mu\text{g/kg/min}$  dose (Carrol *et al.*, 1998; Mizuno *et al.*, 1996; Spadavecchia *et al.*, 2002). In the present study, ABP did not reduce in a dangerous level. But, in 6 horses in group B, ABP decreased under 50 mmHg level. Therefore, dobutamine were used at  $0.43 \pm 13 \text{ } \mu\text{g/kg/min}$  dose. So that, ABP in these horses increased to above 60 mmHg. In present study infusion period of the dobutamine were not fixed. When ABP reached to above 60 mmHg or tachycardia occurred, infusion of this drug ended.

Heart rate were statistically different between two groups in this study at the end of anesthesia. Furthermore, although it was not statistically important heart rate increased in group B more in the

other period of anesthesia. This increase thought to be due to positive chronotropic effect of dobutamine. Furthermore, in group B reductive effect of the used premedican drugs due to time may also play role in the increase of heart rate. Because in group A, mixture was used as infusion. Respiration rate in this study in first 15 min after induction period decreased. Because thiopental are respiratory system depressor (Bennett *et al.*, 1998; Taylor, 1990) in this period mechanical ventilation were applied, then spontane respiration continued. In present study, mechanical ventilation were applied ouly in the beginning of the anesthesia in both groups and later on this application did not require. This station could be due to the anesthetics used in this study were just enough with concern to dose for the anesthesia. In OS anaesthesia, the Sevo has been reported to be used from 2.0 to 3.0% (Carroll *et al.*, 1998; Mizuno *et al.*, 1996; Yamashita *et al.*, 1997). In the present study, 3.3% Sevo required to maintain surgical anesthesia in group B. Under TGM-OS (Group A) anesthesia, 1.5% Sevo required to maintain surgical anesthesia, which was ouly about 50 % of that under OS anesthesia (Group B). In short time sevoflurane anesthesia (depending on induction agents) recovery time from anesthesia has been reported to be around 8-18 min (Aida *et al.*, 1994, 1996; Hikasa *et al.*, 1994; Matthews *et al.*, 1998; Mizuno *et al.*, 1996). In horses under OS anesthesia, time to standing was reported to be 65±27 min. in 8 horses anesthetized for 296±31 min (Carroll *et al.*, 1998), 2 h in a horse anesthetized for 7 h for internal fixation (Mizuno *et al.*, 1996) and 32±6 min in 5 horses anesthetized for 151±32 min (Yamashita *et al.*, 1997). In the present study, standing time in group A was 38±12 min and in group B was 45±17 min anesthetized for 180 min. When anesthesia period taken into consideration, these recovery time were in parallel with the previous studies. However, in the present study standing time were shorter in group A compared to group B.

In conclusion, the infusion of thiopental (6 g L<sup>-1</sup>)-guaafinesine (75 g L<sup>-1</sup>)-medetomidine (3 mg L<sup>-1</sup>) combination at 0.30 mL/kg/ h dose in horses receiving low concentrations of sevoflurane appears to be a safe technique for producing prolonged anesthesia. Compared with the use of sevoflurane alone, the combined infusion-inhalation technique produced more stable anesthesia, cardiopulmonar function was adequate, sympatomimetic drugs were not required. Recovery was normally rapid and of good quality.

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