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Anesthetic and Cardiorespiratory Effects of Propofol, Medetomidine, Lidocaine and Butorphanol Total Intravenous Anesthesia in Horses

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ABSTRACT. Anesthetic and cardiorespiratory effects of medetomidine, lidocaine, butorphanol and propofol total intravenous anesthesia (MLBP-TIVA) were evaluated in horses undergoing an experimental surgery. Ten horses were premedicated with an intravenous injection (IV) of medetomidine (5 μg/kg) and butorphanol (20 μg/kg). Anesthesia was induced by administration of 1% propofol (3 mg/kg, IV) at a rate of 1 mg/kg/min (n=5, group-1) or 2% propofol administered at a rate of 6 mg/kg/min (n=5, group-2) following administration of lidocaine (1 mg/kg, IV) and then maintained by infusions of propofol, medetomidine (3.5 μg/kg/hr), lidocaine (3 mg/kg/hr) and butorphanol (24 μg/kg/hr). The mean durations of anesthesia and propofol infusion rate required for maintaining surgical anesthesia were 130 ± 17 min and 0.10 ± 0.01 mg/kg/min in group 1 and 129 ± 14 min and 0.10 ± 0.02 mg/kg/min in group 2. Four horses in group 1 and 2 horses in group 2 paddled following recumbency during induction of anesthesia. The median quality scores for induction (0–4: poor-excellent) and recovery (0–5: unable to stand-excellent) were 3 and 4 for both groups, respectively. Transition to anesthesia (the first 20-min period after induction) was uneventful in group 2, while all horses showed a light plane of anesthesia in group 1. The quality score (0–3: poor-excellent) for the transition to anesthesia in group 2 was significantly higher than in group 1 (median 3 versus 1, P=0.009). Heart rate and arterial blood pressure were maintained within acceptable ranges, but hypercapnia occurred during anesthesia in both groups. In conclusion, MLBP-TIVA may provide clinically useful surgical anesthesia in horses. A rapid induction with propofol may improve the qualities of induction and transition to MLBP-TIVA.

KEY WORDS: butorphanol, horse, lidocaine, medetomidine, propofol.

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Propofol is a rapid-acting, short-duration and noncumulative intravenous anesthetic with an ideal pharmacokinetic profile for total intravenous anesthesia (TIVA) in horses [10, 22, 31, 32]. However, potential disadvantages include poor analgesia during lighter stages of anesthesia, respiratory depression and unpredictability such as paddling and apnea and elation during induction to general anesthesia in horses [13]. In addition, the total volume of a conventional 1% propofol solution to produce recumbency is too large to enable rapid injection in adult horses. Therefore, propofol is currently considered to be unsatisfactory as the sole agent for producing anesthesia in horses and has been combined with sedatives, analgesics and centrally acting muscle relaxants to achieve satisfactory surgical anesthesia in horses [4, 7, 10, 12, 24, 31].

Multimodal analgesia encompasses the administration of two or more classes of analgesics that act by different mechanisms in order to take advantage of potential additive or synergistic effects so as to provide superior analgesic efficacy with equivalent or reduced adverse effects. Medetomidine is an α_2-adrenoceptor agonist that has a high selectivity for α_2-receptors [33] and produces potent sedative and analgesic effects at smaller doses than xylazine and detomidine in horses [36]. The combined infusion of propofol and medetomidine provides better quality anesthesia, and a smaller total amount of propofol is required to maintain surgical anesthesia compared with propofol alone in horses [4]. An intravenous infusion of lidocaine, a sodium-channel blocker, produces anesthetic-sparing effects in horses anesthetized with isoflurane [9] and halothane [21]. Butorphanol, a synthetic opioid agonist-antagonist deepens the plane of anesthesia and obtunds sympathetic stimulation from surgical stimulation with no adverse effect [11]. Furthermore, a constant rate infusion of butorphanol ameliorated the clinical signs of postoperative pain during abdominal surgery in horses [30]. The total volume of propofol required to produce induction to general anesthesia is too large to enable rapid injection when a conventional 1% propofol solution is administered to horses. Several studies have investigated the clinical usefulness and effects of 5 and 10% propofol solution on TIVA in horses [5, 20, 27]. Recently, a 2% propofol solution has become available for use in humans in Japan. Theoretically, the total volume of propofol required for induction of anesthesia should be reduced by half when the 2% propofol solution is administered.

The purposes of this study were to evaluate the anesthetic and cardiorespiratory effects of TIVA using a drug

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combination of medetomidine, lidocaine, butorphanol and propofol (MLBP-TIVA) in horses. The quality of anesthesia between a slow induction using the conventional 1% propofol solution and rapid induction using the 2% propofol solution was compared. We hypothesized that MLBP-TIVA would provide clinically effective surgical anesthesia and that the 2% propofol solution would improve the quality of MLBP-TIVA in horses.

MATERIALS AND METHODS

Experimental animals: Ten healthy Thoroughbred horses weighing from 348 to 610 kg (494 ± 87 kg [mean ± SD) and aged from 1 to 20 years (9.3 ± 7.7 years) were randomly allocated to 1 of 2 groups and underwent an experimental surgery in which the right carotid artery was relocated to a subcutaneous position during MLBP-TIVA. Food, but not water, was withheld from horses for 12 hr before anesthesia. The horses were owned by the university and were cared for according to the principles of the "Guide for the Care and Use of Laboratory Animals" prepared by Rakuno Gakuen University. The Animal Care and Use Committee of Rakuno Gakuen University approved the study.

Anesthesia and postoperative management: Each horse was administered an intravenous injection (IV) of medetomidine (5 μg/kg; Domitor, Nippon Zenyaku Kogyo Co., Ltd., Koriyama, Japan) and butorphanol (20 μg/kg; Vetorphale, Meiji Seika Pharma Co., Ltd., Tokyo, Japan) as preanesthetic medication via a 14-gauge, 13.3-cm catheter (BD Angiocath, Becton, Dickinson and Co., Sandy, UT, U.S.A.) placed percutaneously into the left jugular vein (t −6-min). All horses were restrained in a swing-door induction system and administered lidocaine (1 mg/kg, IV; Xylocaine: AstraZeneca, Osaka, Japan) (t −1-min). Anesthesia was induced (t 0-min) by administering a total IV dose of 3 mg/kg of a 1% propofol solution (group 1; n=5) or a 2% solution (group 2; n=5). Group 1, horses were administered 1% propofol solution (Rapinovet, Intervet Co., Ltd., Tokyo, Japan) at a slow rate of 1 mg/kg/min for 3 min. Group 2, horses were administered a 2% propofol solution (2% Propofol Injection "Maruishi," Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) at a rapid rate of 6 mg/kg/min for 30 sec. After the induction of anesthesia, all horses were orotracheally intubated and positioned in left lateral recumbency on an inflated airbed surgical table (SNELL2000, Snell Veterinary Systems, Castle Cary, U.K.). The endotracheal tube was connected to a large animal circle anesthetic system (Model 2800 Large Animal Anesthesia Ventilator System, Mallard Medical, Inc., Redding, CA, U.S.A.) that delivered 100% oxygen (5 *l*/min). Once the horses became recumbent, a constant rate infusion of medetomidine (3.5 μg/kg/hr), lidocaine (3 mg/kg/hr) and butorphanol (24 μg/kg/hr) was started. Specifically, a drug mixture of medetomidine (17.5 μg/m*l*), lidocaine (15 mg/m*l*) and butorphanol (120 mg/m*l*) in saline was infused at a rate of 0.2 m*l*/kg/hr thorough the 14-gauge catheter using an infusion pump (STC-521, Terumo, Tokyo, Japan). A propofol infusion was started (TOP-2200, TOP Corporation, Tokyo, Japan) at the same time, and the surgical depth of anesthesia was adjusted by controlling the infusion rate of the 1% (group 1) or 2% (group 2) propofol solution. The initial propofol infusion rate was 0.1 mg/kg/min. The rate of propofol infusion was increased or decreased by 0.02 mg/kg/min increments when purposeful or spontaneous movement occurred or when the lowest infusion rate that prevented movement was reached, respectively. Incremental IV bolus doses of propofol (1 mg/kg each) were administered when movement was difficult to control by increasing the infusion rate of propofol. Lactated Ringer's solution (Solulact, Terumo Corporation, Tokyo, Japan) was administered IV at a rate of 10 m*l*/kg/hr to all horses during anesthesia.

All drug infusions for MLBP-TIVA were stopped once surgery was completed, and the horses were moved to a padded recovery stall (3.9 × 4.4 m) without full recovery. All horses were assisted to stand using head and tail ropes. After surgery, flunixin meglumine (1 mg/kg, IV; Banamine 5%, Dainippon Sumitomo Pharma, Tokyo, Japan) and penicillin G procaine (4×10^6 U/horse, IM) combined with dihydrostreptomycin sulfate (5 g/horse, IM; Mycillinsol Meiji, Meiji Seika Pharma Co., Ltd.) were administered every 12 hr for 3 days.

Cardiorespiratory monitoring during aesthesia: Baseline heart rate and respiratory rate were determined in all horses standing in stocks before any medication was administered. Once the horses were positioned in lateral recumbency, an 18-gauge catheter (Supercath, Medikit Co., Ltd., Tokyo, Japan) was placed in the right dorsal third metatarsal artery. Arterial blood pressure was monitored by connecting the catheter to a pressure transducer (CDX-A90, Cobe Laboratories, Tokyo, Japan) placed at the level of the right atrium (midsternum region) and zeroed in this position. Arterial blood samples were anaerobically collected from the 18-gauge catheter into a syringe containing heparin at 20-min intervals, and the partial pressure of arterial CO_2 ($PaCO_2$) and O_2 (PaO_2) values were determined immediately by use of a blood gas analyzer (GEM Premier3000, Instrumentation Laboratory, Tokyo, Japan). Base-apex electrocardiography, heart rate and arterial blood pressure values were recorded during anesthesia (DS-5300, Fukuda Denshi, Tokyo, Japan) at 25 min after induction and 5-min intervals thereafter.

Evaluation of the quality of anesthesia: The quality of anesthetic induction, transition to TIVA (from the induction [t 0 min] to t 20 min), maintenance (from t 20 min to the cessation of anesthesia) and recovery from anesthesia were judged in each horse using a subjective scoring system (Table 1). Induction (from t 0 min to recumbency) and recovery times (from the cessation of anesthesia to extubation, first movement, movement to a sternal position and standing) and number of attempts to stand were recorded. The Observer (K.Y.) was aware of the group allocation of each horse.

Statistical analysis: All date are shown as the mean and Standard deviation (SD) or the median. Repeated-measures ANOVA was used to analyze changes in cardiorespiratory data. The Mann-Whitney *U* test was used to compare the times regarding anesthesia, the propofol infusion rate, total infusion volume of propofol and the quality of anesthesia between groups. $P<0.05$ was considered statistically significant.

Table 1. Criteria for scoring the qualities of anesthetic induction, transition to total intravenous anesthesia (TIVA), maintenance of anesthesia, and recovery from anesthesia in horses

Score	Criteria
Anesthetic induction	
0 (Poor)	Ataxia and paddling; danger to horse and handler
1 (Fair)	Purposeful paddling with or without attempt to regain feet
2 (Satisfactory)	Ataxia with or without paddling before falling to the ground
3 (Good)	Horse took 1 or 2 steps with no paddling before falling to the ground
4 (Excellent)	Horse sank smoothly to the ground
Transition to TIVA	
0 (Poor)	Multiple incremental bolus IV doses (1 mg/kg each) of propofol were needed during the first 20-min period to transition to TIVA.
1 (Fair)	Two or three additional bolus IV doses (1 mg/kg each) of propofol were needed during the first 20-min period to transition to TIVA.
2 (Good)	An additional bolus IV dose (1 mg/kg) of propofol was needed during the first 20-min period to transition to TIVA.
3 (Excellent)	Smooth transition; no additional bolus IV dose of propofol was required.
Maintenance of anesthesia	
0 (Poor)	Multiple incremental bolus IV doses (1 mg/kg each) of propofol were required to maintain a surgical plane of anesthesia.
1 (Fair)	Two or three additional bolus IV doses of propofol were required to maintain a surgical plane of anesthesia.
2 (Good)	An additional bolus IV doses of propofol was required to maintain a surgical plane of anesthesia.
3 (Excellent)	Surgical depth of anesthesia was smoothly maintained by controlling the infusion rate of propofol.
Recovery from anesthesia	
0 (Unable to stand)	Horse could not stand for >2 hr after multiple attempts to stand; excitement was evident; injury or high risk of injury
1 (Poor)	Multiple attempts to stand; excitement was evident; high risk of injury
2 (Fair)	Multiple attempts to stand; substantial ataxia
3 (Satisfactory)	Stood after 1 to 3 attempts; prolonged ataxia but no excitement
4 (Good)	Stood after 1 or 2 attempts; mild, short-term ataxia
5 (Excellent)	Stood after the first attempt; no ataxia

RESULTS

Anesthetic effect of MLBP-TIVA: The infusion rate of propofol required to maintain a surgical depth of anesthesia is shown in Fig. 1. Characteristics of anesthesia and recovery associated with MLBP-TIVA are summarized in Table 2. The MLBP-TIVA protocols using 1 and 2% propofol solutions both provided a satisfactory surgical depth of anesthesia for about 2 hr in all horses. Overall mean infusion rates of propofol were 0.10 mg/kg/min in both groups. The employment of 2% propofol solution significantly reduced the total infusion volume of propofol solution by half (P=0.009).

The quality of anesthesia was similar in both groups except for the transition to TIVA. The induction time for the horses in group 1 was significantly longer than that for group 2 (P=0.009). The induction of anesthesia was smooth and excitement free with adequate muscle relaxation and was subjectively scored as good in all horses in group 1 and 4 horses in group 2. Transient, mild and controllable paddling was observed following recumbency in 4 horses in group 1 and 2 horses in group 2. All horses in both groups were uneventfully intubated after induction of anesthesia. All horses in group 1 showed symptoms of a light plane of anesthesia such as nystagmus and movements of the forelegs during the period of the transition to TIVA and received additional

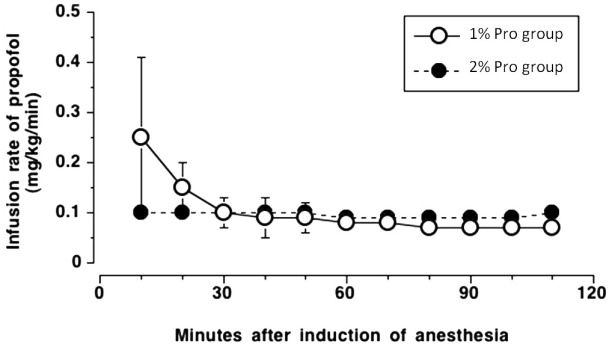

Fig. 1. Propofol infusion rate required to maintain a surgical depth of total intravenous anesthesia in horses anesthetized with total intravenous anesthesia using medetomidine, lidocaine, butorphanol and propofol (MLBP-TIVA). Plots and error bars represent the mean values and standard deviations for 5 horses anesthetized with MLBP-TIVA using a conventional 1% propofol solution (○) or a 2% propofol solution (●). Each horse was premedicated with medetomidine (5 μg/kg, IV) and butorphanol (20 μg/kg, IV). Induction of anesthesia with propofol (3 mg/kg, IV) was started at 0 min following administration of lidocaine (1 mg/kg, IV). All horses were administered a constant rate infusion of medetomidine (3.5 μg/kg/hr), lidocaine (3 mg/kg/hr) and butorphanol (24 μg/kg/hr). The surgical depth of anesthesia was maintained by controlling the infusion rate of propofol.

Table 2. Characteristics of anesthesia and recovery associated with MLBP-TIVA using 1 and 2% propofol solution in horses

Variable	1% Pro group (n=5)	2% Pro group (n=5)	*P* value
Induction time (sec)	149 ± 77	51 ± 12	0.009
Total anesthesia time (min)	130 ± 17	129 ±14	0.917
Infusion rate of propofol (mg/kg/min)	0.10 ± 0.02	0.10 ± 0.01	0.347
Total infusion volume (ml/kg)	1.15 ± 0.21	0.62 ± 0.15	0.009
Quality of anesthesia*			
Induction score	3	3 (2–3)	0.602
Transition score	0 (0–1)	3	0.009
Maintenance score	3	3 (0–3)	0.296
Recovery score	4 (3–5)	4 (4–5)	0.676
Recovery times (min)			
Extubation	34 ± 19	21 ± 7	0.175
First movement	21 ± 16	22 ± 12	0.917
Sternal recumbency	40 ± 10	32 ± 7	0.210
Standing	59 ± 10	46 ± 7	0.117
No. of attempts to stand during recovery	2.4 ± 1.7	1.2 ± 0.4	0.210

With the exception of the scores for the quality of anesthesia, data are shown as the mean ± SD. *: Scores are given as medians and ranges in parentheses.

IV bolus injections of propofol (total: 1.48 ± 0.38 mg/kg) to achieve adequate anesthesia. The transition to TIVA was uneventful in all horses in group 2 and was scored as excellent. The quality of transition to TIVA was significantly better in group 2 compared with group 1 (P=0.009). The quality of maintenance was scored as excellent in all horses in group 1 and 3 horses in group 2. Two horses in group 2 received additional IV bolus injections of propofol (total: 1.8 and 2.5 mg/kg, respectively) to control spontaneous foreleg movements (at t 99-min and t 112-min, respectively), and their maintenance scores were judged as fair. The quality of recovery in group 1 was scored as satisfactory in one horse, good in 3 horses and excellent in one horse. The quality of recovery in group 2 was scored as good in 4 horses and excellent in one horse. The recovery times were 59 ± 10 min in group 1 and 46 ± 7 min in group 2. There was no statistical difference in the recovery times between groups.

Cardiorespiratory effect of MLBP-TIVA: There was no statistical difference in cardiorespiratory parameters during MLBP-TIVA between groups (Table 3). Heart rate and mean arterial blood pressure (MABP) changed within acceptable range in both groups. Mean heart rate was maintained between 31 and 33 beats/min in group 1 and between 34 and 36 beats/min in group 2. MABP was maintained between 94 and 100 mmHg in group 1 and between 104 and 110 mmHg in group 2. Respiratory rate decreased significantly in all horses of both groups after the induction of anesthesia. Apnea lasting for 14 to 17 min was produced in 3 horses in group 1 after the additional IV bolus injections of propofol during the transition to TIVA. Intermittent mandatory ventilation at a respiratory rate of 2 breaths/min was initiated until the horses regained spontaneous breathing. Hypercapnia was observed in all horses of both groups. The mean respiratory rate and $PaCO_2$ during anesthesia ranged from 2 to 4 breaths/min and from 62 to 73 mmHg in group 1 and from 4 to 7 breaths/min and from 69 to 74 mmHg in group 2. The mean PaO_2 ranged from 195 to 368 mmHg in group 1 and from 238 to 262 mmHg in group 2.

DISCUSSION

Our data indicate that MLBP-TIVA can be safely administered to horses for 2 hr, produces good recovery and preserves cardiovascular function. Stable surgical anesthesia was maintained by constant rate infusions of medetomidine at 3.5 μg/kg/hr, lidocaine at 3 mg/kg/hr, butorphanol at 24 μg/kg/hr, and propofol at 0.10 mg/kg/min. Transient paddling can occur following slower induction of anesthesia with propofol, and hypercapnia is common. Hypercapnia may be effectively treated by positive pressure ventilation. The 2% propofol solution reduced the total volume of propofol administered, and the faster rate of administration improved the quality of induction and the first 20-min period of anesthesia (i.e., the transition phase to TIVA).

Multimodal analgesia is proposed to provide superior analgesic efficacy with equivalent or reduced drug dosages and adverse effects. Medetomidine, lidocaine and butorphanol are widely used in equine practice in many countries and produce analgesic effects by different mechanisms. We expected that intraoperative multimodal analgesia using infusions of medetomidine, lidocaine and butorphanol might improve anesthetic efficacy and quality in horses. Bettschart-Wolfensberger *et al.* [2, 4] reported that a constant rate infusion of medetomidine at 3.5 μg/kg/hr provided good quality analgesia and anesthetic-sparing effects in ponies and horses. Doherty and Frazier [8] and Rezende *et al.* [28] reported that a systemic intravenous infusion of lidocaine at 3 mg/kg/hr produced anesthetic-sparing effects in horses. Sellon *et al.* [29] reported that a constant rate infusion of butorphanol at 23.7 μg/kg/hr maintained plasma butorphanol concentrations within a range associated with analgesia in horses. In the present study, we adopted the dose

Table 3. Changes in heart rate (HR), respiratory rate (RR), mean arterial blood pressure (MABP), and arterial partial pressures of CO_2 ($PaCO_2$) and O_2 (PaO_2) during anesthesia in horses anesthetized with MLBP-TIVA using 1% (1% Pro group) or 2% propofol solution (2% Pro group)

Variable	Baseline	Minutes after induction of anesthesia				
		20	40	60	80	100
HR (beats/min)						
1%P-group	47 ± 6	32 ± 6	31 ± 3	31 ± 4	33 ± 3	32 ± 4
2%P-group	41 ± 4	34 ± 2	35 ± 4	35 ± 3	35 ± 4	36 ± 4
MABP (mmHg)						
1%P-group	N.D.	98 ± 13	92 ± 11	94 ± 12	98 ± 12	100 ± 20
2%P-group	N.D.	110 ± 8	108 ± 7	104 ± 8	106 ± 9	108 ± 12
RR (breaths/min)						
1%P-group	23 ± 12	2 ± 2	4 ± 3	4 ± 3	4 ± 1	4 ± 2
2%P-group	16 ± 5	4 ± 3	6 ± 3	6 ± 3	6 ± 4	7 ± 5
$PaCO_2$ (mmHg)						
1%P-group	N.D.	69 ± 10	73 ± 12	68 ± 8	62 ± 11	65 ± 4
2%P-group	N.D.	69 ± 5	73 ± 10	69 ± 7	72 ± 6	74 ± 10
PaO_2 (mmHg)						
1%P-group	N.D.	195 ± 106	292 ± 109	328 ± 124	347 ± 133	368 ± 161
2%P-group	N.D.	238 ± 86	258 ± 101	253 ± 123	248 ± 115	262 ± 118

Data are shown as the mean ± standard deviation. N.D.: not measured. There was no statistical difference in these cardiorespiratory parameters between the 1% Pro and 2% Pro groups.

rates of medetomidine, lidocaine and butorphanol based on these previous reports.

Propofol infusion rates required for maintaining surgical depth of anesthesia were 0.18 mg/kg/min [15] and 0.22 mg/kg/min in horses when propofol was administered as the sole agent for maintaining anesthesia during surgery [31]. Simultaneous infusions of propofol and analgesic agents reduced propofol requirements in horses [4, 10, 24, 31]. The propofol requirements were reduced to 0.098–0.108 mg/kg/min by a simultaneous infusion of medetomidine (3.5 μg/kg/hr) [4], to 0.14 mg/kg/min by infusions of ketamine (1 mg/kg/hr) and medetomidine (1.25 μg/kg/hr) [32] and to 0.16 mg/kg/min by an infusion of ketamine (3 mg/kg/hr) [24]. The propofol requirement in the present study was reduced to 0.10 mg/kg/min, approximately one-half the value compared with those reported in the previous studies [15, 31]. The MLBP-TIVA protocol effectively reduced the propofol requirement in horses undergoing surgery.

Medetomidine infusion (3.5 μg/kg/hr) produced a reduction of 28% in the minimum alveolar concentration (MAC) of desflurane in ponies [3]. Lidocaine infusion (3 mg/kg/hr) produced a reduction of 26.7% in sevoflurane MAC in horses [28]. It was reported that butorphanol did not reduce in halothane MAC in ponies [16]. In addition, a simultaneous infusion of butorphanol (25 μg/kg/hr) with medetomidine (3.5 μg/kg/hr) did not provide a further reduction in anesthetic requirements in horses compared with infusion of medetomidine (3.5 μg/kg/hr) alone [1]. On the other hand, intraoperative injection of butorphanol deepened the plane of anesthesia and obtunded sympathetic stimulation from a surgical procedure [12], and postoperative infusion of butorphanol ameliorated clinical signs of postoperative pain during abdominal surgery [29]. Theoretically, it is expected that the combination of medetomidine, lidocaine and butorphanol can provide a multimodal analgesic effect and significantly reduce anesthetic requirements. Further studies are necessary to confirm the usefulness of butorphanol for TIVA in horses.

The low dose of propofol (0.35 mg/kg, IV) provided brief and mild sedation [6] but anesthetic doses (2–8 mg/kg, IV) occasionally produced undesirable side effects during induction including excitement, increased muscle activities, and paddling in the early recumbent phase in horses [13, 35]. These undesirable characteristics are transient (about 1 min) but may predispose the horse or attendants to injury [13, 35]. Levels of central nervous system (CNS) depression induced by anesthetics have been divided into 4 stages depending on neuromuscular signs [17]. Reflexes become more primitive and exaggerated as CNS depression progresses to Stage 2 (the stage of delirium or involuntary movement). We speculated that the undesirable characteristics of propofol induction might be associated with Stage 2. Premedication with α_2-adrenoceptors such as xylazine (0.5–1 mg/kg, IV) and detomidine (15–30 μg/kg, IV) only partially improved the undesirable characteristics of propofol induction in horses [14, 15]. Premedication with a combination of xylazine (1 mg/kg, IV) and midazolam (50 μg/kg, IV) also failed to prevent the undesirable characteristics of propofol induction (3 mg/kg, IV) in horses [26]. Consistent with these previous studies, 6 of 10 horses premedicated with medetomidine (5 μg/kg, IV) and butorphanol (20 μg/kg, IV) showed transient mild paddling in the early recumbent phase after induction with propofol in the present study. An experimental study showed that IV administration of guaifenesin (78 ± 18 mg/kg) followed by a bolus IV of propofol (2 mg/kg) was sufficient to prevent adverse anesthetic induction events caused by propofol in horses [7]. The addition of a muscle relaxant as preanesthetic medication will likely improve the quality

of induction of anesthesia.

Interestingly, transient paddling after induction of anesthesia was observed in only 2 of 5 horses administered a rapid injection of 2% propofol solution, but it was observed in 4 of 5 horses administered a slow injection of 1% propofol solution. This response was anticipated and was attributed to the much more rapid rate of propofol administration (approximately 6 times faster). In addition, the quality of transition to TIVA was significantly better in horses administered the 2% propofol solution. Matthews *et al.* [15] suggested that administration of propofol over 2 min produced a smoother induction than if administered over 1 min. On the other hand, Ohta *et al.* [24] reported that the slow injection of propofol failed to prevent the undesirable characteristics of anesthetic induction in horses. We propose that the rapid administration of a 2% propofol solution provides a prompt increase in plasma propofol concentration, producing an adequate level of CNS depression and a better quality of anesthetic induction. Our data also suggest that rapid administration of 2% propofol solution achieves a stable anesthetic level faster than slower administration rates. Further investigations including pharmacokinetics and detailed cardiorespiratory studies of propofol are required to confirm the effect of a rapid propofol induction in horses.

Tachycardia and hypertension developed in unpremedicated horses anesthetized with propofol [13, 35]. Increased cardiovascular function might be caused by excitement and sympathetic activation during Stage 2 of anesthesia and modified or prevented by premedication using an α_2-adrenoceptor agonist such as xylazine and detomidine [14, 22, 26]. Tachycardia and hypertension were not observed in the present study. The CNS and analgesic effects produced by medetomidine (5 μg/kg, IV) and butorphanol (20 μg/kg, IV) undoubtedly modify the cardiostimulatory effects produced by light planes of propofol anesthesia in horses.

It is considered that cardiovascular function is well maintained in horses anesthetized with TIVA protocols using propofol with or without the simultaneous infusion of analgesic agents [4, 10, 15, 22, 25, 32, 35]. Consistent with previous reports, heart rate and arterial blood pressure were well maintained in all horse anesthetized with MLBP-TIVA in the present study. Continuous infusion of propofol from 0.14 to 0.3 mg/kg/min produced a dose-dependent decrease in stroke volume and decreased systemic vascular resistance at a higher dose (0.3 mg/kg/min) in horses that were premedicated with xylazine (1 mg/kg, IV) [28]. Simultaneous infusions of medetomidine, lidocaine and butorphanol reduced the propofol requirement to 0.1 mg/kg/min. Therefore, the dose-dependent cardiovascular depression caused by propofol could be decreased in horses anesthetized with MLBP-TIVA. Other studies in horses have indicated that a lidocaine infusion (3.0 mg/kg/min) did not alter cardiovascular function during sevoflurane anesthesia [34] and that the simultaneous infusion of butorphanol (25 μg/kg/hr) did not influence cardiovascular function in horses anesthetized with isoflurane and medetomidine infusion (3.5 μg/kg/hr) [1]. On the other hand, medetomidine can produce vasoconstriction by stimulating α_2-adrenoceptors on peripheral vasculatures [19]. Furthermore, medetomidine-induced peripheral vasoconstriction may be a factor contributing to increase in blood pressure and/or decrease in stroke volume. We conjecture that MLBP-TIVA causes minimal depression of cardiovascular function because heart rate and MABP were maintained within clinically acceptable ranges during anesthesia, although detailed measurements of cardiovascular function are required to confirm this.

Respiratory depression and apnea are expected potential adverse effects after the IV administration of propofol, particularly when administered at rapid rates of infusion [18]. A decrease in respiratory rate and increase in $PaCO_2$ were observed after induction of anesthesia when relatively large doses of propofol were administered to horses (8 mg/kg, IV) [22]. Anesthesia induction with propofol (2 mg/kg, IV) after premedication with xylazine (0.5–1 mg/kg, IV) or detomidine (15–30 μg/kg, IV) caused greater respiratory depression in comparison with a single IV bolus of propofol in horses [13, 14]. It was proposed that drug interaction between propofol and medetomidine might have exacerbated respiratory compromise in horses [31]. Furthermore, it was reported that horses sedated with a combination of detomidine (20 μg/kg, IV) and butorphanol (25 μg/kg, IV) exhibited significant decreases in respiratory rate and increase in $PaCO_2$ compared with horses sedated with detomidine alone (20 μg/kg, IV) [23]. Consistent with these reports, we observed significant decreases in respiratory rate and increase in $PaCO_2$ in all horses after the induction of anesthesia with propofol following premedication with medetomidine and butorphanol.

Hypoxia was successfully prevented in our horses by inhalation of 100% oxygen. However, hypercapnia due to a significant decrease in respiratory rate developed during MLBP-TIVA. Flaherty *et al.* [10] reported that a marked respiratory depression was evident in ponies receiving propofol infusion (0.33 mg/kg/min). Lidocaine infusion (3.0 mg/kg/min) did not alter respiratory function during sevoflurane anesthesia in horses [34], and simultaneous infusion of butorphanol (25 μg/kg/hr) did not influence respiratory function in horses anesthetized with isoflurane and medetomidine infusion (3.5 μg/kg/hr) [1]. Bettschart-Wolfensberger *et al.* [4] reported that positive pressure ventilation was required to improve respiratory depression in 23 of 50 horses anesthetized with total intravenous anesthesia using a drug combination of medetomidine (3.5 μg/kg/hr) and propofol (0.098–0.108 mg/kg/min). Therefore, drug interactions and the combined respiratory effects of propofol and medetomidine or other potential respiratory depressants likely contribute to the hypercapnia produced by MLBP-TIVA. Hypercapnia occurring in horses during general anesthesia in horses can be treated with positive pressure ventilation [18]. But, it may contribute to decreases in cardiac output and arterial blood pressure secondary to increases in intrathoracic pressure that can decrease venous return. Further investigation is required to confirm the cardiopulmonary effects of positive pressure ventilation during MLBP-TIVA in horses.

Recovery from anesthesia is influenced by many factors including variability in the horse's temperament, development of hypotension during anesthesia, type of surgical

procedure, duration of anesthesia, external stimuli and use of sedatives and other adjunctive drugs [18]. The quality of recovery from propofol anesthesia is generally considered to be acceptable to good in horses anesthetized with various TIVA protocols with or without simultaneous infusions of analgesic agents [4, 10, 15, 22, 25, 32, 35]. Matthews *et al.* [15] reported that time to standing after the cessation of anesthesia (standing time) was 62 ± 29 min in 12 horses that had been anesthetized for 61 ± 19 min with propofol infusion (0.18 ± 0.04 mg/kg/min) and subjected to abdominal surgery. Umar *et al.* [31] reported that the time to standing was 87 ± 36 min in 6 horses undergoing surgical translocation of their carotid artery that had been anesthetized for 112 ± 11 min with propofol infusion (0.22 ± 0.03 mg/kg/min). Ohta *et al.* [24] reported that the time to standing was 70 ± 23 min in 7 horses undergoing internal fixation of fracture that had been anesthetized for 124 ± 11 min with simultaneous infusions of propofol (0.16 ± 0.02 mg/kg/min) and ketamine (3 mg/kg/hr). Bettschart-Wolfensberger *et al.* [4] reported that the time to standing was 42 ± 20 min in 50 horses that had been anesthetized for 112 ± 41 min with simultaneous infusions of propofol (0.098–0.108 mg/kg/min) and medetomidine (3.5 μg/kg/hr) and subjected to various surgical procedures (33 orthopedic surgery, 7 integumentary surgeries and 10 elective abdominal surgeries). Umar *et al.* [31] reported that the time to standing was 62 ± 10 min in 6 horses undergoing surgical translocation of the carotid artery that had been anesthetized for 115 ± 17 min with simultaneous infusions of propofol (0.14 ± 0.02 mg/kg/min), ketamine (1 mg/kg/hr) and medetomidine (1.25 μg/kg/hr). The quality of recovery was judged as good to excellent in most horses in the present study, and the standing time was about 50 to 60 min following general anesthesia of about 2 hr in duration. MLBP-TIVA provided a similar quality of recovery from anesthesia and time to standing as reported for the various TIVA protocols using simultaneous infusions of propofol and analgesic agents in horses [4, 24, 31].

In conclusion, MLBP-TIVA provides effective general anesthesia and good recovery in horses while preserving cardiovascular function. Employment of 2% propofol solution and the rapid rate of administration of propofol improve the quality of induction and the transition to TIVA in horses.

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