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A retrospective comparison of induction with thiopental/guaifenesin and propofol/ketamine in Thoroughbred racehorses anesthetized with sevoflurane and medetomidine during arthroscopic surgery

Hirotaka TOKUSHIGE[1]*, Masanari ARAKI[2], Kanichi KUSANO[2], Daisuke ARIMA[2], Hideki ITO[2], Yosuke YAMAZAKI[2], Shuntaro URAYAMA[2], Yoshinori KAMBAYASHI[2], Oki TATENO[2] and Minoru OHTA[1]

[1]Equine Research Institute, Japan Racing Association, Tochigi 329-0412, Japan
[2]Racehorse Clinic, Miho Training Center, Japan Racing Association, Ibaraki 300-0493, Japan

This study compares clinical characteristics between induction with thiopental/guaifenesin and propofol/ketamine in Thoroughbred racehorses anesthetized with sevoflurane and medetomidine. Clinical records of 214 horses that underwent arthroscopic surgery between 2015 and 2016 were retrospectively retrieved. Horses were premedicated with medetomidine and midazolam to sedate at the adequate level for smooth induction, and then induced with either thiopental (4.0 mg/kg) and guaifenesin (100 mg/kg) in Group TG (n=91) or propofol (1.0 mg/kg) and ketamine (1.0 mg/kg) in Group PK (n=123). Anesthesia was maintained using sevoflurane with constant rate infusion of medetomidine. Quality of induction/recovery, sevoflurane requirement, cardiovascular function and recovery characteristics were evaluated. Anesthetic induction scores (median, range) for Group TG (5, 2–5) and Group PK (5, 2–5) were not significantly different. There were no significant differences in end-tidal sevoflurane concentration (mean ± standard deviation) between Group TG and Group PK (both 2.4 ± 0.2%). Dobutamine infusion rate (µg/kg/min) required for keeping mean arterial blood pressure (MAP) above 70 mmHg in Group PK (0.43, 0.10–1.40) was significantly lower than in Group TG (0.67, 0.08–1.56). Recovery score in Group PK (5, 2–5) was significantly higher than in Group TG (4, 2–5). Both propofol/ketamine and thiopental/guaifenesin provided a smooth induction of anesthesia. Moreover, induction with propofol/ketamine resulted in lower dobutamine requirements for keeping MAP above 70 mmHg during maintenance, and better quality of recovery. Induction with propofol/ketamine would be preferable to thiopental/guaifenesin in Thoroughbred racehorses anesthetized with sevoflurane and medetomidine during arthroscopic surgery.
Key words: *induction, propofol/ketamine, racehorse, sevoflurane, thiopental/guaifenesin*

Thiopental and guaifenesin are used to induce general anesthesia in horses undergoing surgery [2, 14]. Several studies have reported that induction with thiopental/guaifenesin is particularly smooth and uneventful [2, 6, 9]. In reference to those reports, Thoroughbred racehorses undergoing arthroscopic surgery at the Japan Racing Association (JRA) racehorse clinics are routinely induced with thiopental/guaifenesin. Although horses can be successfully induced with thiopental/guaifenesin, these anesthetics are known to induce cardiopulmonary depression [2, 10]. Moreover, Young and Taylor pointed out that induction with guaifenesin impaired the quality of recovery after anesthesia lasting

an average of 60 min [23].

Propofol is a popular intravenous (IV) anesthetic in humans, dogs, and cats. In horses, propofol is characterized by a smooth and rapid recovery, and is suitable for total intravenous anesthesia (TIVA) for >2-hr anesthesia because the degree of cardiovascular depression is less than that for inhalation anesthesia [4, 15, 16]. However, it is reported that unpredictable behavioral responses, including paddling limb movements, are frequently observed during the induction of anesthesia with propofol in horses [5, 12, 13]. In contrast, earlier works show that combining propofol with ketamine provides satisfactory anesthetic induction and recovery without any clinically relevant adverse events [8, 17]. Hence, the racehorse clinic at the Miho Training Center of the JRA began using propofol with ketamine for the induction of anesthesia in racehorses in 2015. However, no information is available showing a direct comparison between thiopental/guaifenesin and propofol/ketamine as induction agents in Thoroughbred racehorses.

The aim of this study is to compare clinical characteristics (the quality of induction/recovery, sevoflurane requirement, cardiovascular function and recovery characteristics) between two induction protocols (thiopental/guaifenesin and propofol/ketamine) in Thoroughbred racehorses anesthetized with sevoflurane and medetomidine during arthroscopic surgery.

Materials and Methods

Horses

Clinical records of all Thoroughbred racehorses that underwent arthroscopic surgery at the Miho Training Center between 2015 and 2016 were retrieved. Data recorded included: demographics, drugs administered (dose and route), need for rescue thiopental, duration of anesthesia and surgery, cardiovascular parameters, induction/recovery characteristics (the quality of induction/recovery, the number of attempts to stand, and the times taken from the end of anesthesia to appearance of spontaneous respiration, extubation, first movement, sternal recumbency, first attempt to stand, and standing), and any adverse events noted on the anesthetic record.

The clinical records were analyzed by one investigator and each case was assigned to Group TG or Group PK. Horses were assigned to Group TG, if thiopental and guaifenesin were administered IV at induction. Horses were assigned to Group PK, if propofol and ketamine were administered IV at induction.

Anesthesia and instrumentation

All horses subject to this study had undergone a preanesthetic blood examination and electrocardiographic reading.

No abnormality was found in any horse with respect to the preanesthetic blood examination or electrocardiography. Food, but not water, was withheld for 12 hr prior to anesthesia. All horses were premedicated IV with medetomidine (Dorbene, Vetcare Oy, Salo, Finland) in combination with midazolam (0.02 mg/kg: Dormicum, Astellas Pharma Inc., Tokyo, Japan) to sedate at the adequate level for smooth induction. Horses were induced either with a rapid injection of 5% guaifenesin (100 mg/kg IV: 5% Guaifenesin, Shinyo Pure Chemicals Co., Ltd., Osaka, Japan) and thiopental sodium (4.0 mg/kg IV: Ravonal, Mitsubishi Tanabe Pharma Co., Osaka, Japan) (Group TG), or with 1% propofol (1.0 mg/kg IV: 1% Propofol, Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan) and ketamine (1.0 mg/kg IV: Ketalar, Daiichi-Sankyo Co., Ltd., Tokyo, Japan) (Group PK). After induction of anesthesia, the horses were intubated endotracheally and positioned in dorsal recumbency. Anesthesia was maintained with sevoflurane (Sevofrane, Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) and oxygen (approximately 5 *l*/min) combined with a constant rate infusion (CRI) of medetomidine (3.0 μg/kg/hr) to produce a surgical plane of anesthesia. The horses were connected to a circle system and intermittent positive pressure ventilation (MOK 94, Silver Medical Co., Tokyo, Japan) was initiated with a peak airway pressure of 25 cmH$_2$O. The ventilator settings were chosen to maintain the arterial carbon dioxide partial pressure (PaCO$_2$) at between 45 and 55 mmHg. Lactated Ringer's solution was administered at a rate of approximately 10 m*l*/kg/hr throughout anesthesia. To prevent the involuntary body movements during anesthetic induction and surgery, an intravenous bolus dose 1.0 g/head thiopental sodium was administered as a rescue injection.

A base-apex lead electrocardiogram was used to monitor heart rate (HR) and rhythm. Arterial blood pressures were measured directly through the catheter by a transducer system. Respiratory gas was collected continuously, and the end-tidal sevoflurane concentration (ET$_{SEVO}$) was determined by infrared absorption. ET$_{SEVO}$ was recorded throughout anesthesia, and HR, systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP) and mean arterial blood pressure (MAP) were recorded every 5 min by an anesthesia monitoring system (BP608, Omron Colin Co., Ltd., Tokyo, Japan). Arterial blood samples were collected every 15 min and PaCO$_2$, arterial oxygen partial pressure (PaO$_2$) and pH were immediately analyzed by a blood-gas analyzer (ABL800 FLEX, Radiometer Co., Ltd., Tokyo, Japan). Hypotension was defined as MAP <70 mmHg and was corrected with dobutamine (Dobutrex, Shionogi & Co., Ltd., Osaka, Japan) infusion. If bradycardia or hypotension was not improved even after administration of dobutamine, the medetomidine infusion rate was reduced. The vaporizer settings for sevoflurane were based

on observations of standard clinical signs for achieving a surgical plane of anesthesia. Anesthetic depth was judged to be light, if movement, brisk palpebral response, spontaneous nystagmus, or sudden changes in arterial blood pressure and HR were observed.

Horses in the two groups were allowed to recover without assistance. Oxygen was supplied until adequate spontaneous respiration appeared, and then the endotracheal tube was removed. Induction/recovery phases were continuously monitored by use of a wide-angle high-resolution camera. On the basis of these images, the induction/quality of recovery was subjectively assessed by experienced anesthetists who were blinded to the induction agents using a scoring of 1–5 (1, poor; 2, marginal; 3, fair; 4, good; 5, excellent) [13]. The number of attempts to stand and times taken from the end of anesthesia to appearance of spontaneous respiration, extubation, first movement, sternal recumbency, first attempt to stand, and standing were recorded.

Statistical analysis

Data from the two groups were tested for normality by using the Kolmogorov-Smirnov test: some variables (body weight and ET_{SEVO}) followed a normal distribution, and some variables (age, duration of maintenance/surgery, preanesthetic medetomidine dose, dobutamine infusion rate, HR, SAP, DAP, MAP, induction/recovery score, the number of attempts to stand as well as the times to appearance of spontaneous respiration, extubation, first movement, sternal recumbency, first attempt to stand, and standing) were non-normally distributed. The χ^2 test for independence was used to compare the sexes of the horses or the numbers of horses administered rescue thiopental boluses. Normally distributed data were analyzed using an unpaired Student's *t*-test, with results presented as mean ± standard deviation (SD).

Non-normally distributed data were compared between the two groups by using the Mann-Whitney's *U*-test. One-way analysis of variance (ANOVA) for repeatedly measured variables (HR, SAP, DAP, MAP) was performed for each group. If statistically significant differences were observed, a Bonferroni's significant difference test was conducted. For comparisons between groups, an unpaired Student's *t*-test was performed at each point. These results are expressed as (median, range). Differences were considered significant if $P<0.05$.

Results

Out of 214 files retrieved, 91 were included in Group TG and 123 in Group PK (Table 1). There was no significant difference between the two groups with regard to body weight, age, or duration of maintenance/surgery.

There was no significant difference between the two groups with regard to the amount of medetomidine in premedication or in ET_{SEVO} during surgery (Table 2). A single rapid intravenous bolus dose of 1.0 g/head thiopental sodium was administered only once during induction in order to achieve optimal position on a padded surgical table in four horses in Group TG and in ten horses in Group PK; no significant difference in the ratio of horses received a rescue injection of thiopental sodium was found between the two groups. Medetomidine infusion rate (μg/kg/hr) was significantly higher ($P<0.001$) in Group PK (3.0, 0.2–3.0) than in Group TG (3.0, 0.0–3.0), and was reduced in 37 horses in Group TG and in 12 horses in Group PK. Average infusion rate of dobutamine (μg/kg/min) required for keeping MAP above 70 mmHg was significantly lower ($P<0.001$) in Group PK (0.43, 0.10–1.40) than in Group TG (0.67, 0.08–1.56).

Table 1. Demographic data retrieved from the files of Thoroughbred racehorses which underwent arthroscopic surgery between 2015 and 2016

	Group		*P*-value
	TG	PK	
Number (*n*) of horses	91	123	
Sex			0.955
Male (*n*)	58	76	
Female (*n*)	30	43	
Gelding (*n*)	3	4	
Body weight (kg)	458 ± 30	455 ± 26	0.425
Age (years)	3.0 (2.0–6.0)	3.0 (2.0–6.0)	0.210
Duration of maintenance (min)	65 (40–115)	65 (40–153)	0.753
Duration of surgery (min)	35 (10–82)	34 (13–118)	0.680

Results are presented as mean ± standard deviation or median (range). Horses in Group TG (n=91) were induced with guaifenesin (100 mg/kg) and thiopental (4.0 mg/kg): horses in Group PK (n=123) were induced with propofol (1.0 mg/kg) and ketamine (1.0 mg/kg).

The HR, SAP, DAP and MAP values during maintenance in the two groups are shown in Table 3. MAP and DAP during maintenance were significantly higher ($P<0.01$) in Group PK than in Group TG. SAP in Group PK was significantly higher ($P<0.01$) than in Group TG at 15 min and 30 min after connection to the breathing circuit. SAP, DAP and MAP in Group PK were stable throughout the maintenance, whereas those parameters in Group TG tended to increase (often significantly, $P<0.01$) as duration of maintenance increased. No horses in either group became hypoxemic or hypercapnic (data not shown).

Anesthetic induction scores for Group TG (5, 2–5) and Group PK (5, 2–5) were not significantly different (Table 4). There was no difference between the two groups with regard

Table 2. Dose requirements (medetomidine for premedication, end-tidal sevoflurane concentration, and medetomidine/dobutamine during maintenance) and the number of horses received a rescue injection of thiopental sodium in 214 Thoroughbred racehorses

	Group		*P*-value
	TG (*n*=91)	PK (*n*=123)	
Preanesthetic medetomidine dose (μg/kg)	6.5 (5–8.5)	6 (4.8–8)	0.354
End-tidal sevoflurane concentration (%)	2.4 ± 0.2	2.4 ± 0.2	0.578
Medetomidine infusion dose rate (μg/kg/hr)*	3.0 (0.0–3.0)	3.0 (0.2–3.0)	**<0.001**
Dobutamine infusion rate (μg/kg/min)*	0.67 (0.08–1.56)	0.43 (0.10–1.40)	**<0.001**
Number (*n*) of horses received a rescue injection of thiopental sodium (1.0 g/head)	4	10	0.274

Results are presented as mean ± standard deviation or median (range). *Significant difference between two groups. For group definitions and doses of induction agents, see Table 1.

Table 3. Heart rate (HR), and systolic (SAP), diastolic (DAP) and mean (MAP) arterial blood pressure during the maintenance of anesthesia in 214 Thoroughbred racehorses of Group TG (*n*=91) and Group PK (*n*=123)

Variable	Group	Time after connection to breathing circuit (min)				
		0	15	30	45	60
HR (beats/min)	TG	29 (23–36) A	28 (17–41) AB	27 (15–36) B	28 (20–36) AB	28 (22–37) AC
	PK	28 (18–33) A	27 (15–40) A	27 (15–45) A	27 (17–46) A	28 (20–37) A
SAP (mmHg)	TG	NR	92 (70–112) A	97 (63–115) B	100 (85–137) C	102 (80–125) C
	PK	NR	100 (73–138) A*	100 (72–125) A*	102 (85–133) AB	103 (84–137) B
DAP (mmHg)	TG	NR	50 (33–78) A	53 (26–77) AB	55 (33–81) B	56 (28–71) B
	PK	NR	61 (30–95) A*	59 (39–78) A*	59 (45–76) A*	59 (47–76) A*
MAP (mmHg)	TG	NR	64 (43–87) A	68 (43–85) AB	70 (50–86) C	71 (51–88) AB
	PK	NR	75 (45–96) A*	73 (49–96) A*	73 (58–87) A*	75 (56–85) A*

Results are presented as median (range). Data indicated with the same uppercase letter are not significantly different from each other within the same row. *Significant difference from Group TG ($P<0.05$). NR: not recorded. For group definitions and doses of induction agents, see Table 1.

Table 4. Induction score, recovery times (appearance of spontaneous respiration, extubation, first movement, sternal recumbency, first attempt to stand, and standing), and recovery score in 214 Thoroughbred racehorses

	Group		*P*-value
	TG (*n*=91)	PK (*n*=123)	
Induction score	5 (2–5)	5 (2–5)	0.414
Time to appearance of spontaneous respiration (min)	8 (1–40)	8 (1–20)	0.218
Time to extubation (min)*	15 (7–44)	13 (5–29)	**0.001**
Time to first movement (min)*	50 (29–70)	32 (1–60)	**<0.001**
Time to sternal recumbency (min)*	60 (30–95)	39 (15–65)	**<0.001**
Time to first attempt to stand (min)*	65 (35–95)	42 (20–65)	**<0.001**
Time to standing (min)*	65 (35–100)	42 (20–65)	**<0.001**
Recovery score*	4 (2–5)	5 (2–5)	**0.003**

*Significant difference between the two groups. The recovery times and scores for induction/recovery (1 [poor] to 5 [excellent]) are expressed as median (range). For group definitions and doses of induction agents, see Table 1.

to the time to appearance of spontaneous respiration. In contrast, the recovery times to extubation, first movement, sternal recumbency, first attempt to stand, and standing were significantly shorter (P=0.001, P<0.001, P<0.001, P<0.001, P<0.001, respectively) in Group PK than in Group TK. Recovery score was significantly better (P=0.003) in Group PK (5, 2–5) compared with Group TG (4, 2–5). The number of attempts to stand was significantly fewer (P<0.001) in Group PK (one attempt, 101 horses [82%]; two, 14 [11%]; three, 6 [5%]; four, 1 [1%], five, 1 [1%]) than that in Group TG (one attempt, 52 horses [57%]; two, 26 [29%]; three, 6 [7%]; four, 5 [5%], five, 2 [2%]).

Discussion

The present study in Thoroughbred racehorses indicates that propofol/ketamine is as good as thiopental/guaifenesin in terms of quality of anesthetic induction. Moreover, induction with propofol/ketamine resulted in lower dobutamine requirements for keeping MAP above 70 mmHg during maintenance, shorter recovery times, and better quality of recovery. Therefore, according to this retrospective study, administration of propofol/ketamine would be preferable to thiopental/guaifenesin for induction of anesthesia in Thoroughbred racehorses anesthetized with sevoflurane and medetomidine during arthroscopic surgery.

The lack of a statistically significant difference in induction score indicates that the quality of induction with propofol/ketamine is generally as excellent as thiopental/guaifenesin, which is commonly used for routine general anesthesia at JRA racehorse clinics. The induction dose of propofol/ketamine was based on a single study comparing induction with propofol, thiopental, and ketamine in horses [21]. Wagner *et al.* demonstrated that the best scores for induction quality were associated with ketamine (1.5 mg/kg) and propofol (0.5 mg/kg); however, there were no significant differences in quality between the above protocol and induction with ketamine (1.0 mg/kg) and propofol (1.0 mg/kg). Mama *et al.* speculated that combining propofol with other induction drugs such as ketamine or thiopental may enhance the quality of induction [13]. In a retrospective study, a combination of propofol (0.40 mg/kg) and ketamine (2.8 mg/kg) was associated with satisfactory anesthetic inductions and recoveries in horses [17]. The doses of induction agents and premedication used in those previous studies differed slightly from those that we used here. The current study indicated that combining propofol (1.0 mg/kg) with ketamine (1.0 mg/kg) resulted in smooth induction despite the use of more propofol and less ketamine than the protocol (ketamine, 1.5 mg/kg; propofol, 0.5 mg/kg) in a previous report [21]. Wagner *et al.* administered xylazine (1.0 mg/kg) for premedication; on the other hand, we did medetomidine

and midazolam. The difference in anesthetic premedication may be associated with the results indicating that the quality of induction did not decline.

In the current study, recovery times after surgery in horses induced with propofol/ketamine were shorter compared to thiopental/guaifenesin. In addition, horses that received propofol/ketamine required significantly fewer attempts to stand than horses that received thiopental/guaifenesin. Not surprisingly, scores for quality of recovery were also better for horses that received propofol/ketamine compared to thiopental/guaifenesin. In our previous study, recovery time to standing was 63 ± 11 min, and recovery score was G5 for 13 horses (52%), G4 for 10 (40%), and G3 for 2 (8%) in Thoroughbred racehorses anesthetized with sevoflurane and medetomidine following premedication with medetomidine (5.0 μg/kg IV), thiopental (4.0 mg/kg IV) and guaifenesin (100 mg/kg IV) [19]. We also reported that recovery time to standing was 40 ± 6 min, and that recovery score was G5 for 7 horses (70%), and G3 for 3 (30%) in Thoroughbred racehorses anesthetized with sevoflurane and medetomidine following premedication with medetomidine (6.0 μg/kg IV), midazolam (0.02 mg/kg IV), ketamine (1.0 mg/kg IV) and propofol (1.0 mg/kg IV) [20]. Due to the different pharmacological interactions of the different combinations of induction agents used, the reason for the significant difference in the quality of recovery between propofol/ketamine and thiopental/guaifenesin cannot be determined from this study and requires further investigation. However, the doses of medication used in these previous studies were rarely different from those that we used here. Therefore, it appeared that shorter recovery times in Group PK might be associated with rapid elimination of induction agents.

Although propofol is popularly used in the anesthesia of humans and small animals because it allows rapid awakening, until recently, it has not been as widely used in horses, partly because of its expense, and partly because administration of propofol to horses does not necessarily produce smooth inductions [12, 13]. Based on its unsatisfactory anesthetic induction [5, 12, 13], JRA racehorse clinics have avoided the clinical use of propofol for induction. However, recent studies reveal that combining propofol with ketamine offers the possibility of improving recovery [11, 17, 21]. Jarrett *et al.* report that for horses undergoing general anesthesia, quality of recovery may be better following induction with propofol (0.5 mg/kg) and ketamine (3.0 mg/kg) compared to that with midazolam and ketamine [11]. Wagner *et al.* commented that the quality of early recovery from anesthesia in horses may be improved by some combinations of propofol (0.5–1.5 mg/kg) with ketamine (0.5–1.5 mg/kg) [21]. Because our results indicated that combining propofol (1.0 mg/kg) with ketamine (1.0 mg/kg) might produce a smoother, more coordinated

recovery as with those reports, it was supposed that induction with propofol/ketamine may have a place in equine anesthesia. It also provides uneventful and rapid recovery from anesthesia, thus reducing risks associated with anesthesia in Thoroughbred racehorses.

HR and blood pressure during maintenance after induction with both propofol/ketamine and thiopental/guaifenesin were maintained within a clinically acceptable range. Although MAP in Group TG was significantly lower than that in Group PK, it remained within commonly acceptable limits for horses under general anesthesia. Generally, a MAP of >70 mmHg is considered necessary for preventing postoperative myopathy. Sevoflurane induces a dose-dependent decrease in hemodynamic variables in horses [1, 18]. In addition, α_2-adrenergic receptor agonists including medetomidine cause an initial period of hypertension and bradycardia, followed by a longer period of hypotension [7, 22], although another study demonstrated that 2-hr medetomidine CRI caused minimal cardiopulmonary effects (e.g., a slight reduction in MAP) compared with a bolus administration in conscious ponies [3]. Notably, the medetomidine infusion rate in Group TG was decreased in order to avoid further hypotension and this resulted in a significant decrease in medetomidine dose during maintenance compared to that in Group PK. The results of our current study indicated that induction agents (propofol/ketamine or thiopental/guaifenesin) were not associated with ET_{SEVO} during surgery. Therefore, we speculate that the differences between induction agents might be associated with the significant difference in blood pressure and the requirement of dobutamine or medetomidine for maintenance.

In conclusion, both propofol/ketamine and thiopental/guaifenesin provided a smooth induction of anesthesia in Thoroughbred racehorses. Moreover, induction with propofol/ketamine resulted in lower dobutamine requirements for keeping MAP above 70 mmHg during maintenance, shorter recovery times, and better quality of recovery. Therefore, according to this retrospective study, induction with propofol/ketamine would be preferable to thiopental/guaifenesin in Thoroughbred racehorses anesthetized with sevoflurane and medetomidine during arthroscopic surgery.

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