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Total intravenous anesthesia with propofol–ketamine–xylazine with or without remifentanil in thoroughbred horses undergoing castration

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We evaluated the clinical efficacy of total intravenous anesthesia (TIVA) with propofol–ketamine–xylazine (PKX) with or without remifentanil for castration in horses. Twenty-four Thoroughbred horses were premedicated with intravenous (IV) xylazine (1.0 mg/kg) and midazolam (0.02 mg/kg) and anesthetized with IV ketamine (1.5 mg/kg) and propofol (1.0 mg/kg). Surgical anesthesia was maintained with constant infusion of propofol (3.0 mg/kg/hr)–ketamine (3.0 mg/kg/hr)–xylazine (1.0 mg/kg/hr) (group PKX: n=8), PKX combined with remifentanil (3.0 μg/kg/hr) (group PKXR3: n=8), or PKX combined with remifentanil (6.0 μg/kg/hr) (group PKXR6: n=8). During anesthesia, none of the horses showed any limb movements, but five, two, and two horses in the PKX, PKXR3, and PKXR6 groups, respectively, showed cremaster muscle contractions. One horse in the PKX group required doubling the PKX infusion rate to continue surgery. Adverse effects of remifentanil (trembling of the nose tip or tongue) were observed in one and three horses in the PKXR3 and PKXR6 groups, respectively. Heart rate and arterial blood pressure were well maintained in all groups. Ventilation was assisted in four, five, and six horses in the PKX, PKXR3, and PKXR6 groups, respectively. Recovery scores in the PKX group were fair in one horse, good in three horses, and excellent in four horses, whereas recovery in all horses in the PKXR3 and PKXR6 groups was judged to be excellent. TIVA with PKX combined with remifentanil 3.0 μg/kg/hr could provide more sufficient anesthetic depth than PKX with fewer clinically significant adverse effects than that with remifentanil 6.0 μg/kg/hr.

Key words: *horse, remifentanil, total intravenous anesthesia*

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Remifentanil (4-methoxycarbonyl-4-[(1-oxopropyl) phenylamino]-1-piperidinepropionic acid methyl ester) is an ultra-short-acting, synthetic μ-opioid receptor agonist that produces potent analgesia and sedation in humans [5, 19]. Unlike other opioids, remifentanil is rapidly metabolized by nonspecific plasma and tissue esterases, with little or no accumulation, thereby providing a rapid onset of action, easy titration by continuous infusion, and rapid recovery after cessation of administration in humans [5, 19]. Owing to these pharmacokinetic characteristics, remifentanil has been widely used as an analgesic during maintenance of anesthesia in humans [19] and small animals [4, 12], but reports on its clinical use in horses during anesthesia are still limited.

A pharmacokinetic study in isoflurane-dexmedetomidine-anesthetized horses revealed that remifentanil concentrations decreased rapidly with the cessation of infusion; the mean half-life was 12.8 min [2]. These pharmacological properties suggest that remifentanil would be suitable as part of total intravenous anesthesia (TIVA) in horses. Pallarols *et al.* reported that constant rate infusion (CRI) of xylazine and remifentanil achieves a good degree of sedation for

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60-min standing procedures in horses, with no significant effects on cardiopulmonary function and a full, uneventful, quick recovery [18]. However, they evaluated sedation in standing horses without any surgical stimulations, and they did not measure cardiac output, which is important for evaluating cardiac function. Moreover, Lamuraglia *et al.* reported that remifentanil–isoflurane anesthesia does not have any deleterious cardiopulmonary effects but does shorten recovery times, indicating that remifentanil CRI could be an appropriate adjunct to inhalant anesthesia in horses [21]. However, in their study, they measured heart rate and blood pressure but not cardiac output during anesthesia and administered respiratory management with controlled mandatory ventilation. Furthermore, they reported that the heart rate decreased significantly during the first 25 min after CRI of xylazine and remifentanil, whereas the respiratory rate showed a significant decrease at 20 min and remained significantly low until the endpoint. These previous findings have several limitations, so further investigation is necessary for clinical use of remifentanil as part of TIVA in horses.

A combination of guaifenesin, ketamine, and an alpha-2 agonist (the so-called "triple drip") has traditionally been used for TIVA lasting up to 60 min in horses [9, 15, 25]. However, commercially manufactured guaifenesin is no longer available in many countries, so an alternative TIVA method is needed. Among various combinations without guaifenesin, a combination of propofol–ketamine–xylazine (PKX) has been reported to provide anesthesia for short procedures [22]. Our aim here was to evaluate the clinical efficacy of TIVA with PKX with or without remifentanil in horses. We hypothesized that adding remifentanil to PKX would improve the quality of anesthesia.

Materials and Methods

Horses

Twenty-four Thoroughbred horses undergoing castration were randomly allocated to three groups. Horses in group PKX (n=8; Nos. 1–8) were anesthetized by TIVA with PKX, those in group PKXR3 (n=8; Nos. 9–16) were anesthetized by TIVA with PKX plus 3.0 μg/kg/hr of remifentanil (Ultiva 5 mg, Janssen Pharmaceutical K. K., Tokyo, Japan), and those in group PKXR6 (n=8; Nos. 17–24) were anesthetized by TIVA with PKX plus 6.0 μg/kg/hr of remifentanil. The infusion rate of remifentanil was determined based on previous studies [2, 6, 18], and a loading dose of remifentanil was not administered prior to the infusion based on a previous study [3]. The median (range) age was 3.0 (2–5) years in group PKX, 3.0 (2–12) years in group PKXR3, and 4.0 (2–9) years in group PKXR6. The median body weight was 480 (446–490) kg in group PKX, 475 (424–500) kg in group PKXR3, and 474 (408–526) kg in group PKXR6. Horses were judged to be healthy before the study on the basis of a general physical examination, pre-anesthetic blood examination, and electrocardiography. Food, but not water, was withheld from the horses for 12 hr before the surgery. Before the surgery, all the horses were treated with intramuscular penicillin and streptomycin (8,000 IU/kg and 10 mg/kg, respectively; Mycillin Inj. NZ, Nippon Zenyaku Kogyo Co., Ltd., Fukushima, Japan) and flunixin meglumine (1 mg/kg intravenous [IV]; Banamine injection 5%, DS Pharma Animal Health Co., Ltd., Osaka, Japan). This study was approved by the Animal Care and Use Committee of the Japan Racing Association (approval number: MIHO2019K5).

Anesthesia and surgical protocol

A 14-gauge, 60-mm catheter was placed in the right external jugular vein. Horses were premedicated with 1.0 mg/kg of IV xylazine (Seractal 2%, Elanco Japan Inc., Tokyo, Japan) and 0.02 mg/kg of IV midazolam (Dormicum, Astellas Pharma Inc., Tokyo, Japan) in a single syringe. If sedation was inadequate, additional IV xylazine (0.4 mg/kg) was administered. Ten minutes after the premedication, anesthesia was induced with 1.5 mg/kg of IV ketamine (Ketalar, Daiichi-Sankyo Co., Ltd., Tokyo, Japan) followed immediately by 1.0 mg/kg of IV propofol (1% Propofol, Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan). If voluntarily movements remained after recumbency, additional IV ketamine (0.4–0.8 mg/kg) was administered.

Once immobilized, horses were intubated endotracheally and positioned in dorsal recumbency on a padded surgical mat; the endotracheal tube was connected to a demand valve supplying 100% oxygen; 400 mg of mepivacaine (2% Carbocaine, AstraZeneca Co., Ltd., Osaka, Japan) was then administered by intratesticular injection.

Surgical anesthesia was maintained with CRI of either propofol (3.0 mg/kg/hr)–ketamine (3.0 mg/kg/hr)–xylazine (1.0 mg/kg/hr) (group PKX), PKX combined with remifentanil at 3.0 μg/kg/hr (group PKXR3), or PKX combined with remifentanil at 6.0 μg/kg/hr (group PKXR6). Propofol, ketamine and xylazine were mixed in one bottle and infused at a rate of 0.41 m*l*/kg/hr by using an infusion pump (TE-281N, Terumo, Tokyo, Japan). Remifentanil in 500 m*l* saline was started at the same time and infused at a rate of 0.3 m*l*/kg/hr (group PKXR3) or 0.6 m*l*/kg/hr (group PKXR6) by using another infusion pump. Castration was performed by using a semi-closed surgical technique.

Surgical conditions (limb movement or contraction of the cremaster muscles in response to surgical stimuli) were assessed by the surgeons, who were blind to the anesthetic protocol, and the infusion rate of PKX was doubled if the anesthetists determined that the depth of anesthesia based on

surgical conditions was insufficient to continue the surgical procedure. The traditional indicators of anesthetic depth (eye position, nystagmus, palpebral reflex, muscle tone, sudden increase in heart rate [HR] or arterial blood pressures) were monitored continuously. Ventilation was manually assisted when spontaneous respiration disappeared for 1 min or when the arterial carbon dioxide tension ($PaCO_2$) exceeded 70 mmHg. All horses were allowed to recover unassisted and were re-sedated with IV xylazine (100 mg) at least once (maximum three times) when necessary.

Monitoring

HR was measured by auscultation and respiratory rate (RR) by counting thoracic wall movements just before the start of CRI and then every 10 min after the start of CRI. The electrocardiogram was monitored continuously by using a standard base-apex configuration during CRI. Once the horses were positioned in dorsal recumbency, systolic arterial blood pressure (SAP), mean arterial blood pressure (MAP), and diastolic arterial blood pressure (DAP) were recorded by using a multipurpose monitoring system (BP608, Omron Colin Co., Ltd., Tokyo, Japan) every 10 min via a 20-gauge, 51-mm catheter placed in the facial or transverse facial artery. Arterial blood samples were collected at the same time as HR and RR monitoring after the start of CRI, and arterial oxygen tension (PaO_2) and $PaCO_2$ were analyzed immediately by using a blood gas analyzer (ABL800 FLEX, Radiometer K.K., Tokyo, Japan).

Anesthesia time (duration of CRI), recovery time (time from the end of CRI to standing), number of re-sedations, and number of attempts to stand were recorded. Induction and recovery quality were assessed by the anesthetists, who were blind to the anesthetic protocol, by using a scoring scale of 1 to 5 (1, poor; 2, marginal; 3, fair; 4, good; 5, excellent), as previously described [13].

Statistical analysis

All data were expressed as medians (range). The GraphPad Prism v.7.05 software (GraphPad Software, Inc., San Diego, CA, USA) was used for the statistical analysis. Cardiorespiratory data were analyzed by using two-way repeated measures ANOVA. The Tukey test was used when significant differences were observed. Anesthesia time and recovery data were compared between the groups by using Kruskal-Wallis tests. A level of $P<0.05$ was considered significant.

Results

Induction quality scores are shown in Table 1. No significant differences in induction quality score were observed between the groups. An additional IV administration of xylazine (0.4 mg/kg) was given to one horse (No. 8) in group PKX, and additional IV administrations of ketamine were given to two horses (No. 7, 0.4 mg/kg, No. 8, 0.5 mg/kg) in group PKX and one horse (No. 14, 0.8 mg/kg) in group PKXR3. No limb movements were observed during the maintenance period in any horses. Contraction of the cremaster muscles in response to surgical stimulation was observed in five horses in group PKX, in two horses in group PKXR3, and in two horses in group PKXR6. After moving to a surgical table, one horse (No. 8) in group PKX showed symptoms of a light plane of anesthesia, such as nystagmus and mild neck tension, and needed a double infusion rate of PKX for 10 min to continue the surgical procedure. Because one horse (No. 21) in group PKXR6 showed severe muzzle tremors and face muscle twitches, intravenous anesthesia was interrupted and switched to inhalation anesthesia, so the data for this horse were excluded from the statistical analysis. Trembling of the nose tip or tongue was observed in one horse in group PKXR3 and in two horses in group PKXR6, but it disappeared soon after remifentanil infusion was ceased.

The time courses of changes in cardiovascular parameters are shown in Table 2. There were no significant differences in HR among the groups at any time points. No cardiac arrhythmia was detected throughout anesthesia. Although a transient increase in blood pressure in response to surgical

Table 1. Induction quality scores, anesthesia and recovery times, number of re-sedations, number of attempts to stand, and recovery quality scores in the horses in groups PKX (n=8), PKXR3 (n=8), and PKXR6 (n=7)

	Group PKX	Group PKXR3	Group PKXR6
Induction quality score	4.9 (4–5)	4.9 (4–5)	5 (5–5)
Anesthesia time (min)	44 (35–50)	47 (40–68)	41 (30–53)
Recovery time (min)	35 (24–51)	38 (21–56)	34 (24–39)
Number of re-sedations	1.5 (1–3)	2 (1–2)	1 (1–3)
Number of attempts to stand	1 (1–2)	1 (1–1)	1 (1–1)
Recovery quality score	4.5 (3–5)	5 (5–5)*	5 (5–5)*

Data are expressed as medians (range). PKX: propofol–ketamine–xylazine. *Significantly different from group PKX ($P<0.05$).

Table 2. Heart rate (HR), systolic arterial blood pressure (SAP), mean arterial blood pressure (MAP), and diastoloc arterial blood pressure (DAP), in the horses in groups PKX (n=8), PKXR3 (n=8), and PKXR6 (n=7) after premedication and at 10-min intervals during anesthesia

		After premedication	10 min	20 min	30 min	40 min
HR (beats/min)	Group PKX	30 (25–33)	29 (24–32)	30 (24–35)	30 (26–34)	30 (25–35)
	Group PKXR3	28 (27–33)	29 (23–33)	29 (25–30)	29 (24–31)	29 (25–31)
	Group PKXR6	25 (18–36)	25 (20–31)	29 (24–32)	30 (24–32)	30 (24–31)
SAP (mmHg)	Group PKX	N.D.	151 (120–182)	151 (124–180)	149 (126–179)	152 (122–178)
	Group PKXR3	N.D.	158 (89–197)	166 (109–195)	155 (113–199)	164 (113–202)
	Group PKXR6	N.D.	138 (96–166)	138 (94–180)	139 (90–186)	141 (125–185)
MAP (mmHg)	Group PKX	N.D.	113 (98–132)	116 (95–128)	116 (91–130)	117 (82–127)
	Group PKXR3	N.D.	124 (71–147)	127 (81–146)	121 (89–159)	121 (89–148)
	Group PKXR6	N.D.	107 (77–121)	107 (70–136)	104 (65–136)	101 (95–138)
DAP (mmHg)	Group PKX	N.D.	95 (83–109)	97 (78–107)	97 (72–107)	99 (67–103)
	Group PKXR3	N.D.	105 (63–125)	103 (67–120)	101 (75–143)	101 (73–121)
	Group PKXR6	N.D.	91 (64–106)	91 (57–114)	89 (50–113)	85 (80–115)

PKX: propofol–ketamine–xylazine, N.D.: not determined. Data are expressed as medians (range).

stimulation was observed in one horse each in groups PKXR3 and PKXR6, there were no significant differences in SAP, MAP, or DAP either among the groups or among any time points.

The time course changes in respiratory parameters in individual horses are shown in Table 3. Ventilation was assisted in four horses in group PKX, in five horses in group PKXR3, and in six horses in group PKXR6. As a result, no significant differences were observed in $PaCO_2$ among the groups, although the PaO_2 values in group PKXR3 were significantly lower than those in group PKX throughout anesthesia.

Anesthesia and recovery times, number of re-sedations, number of attempts to stand, and recovery quality scores are shown in Table 1. Horse No. 8, for which anesthesia was deepened with a double infusion rate of PKX during surgery, achieved standing on the first attempt with a good recovery quality score, a recovery time of 46 min, and a number of re-sedations of two, which did not affect the recovery quality. Recovery quality in group PKX was fair in one horse, good in three horses, and excellent in four horses, whereas all horses in groups PKXR3 and PKXR6 were judged to have excellent recoveries. Recovery quality scores in groups PKXR3 and PKXR6 were significantly higher than those in group PKX. No significant between-group differences were observed in anesthesia or recovery time, number of re-sedations, or number of attempts to stand.

Discussion

We found here that TIVA with PKX combined with remifentanil at the doses studied provided clinically acceptable anesthetic depth for castration. Sage *et al.* reported that the anesthesia depth achieved by PKX was superior to that of midazolam–ketamine–xylazine in nonstimulated horses [22]. The maintenance dose of ketamine in our study (3.0 mg/kg/hr) was higher than that in the study of Sage *et al.* (1.8 mg/kg/hr), and it is expected to contribute to adequate anesthetic depth for castration. However, the muscle relaxation achieved by PKX with or without remifentanil in our study was insufficient to prevent cremaster muscle contraction in stimulated horses, even though all horses received a preoperative intratesticular injection of mepivacaine. In our study, there are several concerns regarding muscle relaxation under surgical stimulation with PKX, but adding remifentanil to PKX may have improved the quality of anesthesia due to the production of an additional analgesic effect and the facilitation of pain control, although there was no significant difference.

In one horse (No. 21), 10 min after the start of CRI, minor muzzle tremors were observed. However, from 12 min onward, the muzzle tremors became severe, and face muscle rigidity developed, posing a risk of more intense physical movement. Therefore, to prioritize the safety of the horse and the surgical staff, we switched to inhalation anesthesia to ensure complete immobilization. As in the above case, remifentanil-induced adverse effects have been described in horses. Funcia *et al.* found that IV bolus administration of xylazine (0.8 mg/kg) and remifentanil (0.0005 mg/kg) followed by CRI of xylazine (0.65 mg/kg/hr) and remifentanil (0.0225 mg/kg/hr) resulted in excitation, a significant increase in locomotor activity (more evident in the hind limbs), muzzle tremors, and facial muscle twitches [7]. Another study by the same group found that use of a lower dose of remifentanil (CRI of 6.0 μg/kg/hr) reduced

Table 3. Changes in respiratory rate (RR), arterial oxygen tension (PaO_2), and arterial carbon dioxide tension ($PaCO_2$) in individual horses in groups PKX (n=8), PKXR3 (n=8), and PKXR6 (n=7) after premedication and at 10-min intervals during anesthesia

		RR (breaths/min)					PaO_2 (mmHg)					$PaCO_2$ (mmHg)				
		After pre-medication	10 min	20 min	30 min	40 min	After pre-medication	10 min	20 min	30 min	40 min	After pre-medication	10 min	20 min	30 min	40 min
Group PKX	No. 1	3	3	4	4	4	N.D.	474	477	476	470	N.D.	59.0	56.7	56.0	56.4
	No. 2	4	3	3	5 (AV)	5 (AV)	N.D.	457	522	537	531	N.D.	56.7	71.1	66.5	62.1
	No. 3	3	8 (AV)	8 (AV)	8 (AV)	8 (AV)	N.D.	140	289	303	303	N.D.	73.8	50.8	50.2	49.4
	No. 4	1	2	4	5	5	N.D.	103	94.9	82.0	79.6	N.D.	62.2	60.6	58.2	57.8
	No. 5	7	6	6	6	6	N.D.	505	522	525	527	N.D.	61.1	61.5	59.5	59.0
	No. 6	3	6	8 (AV)	8 (AV)	8 (AV)	N.D.	404	546	538	N.D.	N.D.	47.8	46.6	46.8	N.D.
	No. 7	3	4	5	5	5	N.D.	229	233	240	238	N.D.	60.0	55.3	57.5	58.6
	No. 8	2	8 (AV)	8 (AV)	8 (AV)	8 (AV)	N.D.	312	352	357	371	N.D.	49.1	51.9	56.4	55.4
	Medians	3	8 (AV)	8 (AV)	8 (AV)	8 (AV)	N.D.	358*	415*	417*	371*	N.D.	59.5	56.0	57.0	57.8
Group PKXR3	No. 9	2	2	8 (AV)	8 (AV)	8 (AV)	N.D.	120	85.1	105	150	N.D.	64.5	53.0	49.5	48.1
	No. 10	3	8 (AV)	8 (AV)	8 (AV)	8 (AV)	N.D.	166	119	96.7	79	N.D.	50.9	52.3	53.5	55.4
	No. 11	2	3	5	5	5	N.D.	409	415	326	291	N.D.	52.9	53.5	52.6	62.0
	No. 12	4	8 (AV)	8 (AV)	9 (AV)	10 (AV)	N.D.	52.8	53.6	52.6	50.3	N.D.	50.1	54.1	52.9	52.2
	No. 13	4	2	2	9 (AV)	9 (AV)	N.D.	107	124	137	243	N.D.	64.1	68.9	60.2	51.0
	No. 14	4	3	2	2	2	N.D.	130	115	99.8	133	N.D.	68.5	70.0	68.2	64.6
	No. 15	2	2	4	4	3	N.D.	225	107	107	121	N.D.	51.6	60.7	67.8	64.0
	No. 16	4	3	8 (AV)	8 (AV)	8 (AV)	N.D.	50.3	148	387	387	N.D.	53.0	53.2	54.6	55.2
	Medians	3.5	3	6.5	8	8	N.D.	125*	117*	106*	142*	N.D.	53.0	53.8	54.1	55.3
Group PKXR6	No. 17	2	2	3	4	5	N.D.	346	279	323	N.D.	N.D.	64.2	70.0	67.1	N.D.
	No. 18	4	5 (AV)	5 (AV)	5 (AV)	5 (AV)	N.D.	105	95.6	115	N.D.	N.D.	59.9	70.6	67.7	N.D.
	No. 19	3	8 (AV)	8 (AV)	8 (AV)	8 (AV)	N.D.	395	N.D.	499	N.D.	N.D.	54.0	51.0	50.3	N.D.
	No. 20	4	8 (AV)	8 (AV)	8 (AV)	8 (AV)	N.D.	296	309	320	335	N.D.	57.8	58.4	58.5	60.9
	No. 22	2	8 (AV)	8 (AV)	8 (AV)	8 (AV)	N.D.	N.D.	N.D.	333	N.D.	N.D.	N.D.	N.D.	43.8	N.D.
	No. 23	3	8 (AV)	8 (AV)	8 (AV)	8 (AV)	N.D.	306	314	270	N.D.	N.D.	48.8	49.9	52.3	N.D.
	No. 24	3	8 (AV)	8 (AV)	8 (AV)	8 (AV)	N.D.	224	253	253	245	N.D.	45.8	47.4	48.8	50.0
	Medians	3	8	8	8	8	N.D.	301	279	320	290	N.D.	55.9	51.0	52.3	55.5

PKX: propofol–ketamine–xylazine, N.D.: not determined. AV indicates that the ventilation was assisted. *Significantly different between two groups ($P<0.05$).

the adverse effects, indicating that such effects could be dose-dependent [18]. Similarly, in our study, either dose rate of remifentanil induced trembling of the muzzle or tongue in some horses, but remifentanil at the lower dose rate appeared to reduce the adverse effects. It was possible that the other anesthetic drugs that we gave (propofol and ketamine) might have suppressed the adverse effects of remifentanil.

Ketamine produces rapid induction with minimum cardiovascular depression, but with muscle tremors and/or rigidity, resulting in rough induction occurring in some horses [1]. Propofol also produces rapid induction, but unpredictable behavioral responses, including paddling limb movements, are frequently observed [13]. In contrast, several studies have revealed that combining ketamine with propofol provides satisfactory anesthesia induction without any clinically relevant adverse events [20, 23]. Therefore, we chose this induction protocol. A bolus injection as a loading dose, followed by CRI, is effective for keeping drug concentrations high during the maintenance period. In our study, xylazine administered for premedication and ketamine and propofol administered for induction served as loading doses. This is another reason why we chose this induction protocol.

In equine anesthesia management, it is recommended to maintain the mean arterial pressure at 60–70 mmHg or higher during anesthesia to prevent the risk of postanesthetic complications, such as myopathy and lameness [8, 11]. Therefore, in our study, the HR and arterial blood pressures were maintained within clinically acceptable levels, but remifentanil appeared to cause respiratory depression. Propofol also causes dose-dependent respiratory depression [13, 16], so if the dose of propofol were to be decreased instead of remifentanil being added, respiratory depression could be reduced to some extent. Regardless, respiratory support is essential. In our horses, $PaCO_2$ did not differ among the groups, but PaO_2 varied widely between the groups. Although our horses breathed 100% oxygen, insufficient oxygenation was observed in the horses of each group, particularly in group PKXR3. Anesthetized horses showed the enlargement of alveolar-arterial oxygen differences due to the increased ventilation to blood flow (V/Q) mismatch,

and this results in hypoxemia [10, 17]. Moreover, Marntell *et al.* reported that breathing more than 95% oxygen increased intrapulmonary shunt and caused hypoventilation [14]. The intrapulmonary shunt during anesthesia by high inspired oxygen concentrations developed progressively, indicating that absorption atelectasis persisted throughout anesthesia [14]. Therefore, it is possible that a V/Q mismatch and intrapulmonary shunt may be responsible for the insufficient oxygenation observed in our horses. Among them, one horse (No. 12) showed severe hypoxemia (PaO_2 50–55 mmHg). Sage *et al.* reported that all horses spontaneously breathing room air were normocapnic but became hypoxemic (PaO_2<80 mmHg) during TIVA using IV infusion of xylazine (0.96 mg/kg/hr) and ketamine (1.8 mg/kg/hr) combined with midazolam at 0.12 mg/kg/hr, propofol at 3 mg/kg/hr, or propofol at 6 mg/kg/hr [22]. In addition, Yamashita *et al.* reported that horses spontaneously breathing room air showed mild hypercapnia ($PaCO_2$ approximately 50 mmHg) and became hypoxic (PaO_2 50–60 mmHg) during TIVA with an IV infusion of medetomidine (0.01 mg/kg/hr) and ketamine (4 mg/kg/hr) in combination with midazolam (0.08 mg/kg/hr) [24]. Based on these previous findings, it is possible that one horse (No. 12) was supplied room air instead of 100% oxygen due to some human factors.

Recovery quality scores in groups PKXR3 and PKXR6 were excellent, but we do not know whether remifentanil has a direct effect on recovery quality. It is clear that, to evaluate the effects of remifentanil on recovery quality, horses should not be re-sedated during the recovery period. However, here, we performed re-sedation for the safety of the horses and the staff. This is one of the limitations of our study. We do not know whether remifentanil had any adverse effects on recovery, but appropriate re-sedation resulted in safe and smooth recovery in all group PKXR3 and PKXR6 horses.

In conclusion, TIVA with PKX combined with remifentanil at 3.0 μg/kg/hr could provide more sufficient anesthetic depth than PKX with fewer adverse effects than with remifentanil 6.0 μg/kg/hr. However, respiratory support during the maintenance period is necessary in clinical use.

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