Combination of Continuous Intravenous Infusion Using a Mixture of Guaifenesin-Ketamine-Medetomidine and Sevoflurane Anesthesia in Horses

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ABSTRACT. The anesthetic and cardiovascular effects of a combination of continuous intravenous infusion using a mixture of 100 g/L guaifenesin-4 g/L ketamine-5 mg/L medetomidine (0.25 ml/kg/hr) and oxygen-sevoflurane (OS) anesthesia (GKM-OS anesthesia) in horses were evaluated. The right carotid artery of each of 12 horses was raised surgically into a subcutaneous position under GKM-OS anesthesia (n=6) or OS anesthesia (n=6). The end-tidal concentration of sevoflurane (EtSEV) required to maintain surgical anesthesia was around 1.5% in GKM-OS and 3.0% in OS anesthesia. Mean arterial blood pressure (MABP) was maintained at around 80 mmHg under GKM-OS anesthesia, while infusion of dobutamine ($0.39 \pm 0.10 \mu\text{g/kg/min}$) was necessary to maintain MABP at 60 mmHg under OS anesthesia. The horses were able to stand at 36 ± 26 min after cessation of GKM-OS anesthesia and at 48 ± 19 minutes after OS anesthesia. The cardiovascular effects were evaluated in 12 horses anesthetized with GKM-OS anesthesia using 1.5% of EtSEV (n=6) or OS anesthesia using 3.0% of EtSEV (n=6). During GKM-OS anesthesia, cardiac output and peripheral vascular resistance was maintained at about 70% of the baseline value before anesthesia, and MABP was maintained over 70 mmHg. During OS anesthesia, infusion of dobutamine ($0.59 \pm 0.24 \mu\text{g/kg/min}$) was necessary to maintain MABP at 70 mmHg. Infusion of dobutamine enabled to maintain cardiac output at about 80% of the baseline value; however, it induced the development of severe tachycardia in a horse anesthetized with sevoflurane. GKM-OS anesthesia may be useful for prolonged equine surgery because of its minimal cardiovascular effect and good recovery.—**KEY WORDS:** equine, guaifenesin, ketamine, medetomidine, sevoflurane.

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Sevoflurane is a volatile anesthetic agent characterized by a low blood/gas partition coefficient [22], and its minimum alveolar concentration (MAC) in horses is 2.31% [1]. In horses, it has the advantages of rapid induction, easy management of anesthesia, and rapid recovery [1, 2, 5, 9, 11, 15]. It has also been reported that sevoflurane might be a safe anesthetic for prolonged inhalation anesthesia in horses [5, 16]. However, sevoflurane causes dose-dependent cardiopulmonary depression as well as hypoventilation and hypotension at the stage of surgical anesthesia [2, 9]. Therefore, assisted or controlled ventilation and the administration of vasopressors should be considered during oxygen-sevoflurane (OS) anesthesia in horses. Generally, intermittent positive pressure ventilation (IPPV) is used to improve hypoventilation during anesthesia in horses, but this also leads to further cardiac depression [10, 17, 20]. A low dose of dobutamine infusion is recommended to prevent or treat hypotension that develops in horses anesthetized with a volatile anesthetic agent [6, 10, 13, 17, 19, 20, 27]. However, in horses anesthetized with halothane, the infusion of dobutamine sometimes leads to the development of cardiac arrhythmias and tachycardia [6, 13, 19, 27].

The concentrations of volatile anesthetic agents required during surgery can be reduced by the administration of sedatives, analgesics, and injectable anesthetics [10, 17, 20]. It has been reported that the combination of continuous intravenous infusion using a mixture of guaifenesin-ketamine-xylazine and OS anesthesia (GKX-OS anesthesia) could minimize cardiovascular effects by reducing the

requirement of sevoflurane for the maintenance of surgical anesthesia in horses [25]. During GKX-OS anesthesia, arterial blood pressure (ABP) was maintained at an appropriate level without the administration of vasopressors [25].

Medetomidine is a more specific α_2 -adrenoceptor agonist (α_2 -agonist) compared to detomidine and xylazine [10, 17, 20, 21]. It is more potent than either detomidine or xylazine in both behavioral and neurochemical effects [4, 7, 10, 17, 20, 23, 24]. Therefore, we expect that a mixture of guaifenesin-ketamine-medetomidine would be more potent than that of guaifenesin-ketamine-xylazine. The purpose of the present study was to evaluate the anesthetic and cardiovascular effects of a combination of continuous intravenous infusion using a mixture of guaifenesin-ketamine-medetomidine and OS anesthesia (GKM-OS anesthesia) in horses.

MATERIALS AND METHODS

Experimental animals: Four groups of six horses each were used in this study. Group A consisted of four Thoroughbred and two Anglo-Arabian horses, aged from two to 11 (mean $\pm$ standard deviation: 6.8 ± 3.7) years and weighing 426 to 508 (462.7 ± 30.3) kg. Group B consisted of 6 Thoroughbred horses, aged from two to 15 (6.0 ± 4.9) years and weighing 414 to 540 (493.7 ± 45.0) kg. Group C consisted of three Thoroughbred and three Anglo-Arabian horses, aged from four to 17 (9.7 ± 4.7) years and weighing

410 to 540 (488.3 ± 47.0) kg. Group D consisted of 6 Thoroughbred horses, aged from four to 15 (9.2 ± 5.3) years and weighing 406 to 562 (477.0 ± 47.0) kg. In each of the horses in groups C and D, the right carotid artery was replaced into a subcutaneous position under GKM-OS or OS anesthesia at least 2 months before they were used in this study. They were starved for 12 hr prior to anesthesia, but water was always made available.

Experimental anesthesia and surgery in groups A and B: All horses in groups A and B were premedicated with 0.005 mg/kg of medetomidine (Domitor, Meiji Seika Co., Tokyo, Japan) and 0.04 mg/kg of diazepam (Horizon, Yamamouchi Pharmaceutical Co., Tokyo, Japan) intravenously and anesthetized with 2.5 mg/kg of ketamine (Ketalar, Sankyo Co., Tokyo, Japan) intravenously. After orotracheal intubation, the horses were positioned in left lateral recumbency and the right carotid artery was raised surgically into a subcutaneous position under GKM-OS anesthesia in group A and under OS anesthesia in group B. In group A, a GKM mixture containing 100 g/L of guaifenesin (Alps Pharmaceutical Industry Co., Gifu, Japan), 4 g/L of ketamine, and 5 mg/L of medetomidine in 5% dextrose (Daiichi Pharmaceutical Co., Tokyo, Japan) was injected at 0.25 ml/kg/hr through a 16-gauge catheter (Happycath Z, Medikit Co., Tokyo, Japan) placed in the jugular vein, and surgical anesthesia was maintained by controlling the concentration of inhaled sevoflurane. In group B, surgical anesthesia was maintained by OS anesthesia. The GKM mixture was administered by a syringe infusion pump (STC-521, Terumo, Tokyo, Japan). Sevoflurane (Sevofrane, Maruishi Pharmaceutical Co., Osaka, Japan) was delivered with oxygen using one or two vaporizers (Sevotec 3, Ohmeda, West Yorkshire, U.K.) via a large animal circle system (LAVAC-2000, JD Medical, Phoenix, U.S.A.) incorporating a ventilator (Mark 7, Bird, Palm Springs, U.S.A.). All horses were ventilated by IPPV to maintain a partial pressure of arterial CO_2 (Paco_2) between 40 and 50 mmHg. They were intravenously injected with 1:1 of saline and 5% dextrose at 10 ml/kg/hr. When ABP decreased, dobutamine (Dobutrex, Shionogi, Osaka, Japan) was administered intravenously to maintain the mean ABP (MABP) at approximately 60 mmHg. After anesthesia, horses were not assisted in recovery.

Monitoring during anesthesia in groups A and B: Respiratory gas was collected continuously from the oral end of the endotracheal tube, and respiratory rate (RR) and the end-tidal concentration of sevoflurane (EtSEV) were measured with an anesthetic gas monitor (Type 1304, Bruel & Kjaer, Copenhagen, Denmark). Heart rate (HR), electrocardiogram (ECG), ABP, and body temperature (BT) were recorded by an anesthetic monitoring system (DS-5300, Fukuda Denshi, Tokyo, Japan). ABP was measured by connecting an 18-gauge catheter (Happycath Z, Medikit) placed into the right dorsal metatarsal artery to a pressure transducer (CDX-A90, Cobe Laboratories, Tokyo, Japan). This pressure transducer was placed at the level of the sternum. Arterial blood samples were withdrawn

anaerobically from a catheter placed into the right dorsal metatarsal artery into a heparinized syringe and analyzed by a blood gas analyzer (M-248, Chiron, Tokyo, Japan).

Cardiovascular measurements during GKM-OS anesthesia in groups C and D: The horses were restrained in wooden stocks, and an 18-gauge catheter (Happycath Z, Medikit Co.) was placed in the raised right carotid artery. An 8-french introducer (Exacta percutaneous sheath introducer, Ohmeda) was placed in the right jugular vein under local anesthesia. A 9-french introducer (Exacta percutaneous sheath introducer, Ohmeda) was also placed in the right jugular vein 30 cm cranial to the 8-french introducer under local anesthesia. A 7-french thermodilution catheter (Criticath SP-5107, Ohmeda) was placed into the pulmonary artery through the 8-french introducer. An 8-french catheter 100 cm in length (Intervac super guiding catheter, Fuji Systems Co., Tokyo, Japan) was placed in the right atrium through the 9-french introducer. The distance between the tips of thermodilution catheter and the 8-french catheter was adjusted to 40–50 cm.

The baseline values of cardiovascular measurements were recorded in all horses resting in wooden stocks. ABP, pulmonary artery pressure (PAP), and right atrial pressure (RAP) were measured by connecting catheters placed in the raised carotid artery, the pulmonary artery, and the right atrium, respectively, to pressure transducers (CDX-A90, Cobe Laboratories). These pressure transducers were placed at the level of the sternum manubrium. Cardiac output (CO) was measured by thermodilution methods [18]. As an indicator, 40 ml of 5% dextrose at 0°C was injected manually for approximately 2 seconds through the 8-french catheter placed in the right atrium. Temperature fluctuation and CO were measured by a thermodilution catheter placed in the pulmonary artery. The CO was measured three times, and the mean value of three measurements was calculated. HR, ABP, PAP, RAP, and CO were recorded by the anesthetic monitoring system (DS-5300, Fukuda Denshi). Cardiac index (CI) was calculated from the body weight and CO; stroke volume (SV) was calculated from the HR and CO; and peripheral vascular resistance (PVR) was determined from the MABP, CO, and mean RAP [17].

All horses in group C or D were premedicated and anesthetized by the same methods as those used in group A or B, respectively. The management of ventilation and fluid therapy during anesthesia were also the same as those used in groups A and B. When ABP decreased, dobutamine was administered intravenously to maintain MABP at approximately 70 mmHg. The horses were anesthetized for 4 hr with GKM-OS anesthesia or OS anesthesia. During anesthesia, the EtSEV in each group was maintained at the mean value that achieved surgical anesthesia in group A or B, respectively. Cardiovascular measurements were recorded every 30 min. The pressure transducers were placed at the level of the sternum. After anesthesia, horses were not assisted in recovery.

Statistical analysis: The differences between data in groups A and B or in groups C and D were statistically

analyzed by the Mann-Whitney *U*-test. Differences were considered to be significant when $p < 0.05$.

RESULTS

A surgical anesthetic depth equal to that classified as 2nd degree, stage III [20] was maintained, and the surgical procedure was successful in all of the horses in groups A and B. In group A, the horses showed occasional spontaneous blinking and slow lateral nystagmus during anesthesia. They also showed a dull palpebral reflex, a strong corneal reflex, and reduced tearing. In the horses of group B, corneal reflex was observed, but spontaneous blinking, nystagmus, and tearing were not seen and palpebral reflexes were slow during anesthesia.

The mean value $\pm$ standard deviation of the total anesthesia time, the time required for the horse to return to the sternal position and to the standing position after the cessation of anesthesia, the number of attempts to stand, and the dose of dobutamine in groups A and B are summarized in Table 1. Skin incisions were made at 52 ± 13 min and at 52 ± 14 min after intubation in group A and group B, respectively. All horses recovered from anesthesia without excitement and incident, and stood with only slight staggering. The times required for the horse to return to the sternal and standing positions in group A tended to be shorter than those in group B, although there was no statistical difference. The number of attempts to stand in group A was almost equal to that in group B. In group B, hypotension developed at the beginning of OS anesthesia, when the concentration of inhaled sevoflurane was increased and IPPV was started. All horses in group B required infusion of dobutamine at a dose of $0.5\text{--}1.0$ $\mu\text{g/kg/min}$ to maintain ABP, and the mean dose rate of dobutamine was 0.39 ± 0.10 $\mu\text{g/kg/min}$ during OS anesthesia.

The changes in EtSEV, HR, RR, BT, MABP, Paco_2 , and partial pressure of arterial O_2 (PaO_2) during anesthesia in groups A and B are summarized in Table 2. The EtSEV required for the maintenance of surgical anesthesia in group A (1.5%, 0.65 MAC) was significantly lower than that in group B (3.0%, 1.3 MAC). In group A, ABP was maintained at an appropriate level, and MABP was significantly higher than that in group B. BT decreased gradually during anesthesia in both groups. HR was stable at about 35 bpm in group A, but it gradually increased in group B. To maintain the Paco_2 levels at between 40 and 50 mmHg, all horses were ventilated by IPPV with 20–25 cmH_2O of peak air-way pressure, at a ratio between inspiratory time and expiratory time of 1:2 and at RR of 8 bpm. Oxygenation was excellent in all horses of both groups and the PaO_2 levels reached about 400 mmHg.

The cardiovascular measurements in groups C and D are summarized in Table 3. EtSEV was maintained at 1.5% and 3.0% in groups C and D, respectively, because these levels achieved surgical anesthesia in groups A and B as mentioned previously. Paco_2 was maintained at between 40 and 50 mmHg by IPPV with 20–25 cmH_2O of peak air-way

Table 1. Total time under anesthesia, time required for the horse to return to the sternal position and to the standing position, number of attempts to stand, and the mean dose rate of dobutamine required to maintain arterial blood pressure in horses in which the right carotid artery was replaced under GKM-OS or OS anesthesia

	GKM-OS anesthesia	OS anesthesia
Anesthesia time (minutes)	187 ± 12	171 ± 17
Sternal position (minutes)	26 ± 19	31 ± 9
Standing position (minutes)	36 ± 26	48 ± 19
Attempts to stand (times)	2.5 ± 1.0	2.7 ± 2.3
Dose of dobutamine ($\mu\text{g/kg/min}$)	0	$0.39 \pm 0.10^{**}$

Data are expressed as mean $\pm$ standard deviation.

Statistical significance **: $p < 0.01$ between GKM-OS and OS.

pressure in both groups. Oxygenation was excellent and the Paco_2 reached about 400 mmHg in both groups. In group C, the cardiovascular measurements were stable during 4 hr of GKM-OS anesthesia. MABP was maintained at an appropriate level without the administration of dobutamine. In horses of group D, hypotension developed within the first 30 min of OS anesthesia with lower CO, CI, SV and PVR. Those horses required infusion of dobutamine to improve and maintain ABP, and the mean dose rate of dobutamine was 0.59 ± 0.24 $\mu\text{g/kg/min}$ during 4 hr of OS anesthesia. During the first 30 min of OS anesthesia, three horses required infusion of dobutamine at a dose of 2.0 $\mu\text{g/kg/min}$ to increase ABP. One of those horses developed severe tachycardia after infusion of dobutamine and the HR reached 95 bpm. The tachycardia was diminished by the suspension of dobutamine infusion. HR in group C was lower than that in group D. CO, CI, and SV were maintained at about 70% of the baseline values in group C. PVR also decreased to about 70% of the baseline value in group C. In group D, CO and CI were maintained at about 80% of the baseline values by the infusion of dobutamine. CO and CI in group D was not statistically different from those in group C. SV and PVR in group D were lower than those in group C.

All horses in groups C and D recovered from anesthesia without excitement and incident, and they stood with only slight staggering. The horses returned to the sternal position at 19 ± 5 min and at 31 ± 15 min after the cessation of anesthesia in groups C and D, respectively. The times required for the horses to stand were 38 ± 17 min and 53 ± 12 min and the number of attempts to stand were 1.5 ± 0.8 times and 3.0 ± 0.9 times in group C and group D, respectively. There was no significant difference between group C and D in the time required for the horse to return to the sternal position and to stand. The number of attempts to stand in group C was significantly smaller than that in group D ($p = 0.025$).

DISCUSSION

The combination of guaifenesin, ketamine, and xylazine

Table 2. Changes in the end-tidal concentration of sevoflurane (EtSEV), heart rate (HR), respiratory rate (RR), body temperature (BT), mean arterial blood pressure (MABP), and the partial pressure of CO₂ (Paco₂) and O₂ (Pao₂) in arterial blood during GKM-OS or OS anesthesia for surgical replacement of the right carotid artery

	Minutes after intubation							
	0	20	40	60	80	100	120	140
EtSEV (%)								
GKM-OS	2.1 ± 0.5*	1.4 ± 0.3**	1.5 ± 0.3**	1.4 ± 0.2**	1.5 ± 0.2**	1.5 ± 0.2**	1.6 ± 0.1**	1.6 ± 0.2**
OS	2.6 ± 0.4	2.9 ± 0.3	2.9 ± 0.8	2.8 ± 0.2	2.9 ± 0.3	3.0 ± 0.3	3.1 ± 0.3	3.1 ± 0.2
BT (°C)								
GKM-OS	37.5 ± 0.4	37.2 ± 0.5	36.9 ± 0.6	36.6 ± 0.7	36.5 ± 0.8	36.5 ± 0.8	36.4 ± 0.8	36.3 ± 0.9
OS	37.2 ± 0.3	37.1 ± 0.2	36.6 ± 0.3	36.2 ± 0.4	35.9 ± 0.5	35.7 ± 0.5	35.5 ± 0.4	35.4 ± 0.4
HR (bpm)								
GKM-OS	34 ± 5	31 ± 3	32 ± 6	32 ± 4	36 ± 4	35 ± 3	35 ± 6	34 ± 5*
OS	32 ± 9	35 ± 6	35 ± 7	36 ± 6	39 ± 7	40 ± 6	41 ± 5	40 ± 5
RR (bpm)								
GKM-OS	7 ± 2	7 ± 1	8 ± 2	9 ± 2	8 ± 2	8 ± 2	9 ± 2	9 ± 2
OS	7 ± 3	8 ± 3	7 ± 2	8 ± 3	8 ± 3	8 ± 3	8 ± 2	8 ± 2
MABP (mmHg)								
GKM-OS	88 ± 16	82 ± 12**	78 ± 9**	77 ± 10*	77 ± 9**	80 ± 10*	88 ± 15**	86 ± 17**
OS	75 ± 13	62 ± 5	60 ± 2	63 ± 4	63 ± 4	63 ± 2	61 ± 2	60 ± 2
Paco ₂ (mmHg)								
GKM-OS	42 ± 3	38 ± 5	39 ± 7	40 ± 4	42 ± 4	45 ± 6	46 ± 5	46 ± 8
OS	47 ± 13	42 ± 13	40 ± 10	41 ± 12	41 ± 13	42 ± 13	42 ± 12	42 ± 13
Pao ₂ (mmHg)								
GKM-OS	384 ± 56	448 ± 81	413 ± 61	416 ± 51	404 ± 61	382 ± 78	401 ± 108	349 ± 126
OS	282 ± 112	360 ± 118	406 ± 102	419 ± 98	403 ± 108	382 ± 103	389 ± 115	377 ± 125

Data are expressed as mean ± standard deviation.

Statistical significance **: p<0.01 and *: p<0.05 compared with OS.

Table 3. Changes in cardiovascular measurements during GKM-OS or OS anesthesia

	Minutes after intubation								
	Base line	30	60	90	120	150	180	210	240
HR (bpm)									
GKM-OS	34 ± 9	35 ± 5	33 ± 4*	35 ± 5	32 ± 4	33 ± 6	33 ± 5	31 ± 4*	32 ± 5
OS	35 ± 4	37 ± 4	38 ± 2	41 ± 7	39 ± 6	38 ± 5	37 ± 4	37 ± 4	36 ± 3
MABP (mmHg)									
GKM-OS	122 ± 11	75 ± 7*	76 ± 7	73 ± 10	75 ± 12	76 ± 13	78 ± 9	77 ± 10	76 ± 8
OS	124 ± 9	68 ± 7	69 ± 4	72 ± 7	72 ± 4	72 ± 3	73 ± 3	72 ± 2	72 ± 2
MPAP (mmHg)									
GKM-OS	23 ± 4	19 ± 7	21 ± 8	21 ± 10	25 ± 8	25 ± 5	26 ± 8	26 ± 8	26 ± 8
OS	26 ± 7	27 ± 8	26 ± 4	24 ± 3	25 ± 3	25 ± 4	25 ± 5	24 ± 6	25 ± 4
MRAP (mmHg)									
GKM-OS	6 ± 3	10 ± 4	11 ± 5	13 ± 5	12 ± 4	13 ± 5	14 ± 7	13 ± 7	13 ± 7
OS	6 ± 4	12 ± 2	13 ± 4	11 ± 3	12 ± 2	12 ± 3	12 ± 3	14 ± 4	12 ± 3
CO (L/min)									
GKM-OS	35 ± 5	25 ± 4	26 ± 4	25 ± 3	25 ± 5	24 ± 4	25 ± 3	24 ± 4	25 ± 5
OS	36 ± 6	22 ± 3	29 ± 4	29 ± 6	28 ± 8	28 ± 8	25 ± 4	25 ± 3	23 ± 3
CI (ml/min/kg)									
GKM-OS	72 ± 11	51 ± 9	54 ± 13	51 ± 8	51 ± 12	49 ± 11	53 ± 11	50 ± 12	53 ± 13
OS	77 ± 15	46 ± 6	61 ± 9	62 ± 16	60 ± 19	59 ± 21	53 ± 12	53 ± 7	49 ± 7
SV (ml/min)									
GKM-OS	1100 ± 285	729 ± 183	780 ± 127	712 ± 114	763 ± 118	729 ± 86	783 ± 74*	770 ± 88	797 ± 94*
OS	1035 ± 205	594 ± 98	757 ± 124	716 ± 112	723 ± 95	712 ± 119	677 ± 74	685 ± 81	648 ± 71
PVR (dyn·sec·cm ⁻⁵)									
GKM-OS	254 ± 30	195 ± 41	185 ± 37*	177 ± 43	190 ± 50	199 ± 64	184 ± 29	196 ± 41	182 ± 38
OS	232 ± 32	172 ± 40	142 ± 33	157 ± 29	160 ± 42	168 ± 52	173 ± 34	170 ± 28	140 ± 99

Data are expressed as mean ± standard deviation.

Statistical significance *: p<0.05 compared with OS.

HR: heart rate, MABP: mean arterial blood pressure, MPAP: mean pulmonary artery pressure, MRAP: mean right atrial pressure, CO: cardiac output, CI: cardiac index, SV: stroke volume, PVR: peripheral vascular resistance.

has been used to induce anesthesia in horses [8, 10, 17, 20, 26]. Young *et al.* reported their experiences with guaifenesin (100 g/L), ketamine (2 g/L), and xylazine (1 g/L) anesthesia in horses undergoing various types of surgery [26], and they found that the average infusion rate to maintain anesthesia was 1.1 ml/kg/hr. Thurmon *et al.* used a mixture of guaifenesin (50 g/L), ketamine (2 g/L), and detomidine (5 mg/L) to anesthetize ponies during castration and found that anesthesia could be maintained at an infusion rate of 2.2 ml/kg/hr [20]. Both of these combinations produced good muscle relaxation and analgesia with minimal cardiopulmonary effects during surgery [8, 20, 26]. Ketamine produces intense analgesia and an elevated pain threshold at sub-anesthetic doses; however, the degree of analgesia appears to be greater for somatic pain than for visceral pain [10, 17, 20]. When α_2 -agonists are combined with ketamine, muscle relaxation and visceral analgesia are improved [10, 17, 20]. Guaifenesin has also been added to a xylazine-ketamine combination to enhance muscle relaxation [10, 17, 20, 26]. However, these techniques have only been successfully used for operations up to 90 min in duration [10, 17, 20, 26]. Inhalation anesthesia is still preferred for prolonged anesthesia in horses [10, 17, 20].

Previously, we reported that GKX-OS anesthesia minimized cardiovascular depression by reducing the concentration of sevoflurane required to maintain surgical anesthesia in horses [25]. It is expected that a combination of guaifenesin, ketamine, and medetomidine would have a more potent anesthetic effect, because medetomidine has a high α_2/α_1 -receptor selectivity binding ratio [21]. In horses, the sedative effect induced by an intravenous injection of xylazine (1.0 mg/kg) was similar to that induced by medetomidine (0.005–0.01 mg/kg) [4, 7, 23, 24]. Solutions containing more than 15% guaifenesin are difficult to maintain, and such solutions have been found to produce significant hemolysis, hemoglobinuria, and urticaria in horses [10, 17, 20]. In GKX-OS anesthesia, the dose rates of guaifenesin, ketamine, and xylazine were 30 mg/kg/hr, 1.2 mg/kg/hr, and 0.3 mg/kg/hr, respectively [25]. In the present study, the concentrations of guaifenesin, ketamine, and medetomidine comprising the GKM mixture were determined on the basis of findings published in these reports. The dose rate of GKM mixture during GKM-OS anesthesia was determined on the basis of the results of a preliminary examination (data not shown). The dose rates of guaifenesin, ketamine, and medetomidine were 25 mg/kg/hr, 1.0 mg/kg/hr, and 0.00125 mg/kg/hr, respectively, in GKM-OS anesthesia. In the present study, the dose rates of guaifenesin and ketamine during GKM-OS anesthesia were about 83% of those during GKX-OS anesthesia [25].

When using inhalation anesthesia, 1.2–1.5 MAC of inhalation anesthetic was required to maintain surgical anesthesia [10, 17, 20]. In OS anesthesia, the EtSEV required to maintain surgical anesthesia was reported to be 2.0 to 3.3% in 8 horses subjected to exploratory laparotomy [5], 2.6 to 2.9% in a horse subjected to internal fixation of a long bone fracture [16], and 2.3 to 2.7% in 4 horses

subjected to arthroscopic surgery and 2.8 to 3.0% in a horse subjected to cryptorchidectomy [25]. In the present study, the EtSEV required to maintain surgical anesthesia was 3.0% under OS anesthesia. It was 1.3 MAC of sevoflurane in horses. Under GKM-OS anesthesia, the EtSEV required to maintain surgical anesthesia was 1.5% (0.65 MAC), which was only about 50% of that under OS anesthesia. The continuous intravenous infusion of GKM mixture could reduce the requirement of sevoflurane for the maintenance of surgical anesthesia in horses. Compared with GKX-OS anesthesia, in which the EtSEV during surgery ranged from 1.5 to 2.1% [25], infusion of the GKM mixture provided an equal or more potent anesthetic effect with lower dose rates of guaifenesin and ketamine.

The degree of hypoventilation varies in anesthetized horses. The compromise produced by hypoventilation is generally well tolerated during a short anesthetic period of less than 45 min [10, 17, 20]. However, the compromise becomes more critical as the duration of anesthesia is prolonged. Sevoflurane causes cardiopulmonary depression in a dose-dependent manner in horses [2], similar to those caused by other inhalation anesthetics [9, 10, 17, 20]. Assisted or control ventilation has been recommended to prevent or improve respiratory depression and hypercapnia induced by sevoflurane [2, 9]. IPPV is widely recommended to assist or control ventilation in horses [10, 17, 20]. IPPV acts to improve hypoventilation during prolonged anesthesia, but it also leads to further cardiac depression [10, 17, 20]. On the other hand, the maintenance of MABP at a level greater than 60 mmHg has been identified as a critical factor in the prevention of post-anesthetic myopathy in horses [10, 17, 20]. Dobutamine is often given by infusion at a dose of 1–5 μ g/kg/min to maintain ABP during anesthesia [5, 7, 10, 16, 17, 20]. In the present study, hypoventilation could be prevented by control ventilation using IPPV. Hypotension was caused by increasing the concentration of inhaled sevoflurane and starting IPPV in horses anesthetized with OS anesthesia. In these horses, infusion of dobutamine was indispensable to maintain ABP during anesthesia. It is a remarkable occurrence that ABP was maintained at an appropriate level without dobutamine infusion during GKM-OS anesthesia.

Infusion of dobutamine is an effective treatment for hypotension in horses anesthetized with volatile anesthetic agents [6, 10, 13, 17, 19, 20, 27]. However, this sometimes leads to the development of cardiac arrhythmias and tachycardia in horses [6, 13, 19, 27]. In the present study, infusion of dobutamine at 0.39 ± 0.10 μ g/kg/min prevented hypotension under 60 mmHg of MABP during OS anesthesia. Moreover, MABP could be maintained at over 70 mmHg by increasing the dose of dobutamine to 0.59 ± 0.24 μ g/kg/min. However, the infusion of dobutamine induced severe tachycardia in a horse anesthetized with sevoflurane. Thus, infusion of dobutamine may lead to the development of tachycardia in horses anesthetized with sevoflurane.

Medetomidine, which was included in the GKM mixture,

has been shown to produce severe cardiovascular depression in a dose-dependent manner [3, 10, 17, 20]. The α_2 -agonists stimulate α_2 -receptors on the smooth muscle of peripheral vessels and induce an increase in PVR caused by vascular constriction, resulting in transient hypertension [3, 8, 10, 17, 20]. While MABP was maintained at over 70 mmHg, there was no increase in PVR during GKM-OS anesthesia. Moreover, CO, CI, and SV were maintained at 70% of baseline values. The cardiovascular measurements during GKM-OS anesthesia were almost equal to those of 1.0 MAC of sevoflurane [2]. The dose rate of medetomidine was only 0.00125 mg/kg/hr during GKM-OS anesthesia. This is a very small quantity compared with the bolus IV dose of medetomidine that induced transient hypertension [3]. Medetomidine may have no cardiovascular effect at this extremely low dose. It was concluded that GKM-OS anesthesia causes minimal cardiovascular depression in horses.

Recovery from anesthesia is a potentially dangerous time for horses and appears to be influenced by many factors, including individual variability, presence of hypotension during anesthesia, type of surgical procedure, duration of anesthesia, external stimuli, and the use of sedatives as adjunctive drugs [10, 17, 20]. Time to standing after OS anesthesia was reported to be from 8 to 18 min depending on the induction drugs used [1, 2, 11, 15]. In horses subjected to surgical procedures under OS anesthesia, time to standing was reported to be 65 ± 27 min in 8 horses anesthetized for 269 ± 31 min for exploratory laparotomy [5], 2 hr in a horse anesthetized for 7 hr for internal fixation of a long bone fracture [16], and 32 ± 6 min in 5 horses anesthetized for 151 ± 32 min for 4 arthroscopic operations and a cryptorchidectomy [25]. In these studies, horses experienced a smooth and safe recovery after maintenance of anesthesia. All of the horses in the present study also experienced a smooth and safe recovery after maintenance of either GKM-OS anesthesia or OS anesthesia. After GKM-OS anesthesia, the time to stand and the number of attempts to stand were both less than those after OS anesthesia.

In conclusion, GKM-OS anesthesia may be useful for prolonged surgery because of its minimal cardiovascular depression and good recovery.

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