



## NOTE

Surgery

# Comparison of intraoperative cardiorespiratory and behavioral responses to medetomidine combined with tramadol or butorphanol during standing laparoscopic ovariectomy in horses

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**ABSTRACT.** The purpose of this study was to assess the cardiorespiratory and behavioral responses to the combination of medetomidine and tramadol (M-T) or butorphanol (M-B) in standing laparoscopic ovariectomy in horses. One ovary was removed under M-T and the contralateral ovary was removed under M-B with at least 4 weeks between operations at random. Horses were sedated using intravenous medetomidine (5 µg/kg) followed by tramadol (1 mg/kg) or butorphanol (10 µg/kg) after 5 min. Sedation was maintained through the repeated injection of medetomidine (1 µg/kg) and tramadol (0.4 mg/kg) or medetomidine (1 µg/kg) and butorphanol (4 µg/kg) every 15 min. Cardiorespiratory function and behavioral responses, including, sedation, ataxia, and analgesia, were assessed during the surgery. There were no significant differences in cardiorespiratory values and sedation and analgesia scores between M-T and M-B. Ataxia scores were significantly lower in M-T than in M-B. This result suggests that M-T could maintain smooth and stable standing surgery with minimal cardiorespiratory changes in horses.

**KEY WORDS:** analgesia, ataxia, horse, sedation, tramadol

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Standing surgical procedures are preferred over general anesthesia because they minimize morbidity and mortality rates and cost in equine practice [7, 20, 22]. Ensuring the correct stage and duration of sedation and analgesia and producing little ataxia are important to perform a stable standing surgery [12, 15, 16]. Agonists of the  $\alpha_2$  adrenoreceptor with opioids are widely applied in horses for standing surgery such as laparoscopic ovariectomy, wound repair, and castration [4, 8, 13].

Medetomidine is an  $\alpha_2$  agonist for horses and induces a stable sedation effect [2]. A clinical study on the combination of medetomidine and morphine in standing horse exploratory laparoscopy showed an adequate level of sedation and analgesia without adverse behavioral changes [20]. Opioid analgesics are used for pain management in horses but have potential side effects, including an excitatory effect [4]. Butorphanol, a synthetic opioid with narcotic agonist and antagonist properties, is commonly used in horses with  $\alpha_2$  agonists [14, 17].

Tramadol is a synthetic opioid analgesic used for pain management [1] that acts on the  $\mu$ -opioid receptor with a low risk of substance dependence [6]. Previous studies have investigated a physiologically based model for tramadol pharmacokinetics [1] and physiological responses to tramadol with xylazine [18] and detomidine [9] in horses. However, there has not been an evaluation of the clinical responses to a tramadol and medetomidine combination during an entire surgical procedure.

Ovariectomy is performed for ovary disorders, such as granulosa-theca cell tumor and ovarian lymphosarcoma [3]. Conventional celiotomy and colpotomy can cause several complications, including wound infection and incision dehiscence [11]. Considering the low risk of complication and less invasiveness, laparoscopic ovariectomy in the standing position was selected in this study.

The objective of the present study was to compare the cardiorespiratory and behavioral responses to the combination of medetomidine and tramadol (M-T) or medetomidine and butorphanol (M-B) in horses undergoing standing laparoscopic ovariectomy.

Six thoroughbred mares (average age  $5.0 \pm 3.7$  years, average weight  $398.3 \pm 97.6$  kg) were used in this experiment. This

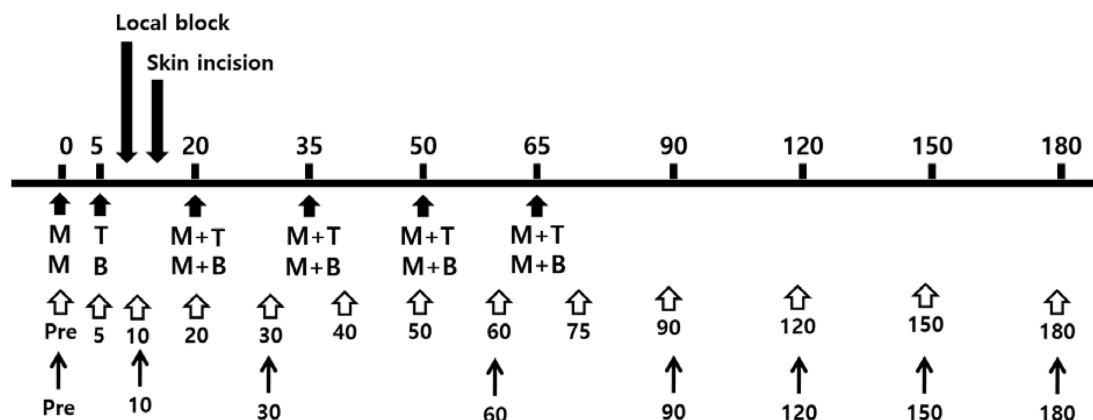
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**Fig. 1.** Timeline of data collection in six horses after the administration of medetomidine with tramadol or butorphanol followed by repeated injection of medetomidine with tramadol or butorphanol during for standing laparoscopic ovariectomy. All drugs were administered intravenously. M: medetomidine (5 µg/kg), T: tramadol (1 mg/kg), B: butorphanol (10 µg/kg), M+T: medetomidine (1 µg/kg) + tramadol (0.4 mg/kg), M+B: medetomidine (1 µg/kg) + butorphanol (4 µg/kg); ⤴: minutes from initial administration of drugs and measure of sedation score (SS), ataxia score (AtS), heart rate (HR), respiratory rate (RR), capillary refilling time (CRT), and rectal temperature (RT); ⤴: minutes from initial administration of drugs and complete blood test (CBC) and arterial blood gas analysis (ABGA).

randomized, blind, two-way crossover design study was approved by the Experimental Animal Committee of Obihiro University of Agriculture and Veterinary Medicine. One ovary was removed under M-T and the contralateral ovary was removed under M-B with at least 4 weeks between operations at random. The horses were weighed and underwent physical examinations before the experiment. Every mare was placed in restraint stocks for 20 min daily for 10 days before the experiment to adapt to this procedure.

For the experiment, the mares were restrained in stocks. After infiltration of skin with 2% lidocaine, the transverse facial artery was catheterized with a 22G, 1.25-inch over-the-needle catheter (BD Angiocath, BD Medical, Sandy, UT, USA) to collect arterial blood pressure and blood gas data. A jugular vein was catheterized with a 14G, 3.5-inch extended use catheter (BD Angiocath) for drug administration and complete blood count analysis. To measure arterial blood pressure, a blood pressure transducer (Transpac IV Monitoring Kit, ICU Medical, San Clemente, CA, USA) was positioned and zeroed at the level of the shoulder joint. Electrocardiogram monitoring pads for base-apex lead and rectal temperature (RT) probe were positioned for data collection. Mares initially received medetomidine (5 µg/kg, IV), followed by tramadol (1 mg/kg, IV) or butorphanol (10 µg/kg, IV) after 5 min. Subsequently, the horses received every 15 min medetomidine (1 µg/kg, IV) and tramadol (0.4 mg/kg, IV) or butorphanol (4 µg/kg, IV) until 65 min after initial administration (Fig. 1).

A laparoscopic ovariectomy was performed using a modified method of Kambayashi *et al.* [8]. Local infiltration anesthesia with 50 ml of 2% lidocaine was performed subcutaneously and intramuscularly. The mares received a 5 cm long skin and muscle incision at the midway between the last rib and the tuber coxae as a camera portal and two other incisions, also a 5 cm, were performed for an instrument portal. After local anesthesia of the mesovarium with lidocaine, the mesovarium was resected with laparoscopic scissors and hemorrhaging was controlled with an ultrasonic scalpel. After the ovary was extracted, the incised muscle and skin were sutured with absorbable suture materials.

To evaluate the cardiorespiratory responses, heart rate (HR), respiratory rate (RR), RT, mean arterial pressure (MAP), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and capillary refilling time (CRT) were measured at 0, 5, 10, 20, 30, 40, 50, 60, 75, 90, 120, 150, and 180 min after the first administration (Fig. 1). HR, RT, MAP, SAP, and DAP were recorded using a Colin BP-500 patient monitor (Nippon Colin, Tokyo, Japan). RR was determined by the movement of the thorax and abdomen. CRT was measured by pressing the horse's gums using the thumb for 2 sec and observing the color change. Samples for the complete blood test and blood gas analysis were collected before administration and 10, 30, 60, 90, 120, 150, and 180 min after administration (Fig. 1).

The degree of sedation as a behavioral response was assessed using the sedation score (SS), which is a modified 4-point analog scale [9, 18]: 1) no sedation defined as a normal behavior and appearance; 2) mild sedation defined as slightly reduced movement, lower head carriage with mouth to shoulder; 3) moderate sedation defined as moderately reduced responsiveness, lower head carriage with mouth to elbow joint, drowsiness, slightly droopy lips and eyelids, and moderately wide-based stance; 4) deep sedation defined as markedly decreased movement, a lower head carriage with mouth to the carpal joint, marked drowsiness, droopy lips and eyelids, and markedly wide-based stance.

The ataxia score (AtS) was evaluated using a modified 4-point criteria scale [18]: 1) no postural instability; 2) stable but slight swaying; 3) swaying and leaning against the wall; 4) swaying, leaning, crossing limbs, and buckling.

The analgesia score (AS) was quantified using a reversed-10 cm visual analog scale at six-time points [15, 21]; 10 cm represented complete analgesia and 0 cm indicated loss of analgesia that required additional sedative or analgesic administration to conduct the surgery. The six time points involved key surgical manipulations: 1) local anesthetic injection; 2) skin and abdominal muscle incision; 3) insertion of the laparoscope; 4) gripping of the ovary; 5) resection of the ovary, and 6) closure of the muscle and skin. The total AS was measured during the entire surgical procedure. Two investigators (surgeon and anesthetist), blinded to

**Table 1.** Cardiorespiratory responses in six horses on standing laparoscopic ovariectomy

Time (min)	HR		RR		RT		CRT	
	M-T	M-B	M-T	M-B	M-T	M-B	M-T	M-B
0	39.8 ± 2.3	36.2 ± 4.8	15.6 ± 2.2	17.6 ± 6.7	37.6 ± 0.3	37.7 ± 1.0	1.2 ± 0.3	1.0 ± 0.0
5	27.0 ± 4.7*	30.2 ± 7.1	13.6 ± 3.0	14.0 ± 9.2	37.5 ± 0.2	37.7 ± 1.0	1.1 ± 0.2	1.1 ± 0.2
10	32.0 ± 5.7*	28.6 ± 3.6*	12.6 ± 3.0	10.2 ± 2.5*	37.4 ± 0.1	37.7 ± 1.0	1.1 ± 0.2	1.0 ± 0.0
20	29.6 ± 1.8*	30.0 ± 5.0*	10.2 ± 1.8*	11.4 ± 0.9	37.2 ± 0.3	37.6 ± 1.0	1.1 ± 0.2	1.1 ± 0.2
30	31.2 ± 2.8*	31.8 ± 5.5	11.4 ± 3.0*	12.0 ± 0.0	37.3 ± 0.2*	37.3 ± 1.0*	1.1 ± 0.2	1.1 ± 0.2
40	31.8 ± 3.0*	31.4 ± 3.3	10.4 ± 4.8	10.2 ± 1.8*	37.3 ± 0.2*	37.2 ± 1.0*	1.2 ± 0.3	1.1 ± 0.2
50	33.2 ± 3.7*	33.0 ± 3.2	10.0 ± 3.9	8.8 ± 1.8*	37.2 ± 0.1*	37.2 ± 1.0*	1.1 ± 0.2	1.1 ± 0.2
60	33.8 ± 3.6	31.6 ± 3.0	10.4 ± 2.2	10.6 ± 3.4*	37.1 ± 0.1*	37.0 ± 1.0*	1.1 ± 0.2	1.0 ± 0.0
75	32.8 ± 3.6*	34.4 ± 3.0	11.6 ± 2.9	9.2 ± 1.9*	37.1 ± 0.2*	37.1 ± 1.0*	1.0 ± 0.0	1.1 ± 0.2
90	32.6 ± 5.6	35.0 ± 3.4	11.0 ± 3.5	9.2 ± 1.8*	37.1 ± 0.2*	37.0 ± 1.0*	1.0 ± 0.0	1.1 ± 0.2
120	37.6 ± 4.6	38.0 ± 4.4	10.8 ± 2.8*	11.2 ± 3.1	37.2 ± 0.5*	37.0 ± 1.0*	1.0 ± 0.0	1.0 ± 0.0
150	39.6 ± 2.7	37.4 ± 3.1	13.2 ± 3.6	12.8 ± 2.3	37.1 ± 0.4*	37.1 ± 1.0*	1.0 ± 0.0	1.0 ± 0.0
180	41.0 ± 4.9	38.0 ± 3.2	15.2 ± 3.6	13.6 ± 3.6	37.1 ± 0.4*	37.2 ± 1.0*	1.0 ± 0.0	1.0 ± 0.0

Time (min)	HR		RR		RT	
	M-T	M-B	M-T	M-B	M-T	M-B
0	160.5 ± 6.0	146.0 ± 7.4	133.8 ± 11.5	126.2 ± 9.5	114.0 ± 12.6	109.8 ± 10.1
5	165.0 ± 26.7	148.8 ± 10.3	141.0 ± 21.6	128.2 ± 12.0	122.5 ± 17.6	109.8 ± 9.8
10	145.3 ± 10.1	140.8 ± 18.6	123.0 ± 13.6	122 ± 16.8	112.8 ± 11.3	105.2 ± 14.0
20	142.0 ± 13.5	136.4 ± 16.0	116.8 ± 9	115.8 ± 16.6	103.3 ± 6.8	100.4 ± 16.6
30	139.5 ± 18.4	131.8 ± 15.8	119.0 ± 13.8	115.4 ± 11.7	99.5 ± 15.7	102.8 ± 9.4
40	140.8 ± 11.4	134.0 ± 12.7	117.0 ± 6.9	113.8 ± 12.0	103.3 ± 6.4	98.8 ± 14.0
50	133.5 ± 19.7	129.0 ± 18.1	114.3 ± 10.4	109.8 ± 12.5	99.5 ± 11.1	94.6 ± 11.8
60	133.8 ± 12.4	129.2 ± 8.9*	116.0 ± 11.5	107.6 ± 13.3	101.5 ± 12.6	91.6 ± 15.2
75	131.5 ± 5.8	129.6 ± 6.4*	111.3 ± 8.1	107.4 ± 9.0	99.0 ± 8.0	92.6 ± 11.1
90	134.0 ± 11.6	127.4 ± 12.7	115.5 ± 7.1	107.4 ± 17.3	98.8 ± 5.9	89.0 ± 18.8
120	143.0 ± 12.4	137.0 ± 13.7	121.8 ± 5.7	110.2 ± 12.4	101.0 ± 7.6	93.2 ± 12.9
150	139.8 ± 4.2	146.8 ± 7.8	125.5 ± 9.3	122.0 ± 10.5	107.5 ± 14.2	100.8 ± 6.8
180	151.3 ± 11.6	148.8 ± 8.2	129.8 ± 11.1	121.4 ± 9.9	115.8 ± 9.4	101.4 ± 7.8

M-T: medetomidine and tramadol treatment, M-B: medetomidine and butorphanol treatment, HR: heart rate, RR: respiratory rate, RT: rectal temperature, CRT: capillary refill time, SAP: systolic arterial pressure, MAP: mean arterial pressure, DAP: diastolic arterial pressure. \*Significantly different ( $P < 0.05$ ) compared to the baseline of the same treatment.

the treatments during the procedure period, recorded the AS at each time point.

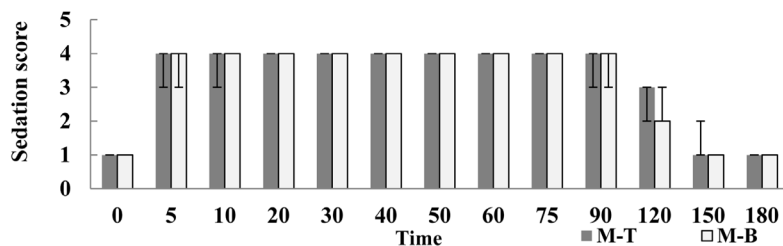
Data are summarized as the mean ± SD and median (range). Statistical analyses were carried out using SPSS 17.0 software (SPSS, Chicago, IL, USA). The cardiorespiratory effects of both methods were evaluated by a two-way repeated measures ANOVA followed by Tukey's test or a paired *t*-test. SS, AtS, and AS were analyzed by nonparametric Friedman's test followed by Wilcoxon signed ranks test. Data were normally distributed. Differences with  $P < 0.05$  were considered significant.

The cardiorespiratory responses are shown in Table 1. The HR was significantly lower than the baseline at 5–50 min and 75 min in the M-T group and 10–20 min in the M-B group. The RR was significantly lower than the baseline at 20–30 min and 120 min in the M-T group and 10 min and 40–90 min in the M-B group. The RT was significantly lower than the baseline at 30–180 min in both groups. The CRT did not show significant differences from the baseline in both groups. MAP and DAP did not show significant differences from the baseline in both groups, but the SAP was significantly lower than the baseline at 60–75 min in the M-B group. The hematology data, including white blood cell count, red blood cell count, packed cell volume, platelet count, and arterial blood gas values (including pH, PaO<sub>2</sub>, PaCO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup>, and electrolytes such as K<sup>+</sup>, Cl<sup>-</sup>, and Na<sup>+</sup>) did not show significant differences and were within normal reference values in both groups. There were no significant differences in cardiorespiratory variables between M-T and M-B groups (Supplementary file).

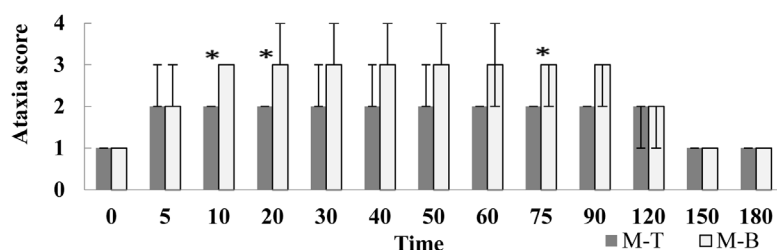
There were no significant differences in the SS between groups (Fig. 2A). The AtS was significantly lower in the M-T group than in the M-B group at 10, 20, and 75 min (Fig. 2B). The AS was not significantly different between groups (Fig. 2C). The average SS was 3.2 ± 0.2 in M-T and 3.2 ± 0.1 in the M-D group. The median (range) SS was 4 (range: 1–4) in M-T and 4 (1–4) in the M-D group. The average AtS was 1.8 ± 0.2 in M-T and 2.4 ± 0.4 in the M-D group. The median SS was 2 (range: 1–3) in M-T and 3 (range: 1–4) in M-B. The average AS was 8.2 ± 0.5 cm in M-T and 8.2 ± 0.4 cm in the M-D group. The median AS was 8 (range: 6–10) in both groups.

Tramadol is an analgesic opioid that acts on μ-opioid receptor with a low risk of substance dependence [6]. There have been studies on the pharmacokinetics for optimal pharmacological treatment and analgesic effects of tramadol in horses [1, 5]. Tramadol with detomidine has a longer analgesic effect than a single administration of detomidine or tramadol [9] and tramadol enhances the

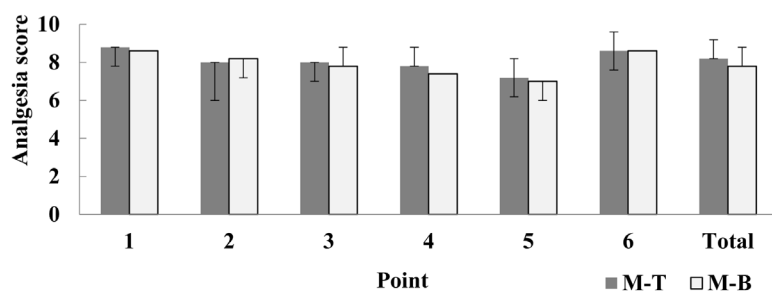
A.



B.



C.



**Fig. 2.** Comparison of behavioral responses between medetomidine and tramadol (M-T) and medetomidine and butorphanol (M-B) groups during standing laparoscopic ovariectomy. The values are shown as median and range. (A) Sedation score (SS), (B) ataxia score (AtS), (C) analgesia score (AS); analgesic scoring point: 1) local anesthetics injection; 2) skin and abdominal muscle incision; 3) insertion of the laparoscopy; 4) gripping of the ovary; 5) resection of the ovary; 6) abdominal muscle and skin closure; Total: the entire surgical procedure. \*Significant difference ( $P < 0.05$ ) between M-T and M-D groups.

effects of xylazine [18]. In this study, horses undergoing standing ovariectomy with M-T showed adequate sedation and analgesia responses without side effects. These results suggest that M-T can be applicable in equine clinical practice.

In previous studies, 3.1 mg/kg of a single administration of tramadol produced minimal transient side effects [3]. A tramadol (2 mg/kg) and detomidine (10 µg/kg) [9] or tramadol (2 mg/kg) and xylazine (1mg/kg) [18] combination showed some side effects. In the present experiment, the initial dose of tramadol was 1 mg/kg, then 0.4 mg/kg of tramadol was administered every 15 min, with the total dose of 2.6 mg/kg of being administered during 65 min after initial administration; no adverse effect such as CNS excitation and a secondary increase in HR and RR were observed. Thus, the repeated injection of  $\alpha_2$  agonist and opioid combinations might have reduced the potential for adverse behavioral effects in this study.

Ringer *et al.* [14] used the initial dose of butorphanol (18 µg/kg) and xylazine (1 mg/kg) followed by CRI of butorphanol (25 µg/kg/hr) and xylazine (0.65 mg/kg/hr). CRI of butorphanol (13 µg/kg/hr) was used for analgesic after colic surgery [17]. In the present experiment, the initial dose of butorphanol was 10 µg/kg, followed by 4 µg/kg of butorphanol administered every 15 min, corresponding to 16 µg/kg dose per hour. As the risk of exaggerated ataxia was shown in a previous study [14], a lower dose range of butorphanol range was used for safety in the surgery. Further studies are needed to evaluate the dose-response of the cardiorespiratory and behavioral effects.

High-dose opioid administration can cause behavioral side effects in horses [4]. A single injection of butorphanol has undesirable effects, such as ataxia, decreased borborygmi, and decreased defecation in the horse [10]. In a previous study, 10–15 min of muscle twitching was observed in horses following the administration of tramadol [19].

However, none of the mares showed behavioral side effects in this study, possibly because the mares received a repeated injection of an opioid and  $\alpha_2$  agonist at a low dose. The administration of analgesics with sedatives leads to fewer potential side

effects in standing surgery than the administration of analgesics alone [13].

No cardiorespiratory measurement was significantly different between the groups. This result suggests that M-T and M-B might induce similar cardiovascular changes throughout the standing procedure. The significant decrease in HR from the baseline was longer in M-T than in the M-B group. Because there were no significant differences between groups, the different baseline in the groups might have influenced the results.

Both groups had adequate sedative and analgesic effects according to the SS, AtS, and AS during surgery (Fig. 2A–C). A butorphanol and xylazine combination causes more ataxic responses than a single administration of xylazine [14]. In the present study, the horses were significantly less ataxic with M-T than with M-B 10–20 and 75 min after the initial administration (Fig. 2B). Currently, the relationship between opioid receptor subtypes and drug-induced locomotion is uncertain [4]. The difference in AtS might have been influenced by different activities related to different opioid receptor types. Ataxia or instability can interfere with the precise surgical procedure during standing surgery. Therefore, the use of M-T might have an advantage over that of M-B in standing surgery of horses.

In conclusion, there were no differences in cardiorespiratory function values, SS, and AS between M-T and M-B group. However, AtS was significantly lower in M-T than in the M-B group. The result suggests that M-T could maintain smooth and stable standing surgery with minimal cardiorespiratory changes in horses.

**CONFLICT OF INTEREST STATEMENT.** The authors declare no financial or personal conflicts of interest.

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