Original Article

Clinical evaluation of xylazine, lidocaine and ketamine intravenous infusion to reduce isoflurane requirement in Thai native cross-bred ponies

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Abstract

Balanced anesthesia in equine could reduce anesthetic-related fatalities. Sedative, anesthetic and analgesic agents currently available in Thailand such as xylazine, ketamine, isoflurane and lidocaine are extensively used in equine practice, but their combination has not been reported. The present study aimed to determine the minimum alveolar concentration (MAC) of isoflurane and clinical parameters in Thai native cross-bred ponies under general anesthesia. Six Thai native cross-bred ponies were examined by a random crossover method. They were categorized into 4 groups according to the maintenance of anesthesia which were isoflurane group (I), isoflurane and lidocaine group (IL), isoflurane, xylazine and ketamine group (IXK) and isoflurane, xylazine, lidocaine and ketamine group (IXKL). Tranquilization was performed with acepromazine (0.04 mg/kg IV), and sedation was performed with xylazine (0.8 mg/kg IV). Anesthesia was induced with ketamine (2 mg/kg IV) and diazepam (0.1 mg/kg IV), and maintained with isoflurane in oxygen and a constant rate infusion (CRI) of injectable drugs. Measurement parameters were heart rate (HR), respiratory rate (RR), mean arterial blood pressure (MAP), blood gases variables (pH, PaO_2, $PaCO_2$), end-tidal isoflurane concentration (ET-iso), end-tidal carbon dioxide concentration (ET-CO_2), MAC and recovery scores. The MAC of isoflurane (mean±SD) in groups I, IL, IXK and IXKL were 0.74±0.2%, 0.67±0.2%, 0.45±0.2% and 0.16±0.1%, respectively. A significant ($p<0.05$) reduction of 78% was found when compared between groups I and IXKL. There was no significant difference in the blood gases variables and recovery scores in all groups. In conclusion, the loading dose of xylazine 0.8 mg/kg followed by infusion of 0.5 mg/kg/h, ketamine 2 mg/kg followed by infusion of 1 mg/kg/h, and lidocaine 1.5 mg/kg within 15 minutes followed by 50 µg/kg/min, combined with isoflurane could reduce isoflurane requirement in Thai native cross-bred ponies with good recovery quality.

Keywords: xylazine, lidocaine, ketamine, Thai native cross-bred ponies, MAC

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Introduction

In horses, general anesthesia has much higher mortality rate compared to anesthesia in humans and small animals (Johnson et al., 2002; Bidwell et al., 2007; Senior, 2013). To easily control anesthetic depth, inhalation agents such as isoflurane are usually used to withstand long operation and make a fast recovery (Steffey et al., 1977; Pöppel et al., 2014). Despite their benefits, inhalation agents have low analgesic effect. The use of high dosage of inhalation agents to maintain an adequate anesthetic depth leads to dose-dependent cardiopulmonary depression (Enderle et al., 2008; Villalba et al., 2011); in this case analgesic agents are proved useful. The analgesic effects could reduce the use of inhalant concentration and increase safety for horses. The combination of inhalation and injectable agents has synergistic effects and provides suitable anesthetic depth to surgery even in a long period, in contrast to the accumulation of one agent which might lead to the occurrence of side effects on the cardiopulmonary system and prolonged recovery (Spadavecchia et al., 2002; Kushiro et al., 2005). The requirement determination of inhalational anesthetic agents and analgesia is expressed with the minimum alveolar concentration (MAC). MAC, defined as the minimum alveolar concentration of volatile anesthetic drugs at 1 atmosphere (at sea level 760 mmHg), prevents purposeful movement in response to noxious stimulus in 50 percent of animals for surgical anesthesia maintenance. Therefore, MAC value is the index of inhalation anesthetic potency.

There are many studies which previously reported the use of constant rate infusion of analgesic drugs in horses. One of the local anesthetic agents commonly used is lidocaine, which is considered as a drug in the amide group (Enderle et al., 2008). Metabolization of lidocaine occurs in the liver and excretion through urine (Gozalo-Marcilla et al., 2014). Lidocaine is used to reduce some side effects such as intestinal prokinetic activity and minimize cardiovascular effects (Valverde, 2013). In many species, lidocaine CRI has been investigated in terms of its effects on MAC such as dogs (Valverde et al., 2004; Matsubara et al., 2009), horses (Dzikiti et al., 2003) and calves (Vesal et al., 2011). It helps decrease the use of isoflurane in horses, halothane in ponies and also minimize alveolar concentration of sevoflurane in horses by 24-25% (Doherty and Frazier, 1998), 15-20% (Dzikiti et al., 2003) and 26.7% (Rezende et al., 2011).

Ketamine is a dissociative anesthetic agent. It has many effects such as analgesia, amnesia and central sympathomimetic effects (Bettschart-Wolfensberger and Larenza, 2007). It helps decrease MAC of halothane and the use of isoflurane by 15-37% (Muir and Sams, 1992) and 12% (Pöppel et al., 2014). Moreover, by stimulating the sympathetic nervous system, it helps improve cardiovascular parameters. During isoflurane anesthesia, the combination of ketamine and lidocaine for partial intravenous anesthesia is proved useful when compared to the stand-alone use of isoflurane. However, it has little inferiority in recovery phase (Enderle et al., 2008; Villalba et al., 2011).

Alpha2-adrenoceptor agonists, such as xylazine, are drugs with effective sedative and analgesic effects (Gozalo-Marcilla et al., 2015). They can reduce the requirement of anesthetic inhalant either by single injection or CRI (Steffey et al., 2000; Ringer et al., 2007). The combination of xylazine and ketamine can lead to a slight increase in arterial blood pressure and respiratory acidosis from respiratory rate reduction (Mama et al., 1998). In horses, xylazine has an effect on the circulatory system including bradycardia and reduces blood pressure (England and Clarke, 1996). However, if used with inhalational anesthetic agents, it affects the cardiopulmonary system (Teixeira et al., 2004).

This study aimed to determine the minimum alveolar concentration (MAC) of isoflurane, clinical parameters and quality of recovery in Thai native cross-bred ponies under general anesthesia with four categories of maintenance anesthesia.

Materials and Methods

The study was in regard to the animal testing regulations and ethics of the Faculty of Veterinary Medicine, Kasetsart University.

Animals: Six clinically healthy Thai native cross-bred ponies (2 geldings and 4 mares), aged between 4.5-7 years, with the height of 118±5.3 cm (mean±SD) and the weight of 248±42 kg (mean±SD), were used in this study. All ponies were determined to be healthy based on physical examination and normal ranges for hematology and serum chemistry. They were housed under field conditions and fed on Pangola hay and commercial concentrates. Each pony was anesthetized on four different occasions using a randomized crossover design, with a washout period of two weeks between treatments (Nóbraga et al., 2013). The experiment was conducted at the Faculty of Veterinary Medicine, Kasetsart University, Nakhon Pathom (an average elevation of 7.46 m above sea level).

***Anesthetic technique*:** Food was withheld overnight but all ponies had free access to water. During the induction process, all ponies were premedicated with acepromazine (Combistress® 20 mg; Phenix Pharmaceuticals N.D., Antwerp, Belgium), 0.04 mg/kg was intravenously injected (IV), followed by xylazine (X-LAZINE® 20 mg; L.B.S. Labolatory LTD., Bangkok, Thailand), 0.8 mg/kg IV after 15 minutes. Then, after peak sedation occurred, a combination of 0.1 mg/kg diazepam (Ropam® 5 mg; L.B.S.Labolatory LTD., Bangkok, Thailand) and 2.0 mg/kg ketamine (Ketamil®; Troy Labolatory PTY., Australia) was intravenously injected. The anesthetized ponies were then placed in dorsal recumbency, endothacheal intubation was performed. General anesthesia (GA) was maintained with isoflurane at the rate of 5 L/min of oxygen using a circle rebreathing system anesthetic machine (MatrxVML®; LesWilkins&Associates INC., Seattle, WA) and CRI of injectable agents in each individual group was given via infusion pump (Mindray 600I infusion pump, NP Intertrade CO., Bangkok, Thailand). After GA induction, one of the 4 treatments was randomly administered as follows:

group I, ponies were given lactate ringer's solution at the rate of 5 mg/kg/h;

group IL, ponies were given a loading dose of lidocaine (Locana®; L.B.S. Labolatory LTD., Bangkok, Thailand), 1.5 mg/kg over 15 minutes after the induction, followed by CRI, 50 µg/kg/min;

group IXK, ponies were given CRI of xylazine, 0.5 mg/kg/h, and CRI of ketamine, 1 mg/kg/h;

group IXKL, ponies were given xylazine and ketamine at the same rate as group IXK and lidocaine at the same rate as group IL.

During the experiment, dopamine might be administered to ponies which had MAP less than 60 mmHg. CRI of dopamine, 0.25 µg/kg/min, was intravenously given until MAP reached 80 mmHg.

***Monitoring*:** Invasive mean arterial blood pressure was measured by a sphygmomanometer (KTJ-20 Aneroid sphygmomanometer; Wuxi Medicalinstrument Factory, Shanghai, China). RR, ET-CO_2 and ET-iso were measured by an infrared gas analyzer (PM-9000 vet; Mindray Medical International, Bangkok, Thailand) which was connected to an endotracheal tube. MAP, ET-CO_2 and ET-iso were recorded after induction (T0) and every 5 minutes (T0, T5 and so on). HR and RR were recorded before induction, after induction (T0) and every 5 minutes thereafter (before, T0, T5, T10 and so on). Arterial blood gases and pH were measured at T0 and every 30 minutes thereafter (T0, T30 and so on). Arterial blood was anaerobically withdrawn, collected using heparinized syringes and analyzed immediately by a blood gas analyzer (Stat profile® pHOx® plus; Nova Biomedical Corporation, USA). The ended recovery status from anesthesia was scored based on the quantitative 10 scoring system according to Donaldson et al. (2000) by the same anesthetist throughout the study.

Determination of MAC: At the first hour of anesthesia, ET-iso was maintained at 1% in group I and at 0.8% in the other groups, and then isoflurane concentration was adjusted in order to study MAC in the next hours. To determine the MAC value, a noxious electrical stimulation (SD9 stimulator, Natus Neurology, Inc., Warwick, RI, USA) was used. The oral mucous membrane was stimulated with 50 V, 5 Hz of frequency and the pulse width of 10 ms via an alligator clip for 60 seconds until a positive response occurred (Villalba et al., 2011). The positive response according to stimulation was declared by the movement of the head or legs of the pony. On the other hand, muscle spasms or muscle cramps indicated a negative response. Results of the response would lead to the adjustment of ET-iso to determine the MAC value. If a negative response was found, the ET-iso would be decreased by 0.2% until a positive response was shown. In contrast, the ET-iso would be increased by 0.2% when a positive response was found and would be increased continously until no response was found. After every step in the anesthetic concentration, it was needed to wait for at least 20 minutes to maintain the equilibrium. Level of MAC was measured in duplicate in each pony. Final measurement MAC value (mMAC) was calculated by the average of the maximum ET-iso which the pony responded to the noxious stimulation and the minimum ET-iso which the pony had no response to the stimulation at all.

MAC value at the sea level (seaMAC) was calculated by multiplication of mMAC and atmospheric pressure at experimental site (exP), 764 mmHg, and divided by atmospheric pressure at the sea level (seaP), 760 mmHg, as shown in the following equation according to Villalba et al. (2011),

$$seaMAC\ (\%) = mMAC\ (\%) \times exP / seaP$$

Recovery: After the experiment completed, all injectable agents for maintainance of GA were discontinued. The ponies were then moved to a recovery room, stayed in lateral recumbency. Endotracheal extubation was done when the pony had swallowing reflex. The assisted recovery technique was used during the recovery period. Recovery quality was assessed, interpretation of the results of the scoring system was based on the method of Donaldson et al. (2000). Total time of anesthesia, time to extubation, time to sternal recumbency, time of sternal to standing, time to standing and frequency of attempts to stand up were recorded.

***Statistical analysis*:** Statistical analysis in this study was run on NCSS 2007 software (Kaysville, Utah). All of the data were shown in the form of mean±standard deviation. Kolmogorov-Smirnov test was employed to determine whether data were normally distributed. Comparison of HR, RR, MAP, ET-iso and ET-CO_2 between each group was revealed by generalized linear model (GLM). One-way ANOVA was used to compare MAC and recovery scores between each group. The repeated measure ANOVA was used to compare pH, PaO_2 and $PaCO_2$ in each period of time between each group. Statistical significance was interpreted as p-value <0.05 in all tests.

Results

The average of total time of anesthesia in groups I, IL, IXK and IXKL were 139±21.5, 145±24.9, 137.5±19.2 and 162.5±11.3 minutes, respectively.

There was no significant difference between the averages of HR in groups I and IL. However, the averages of HR in groups I and IL were significantly higher than those of groups IXK and IXKL. There were significant differences in the averages of RR between groups I and IXKL, IXK and IXKL, and IL and IXK. The average of MAP in group IXKL was the lowest, while there was no significant difference among those of groups I, IL and IXK, as shown in Table 1. The minimum ET-iso was achieved at T75 in group I (0.73±0.16%), at T70 in groups IXK (0.36±0.15%) and IL (0.65±0.09%) and at T110 in group IXKL (0.14±0.05%) (Figure 1). The average of ET-iso in group I was significantly higher than those of the others, however, there was no significant difference between groups IXK and IXKL. The averages of ET-CO_2 among groups I, IL and IXK were significantly different, as shown in Table 1. Significant differences of the averages of MAC among groups I (0.74±0.2%), IXK (0.45±0.2%) and IXKL (0.16±0.1%) were found, as shown in Table 2. No significant difference of the averages of pH, PaO_2 and

$PaCO_2$ was found between each group, as shown in Table 3.

There was no significant difference in the averages of recovery scores between each group (p=0.07) and also in the averages of time to extubation, time to sternal recumbency, sternal-to-standing time, time to standing and frequency of attempts to stand up, as shown in Table 4.

Table 1 Cardiovascular and respiratory parameters during anesthetic administration in 6 Thai native cross-bred ponies

Parameter	Group			
	I	IL	IXK	IXKL
HR (beats minute^{-1})	42±6^{a}	42±4^{a}	35±5^{b}	36±6^{b}
RR (breath minute^{-1})	7±2^{a}	8±1^{a,b}	6±1^{a,c}	8±2^{b}
MAP (mmHg)	94±16^{b}	100±15^{b}	99±15^{b}	90±13^{a}
ET-iso (%)	0.8±0.2^{a}	0.72±0.1^{c}	0.41±0.1^{b}	0.37±0.2^{b}
ET-CO_2 (%)	59±8^{a}	64±13^{b}	55±7^{c}	58±8^{a}

Data are expressed as mean±SD. HR, heart rate; RR, respiratory rate; MAP, mean arterial blood pressure; ET-iso, end-tidal isoflurane concentration; ET-CO_2, end-tidal carbon dioxide concentration

$^{a\ b\ c}$ Superscript letters are significantly different between each group (p<0.05).

Table 2 Individual mean and group (mean±SD) seaMAC values for isoflurane in 6 Thai native cross-bred ponies

Group	Individual mean						Group (mean±SD)
	pony 1	pony 2	pony 3	pony 4	pony 5	pony 6	
I	0.74	0.72	0.47	0.99	0.69	0.85	0.74±0.2^{a}
IL	0.66	0.59	0.30	0.87	0.60	0.98	0.67±0.2^{ac}
IXK	0.29	0.48	0.43	0.75	0.15	0.62	0.45±0.2^{c}
IXKL	0.21	0.12	0.09	0.22	0.11	0.21	0.16±0.1^{b}

Values collected in 1 atmosphere at sea level (seaMAC; 760 mmHg)

$^{a\ b\ c}$ Superscript letters are significantly different between each group (p<0.05).

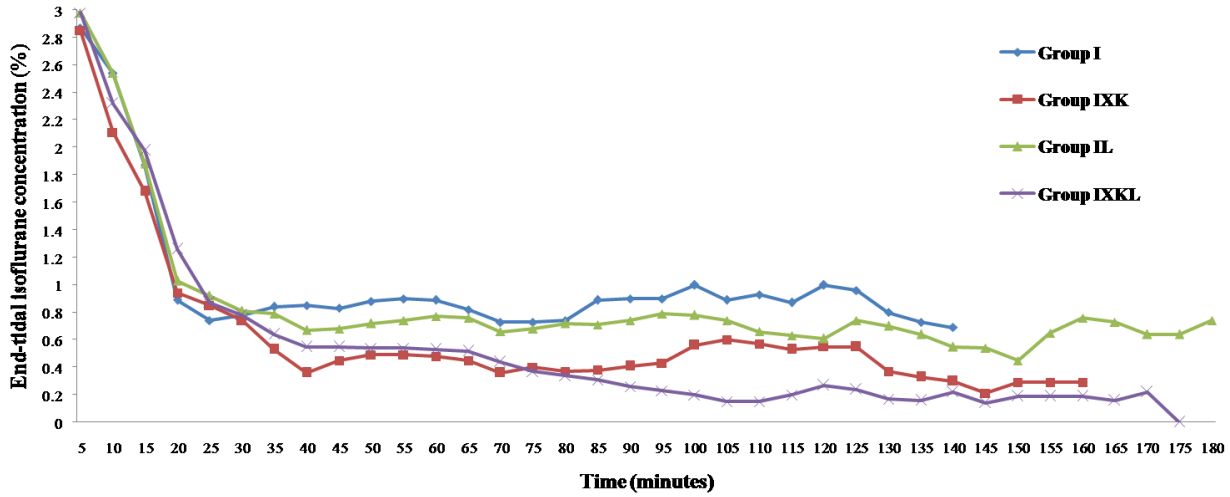


Figure 1 Averages of ET-iso in percentages of expired gas in 6 Thai native cross-bred ponies anesthetized with isoflurane alone (I), isoflurane-lidocaine (IL), isoflurane-xylazine-ketamine (IXK) or isoflurane-xylazine-ketamine-lidocaine (IXKL) every 5 minutes

Table 3 Blood gas values at different points of time after induction of anesthesia from 6 Thai native cross-bred ponies. Data are expressed as mean±SD.

Group	T0	T30	T60	T90	T120
pH					
I	7.46±0.03	7.36±0.06	7.35±0.04	7.37±0.05	7.37±0.04
IL	7.44±0.03	7.34±0.05	7.34±0.06	7.35±0.08	7.38±0.04
IXK	7.46±0.03	7.40±0.05	7.41±0.05	7.42±0.04	7.40±0.02
IXKL	7.44±0.04	7.35±0.05	7.32±0.07	7.38±0.05	7.40±0.05
PaO_2 (mmHg)					
I	59.46±6.37	222.77±52.41	185.03±58.88	170.63±77.35	169.72±89.93
IL	72.52±5.56	282.25±68.29	248.90±75.83	240.28±102.25	233.53±64.22
IXK	86.57±59.35	302.37±50.42	236.53±38.99	236.20±70.26	258.52±139.98
IXKL	95.18±70.56	326.35±152.96	314.93±163.32	296.48±150.63	264.67±159.08
$PaCO_2$ (mmHg)					
I	42.77±3.54	66.95±12.45	71.90±8.80	68.38±11.90	64.57±5.37
IL	46.05±5.87	68.63±14.27	72.52±15.60	73.70±21.35	68.05±10.30
IXK	45.15±8.62	58.67±9.62	61.32±10.69	58.65±7.74	64.42±4.58
IXKL	43.95±8.53	65.32±6.93	69.40±10.89	66.20±9.14	64.72±10.35

Table 4 Quality of recovery and recovery time of 6 Thai native cross-bred ponies anesthetized with isoflurane alone (I), isoflurane-lidocaine (IL), isoflurane-xylazine-ketamine (IXK) or isoflurane-xylazine-ketamine-lidocaine (IXKL). Data are expressed as mean±SD.

	Group			
	I	**IL**	**IXK**	**IXKL**
Total time of anesthesia (min)	139±21.5	145±24.9	137.5±19.2	162.5±11.3
Recovery scores	19.7±4.6	26.7±11.4	19.3±7.2	31.0±8.8
Time to extubation (min)	3.7±2.0	3.3±1.5	4.7±2.6	4.5±1.6
Time to sternal recumbency (min)	7.3±5.8	6.0±3.1	10.7±8.5	13.5±12.5
Time to sternal recumbency to standing up (min)	2.2±3.9	5.2±4.8	1.3±1.5	5.3±7.3
Time to standing up (min)	9.7±5.9	11.2±5.8	12.2±8.0	18.7±12.0
Frequency of attempts to standing up	1±0	3.2±3.7	1.5±0.8	2.8±2.7

Discussion

Six healthy Thai native cross-bred ponies were used as subjects in this study. The randomized crossover design was employed to divide the ponies into 4 groups according to the drug applied during maintenance anesthesia. Each treatment in the experiment was performed for 14 days to prevent the persistence of drug residues among the subjects according to Nóbraga et al. (2013) and to control and prepare external factors which were related to the experiment such as premedication agents and anesthetic induction agents, including setting room temperature at 25°C. Valverde (2013) revealed that CRI of xylazine and ketamine were given at 0.12-1.00 and 1.0-3.6 mg/kg/h, respectively. The CRI of xylazine (0.5 mg/kg/h) and ketamine (1.0 mg/kg/h) in this study kept the ponies under adequate depth of anesthesia without any complications, similar to other studies (Bettschart-Wolfensberger and Larenza, 2007; Valverde, 2013). The loading dose of lidocaine, 1.5 mg/kg, in the first 15 minutes followed by CRI, 50 µg/kg/min, was within the range from previous reports (Dzikiti et al., 2003; Ringer et al., 2007). This dosage was selected in attempt to avoid side effects and toxicity that could occur when lidocaine was given intravenously.

Maintaining general anesthesia in the first hour of the study at 1% ET-iso in group I and at 0.8% ET-iso in the other groups showed that these concentrations were adequate for the beginning of the response test by noxious electrical stimulation because no positive response from any ponies in the first trial was found.

The study of Kemphen et al. (2012) reported that MAC of isoflurane in horses was 1.3%. In this study, the MAC of isoflurane in Thai native cross-bred ponies was 0.74±0.2%, which is lower than the results of the study of Spadavecchia et al. (2010) in miniature ponies (1±0.2%). The combination of isoflurane and injectable anesthetic agents could decrease the requirement of isoflurane concentration, but the MAC of isoflurane between groups I and IL in this study was not significantly different. In contrast, Driessen (2005) reported 25% decrease in MAC of isoflurane. However, the ET-iso in group IL (0.72±0.1%) was significantly decreased when compared to group I (0.8±0.2%). In addition, there was a significant reduction of 78% between the MAC of isoflurane in group I (0.74±0.2%) and group IXKL (0.16±0.1%). This result matches up with that of Kemphen et al. (2012), who studied the effect of the combination of medetomidine, ketamine and lidocaine by CRI together with isoflurane in surgery. They found that the end-tidal isoflurane concentration was 0.65% in the treatment group.

One problem occurred during the step of changing isoflurane concentration to below 0.20% in group IXKL. The vaporizer used in this study had no scale indicating between 0.00% and 0.20%. Thus, the average MAC of this group (0.16%) might not be an accurate value and slightly less than the actual concentration.

Steffey et al. (1987) reported that, in the case of isoflurane induction in a horse without a ventilator for 5 hours, MAP was increased in the first hour and reduced gradually in the next hours, similar to the results found in the present study. No complication which needed the administration of dopamine, such as hypotension and bradycardia, occurred throughout the entire experiment. HR and MAP of group IL were not significantly different from those of group I. Moreover, HR was stable at all times in group IL. It demonstrated that lidocaine did not affect the change in heart rate; similar to the study of Dzikiti et al. (2003), which used a loading dose of lidocaine of 2.5 mg/kg, followed by CRI at 50 µg/kg/min, combined with isoflurane inhalation in horses. Feary et al. (2005) also found that lidocaine had a slight effect on heart rate and blood pressure, even though the dosage used in this study differed from others (loading dose of lidocaine of 1.3 mg/kg, followed by CRI at 50 µg/kg/min, together with sevoflurane inhalation). Furthermore, HR of groups IXK and IXKL were not different, which confirms that the dosage of lidocaine used in this study did not affect the heart rate.

Ketamine has pharmacological effects on the cardiovascular functions. The heart is stimulated by the sympathetic nervous system, which leads to the inhibition of catecholamine secretion and then affects the rise of the heart rate and blood pressure (Gozalo-Marcilla et al., 2014). In practice, ketamine is usually used in combination with other injectable agents such as alpha-2-adrenergic agonist, or inhalational anesthetic agents, to reduce the risk of side effects on the cardiovascular system (Mason, 2004). Pöppel et al. (2014) conducted a study of the administration of ketamine and xylazine, both at 1 mg/kg/h, in horses with isoflurane inhalation. The results showed that the heart rate in the xylazine group was lower than in the ketamine group, unlike the blood pressure, which was higher. Similarly, groups IXK and IXKL in this study had significantly lower HR than group I. This might be the major effect of xylazine which decreased the heart

rate. Also, the combination of xylazine and ketamine decreased the ketamine effect on the heart.

In this study, the experiment was performed without a ventilator. This is the reason why all ponies had high CO_2 in blood circulation. The results agree with the study of Steffey et al. (1987), which found that the limitation of respiratory function raised $PaCO_2$. In the current study, RR and ET-CO_2 were in the normal ranges, which indicated that the isoflurane concentration used in this study did not affect the respiratory system. No significant difference in RR between groups IL and I was found. However, the excretion level of carbon dioxide was as high as that level in hypercapnia. ET-CO_2 in group IL was higher than that of group IXKL, although no difference of RR was found (8±1 and 8±2 bpm, respectively). This phenomenon indicates that lidocaine affects the respiratory system or, in other words, the excretion of carbon dioxide. Moreover, RR and ET-CO_2 in group IXK were significantly lower than those in group IXKL, which indicates that the dose of xylazine and ketamine did not suppress the respiratory functions. Respiratory complications such as hypoventilation and apnea did not occur during the entire experiment.

No difference in every parameter related to recovery quality between each group in this study was found. The ponies could recover and stand up within 10 minutes in group I and within 20 minutes in the other groups. Moreover, no physiological complication was found. The assisted recovery technique helped the recovery process go smoothly in addition to gentle temperament of the ponies. Normally, anesthetic induction with inhalational anesthetic agents tends to cause uncoordinated movement and myasthenia compared to induction with injectable agents which provides better recovery quality. Nowadays, CRI of lidocaine is used frequently in horses both during and after anesthetic induction. However, it also affects their quality of recovery. Horses have a high risk to experience ataxia during the recovery period (Clark-Price, 2013). In this study, inhalational anesthetic agent was withheld from the ponies 5 minutes after all MAC was recorded. It was found that one pony from group IL showed ataxia. This result might relate to the toxicity of lidocaine. Group IXKL had the highest recovery scores. Group IL had higher recovery scores than group I which had similar recovery scores to group IXK. However, no significant difference between each group was detected. This might be the effect of the combination of lidocaine and ketamine for a long duration which led to the occurrence of ketamine side effects such as muscle stiffness, excitation, and ataxia, similar to a previous report (Gozalo-Marcilla et al., 2014). From the results of the current study, lidocaine might be mainly responsible for the quality of recovery because it was given until the end of anesthesia. This increased the chance of getting ataxia and prolonged recovery duration, including a trend to decrease the quality of recovery (Dzikiti et al., 2003; Valverde et al., 2005; Nóbrega et al., 2013). Although lidocaine and ketamine have adverse effects when separately administered at high dose, the combination of lidocaine and ketamine, as shown in the present study, was able to maintain good intraoperative cardiopulmonary functions. However, the recovery quality in the combination of lidocaine and ketamine group was not smoother than the other treatment groups, and there was no significant difference in recovery score among all experimental groups. This study did not determine the concentration of lidocaine and ketamine in blood circulation, thus it could not be explained if the ponies received lidocaine to the level of intoxication. The combination of lidocaine, ketamine and xylazine could be administered for ponies. It is recommended to discontinue CRI of lidocaine, ketamine and xylazine combination 15-30 minutes prior to the end of anesthesia because it decreases the risk of side effects and toxicity from the injectable agents (Gozalo-Marcilla et al., 2014), or to administer the sedative agents after the withdrawal of inhalational anesthetic agents to make the horses calm and allow more time for recovery in order to get rid of the inhalant from the body as much as possible (Santos et al., 2003).

In conclusion, the combination of the loading dose of 0.8 mg/kg xylazine followed by 0.5 mg/kg/h CRI, or 2 mg/kg ketamine followed by 1 mg/kg/h CRI, or 1.5 mg/kg lidocaine followed by 50 μg/kg/min CRI, together with isoflurane inhalation could maintain surgical plane of general anesthesia in healthy Thai native cross-bred ponies, with no life-threatening complications.

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References

Bettschart-Wolfensberger R and Larenza MP 2007. Balanced anesthesia in the equine. Clin Tech Equine Pract. 6(2): 104-110.

Bidwell LA, Bramlage LR and Rood WA 2007. Equine perioperative fatalities associated with general anaesthesia at a private practice - a retrospective case series. Vet Anaesth Analg. 34(1): 23-30.

Clark-Price SC 2013. Recovery of horses from anesthesia. Vet Clin North Am Equine Pract. 29(1): 223-242.

Donaldson LL, Dunlop GS, Holland MS and Burton BA 2000. The recovery of horses from inhalant anesthesia: A comparison of halothane and isoflurane. Vet Surg. 29(1): 92-101.

Doherty TJ and Frazier DL 1998. Effect of intravenous lidocaine on halothane minimum alveolar concentration in ponies. Equine Vet J. 30(4): 300-303.

Driessen B 2005. Intravenous lidocaine infusion in balanced anaesthesia for abdominal surgery: update and clinical experiences. Pferdeheilkunde. 21(2): 133-141.

Dzikiti TB, Hellebrekers LJ and Dijk PV 2003. Effects of intravenous lidocaine on isoflurane concentration, physiological parameters, metabolic parameters and stress-related hormones in horses undergoing surgery. J Vet Med. 50(4): 190-195.

Enderle AK, Levionnois OL, Kuhn M and Schatzmann U 2008. Clinical evaluation of ketamine and lidocaine intravenous infusions to reduce isoflurane requirements in horses under general anaesthesia. Vet Anaesth Analg. 35(4): 297-305.

England GCW and Clarke KW 1996. Alpha$_2$adrenoceptor agonists in the horse-A review. Br Vet J. 152(6): 641-657.

Feary DJ, Mama KR, Wagner AE and Thomasy S 2005. Influence of general anesthesia on pharmacokinetics of intravenous lidocaine infusion in horses. Am J Vet Res. 66 (4): 574-580.

Gozalo-Marcilla M, Gasthuys F and Schauvliege S 2014. Partial intravenous anesthesia in the horse: a review of intravenous agents used to supplementequine inhalation anesthesia.Part 1: lidocaine and ketamine. Vet Anaesth Analg. 41(4): 335-345.

Gozalo-Marcilla M, Gasthuys F and Schauvliege S 2015. Partial intravenous anesthesia in the horse: a review of intravenous agents used to supplementequine inhalation anesthesia. Part 2: opioids and alpha-2 adrenoceptor agonists. Vet Anaesth Analg. 42(1): 1-16.

Johnson GM, Eastment JK, Wood JLN and Taylor PM 2002. The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results of phase 1 and 2. Vet Anaesth Analg. 29(4): 159-170.

Kemphen S, Kuhn M, Spadavecchia C and Levionnois OL 2012. Medetomidine continuous rate intravenous infusion in horses in which surgical anaesthesia is maintained with isoflurane and intravenous infusion of lidocaineand ketamine. Vet Anaesth Analg. 39(3): 245-255.

Kushiro T, Yamashita K, Umar MA, Maehara S, Wakaiki S, Abe R, Seno T, Tsuzuki K, Izumisawa Y and Muir WW 2005. Anesthetic and cardiovascular effects of balanced anesthesia using constant rate infusion of midazolam-ketamine-medetomidine with inhalation of oxygen-sevoflurane (MKM-OS anesthesia) in horses. J Vet Med Sci. 67(4): 379-384.

Mama KR, Pascoe PJ, Steffey EP and Kollias-Baker C 1998. Comparison of two techniques for total intravenous anesthesia in horses. Am J Vet Res. 59(10): 1292-1298.

Mason DE 2004. Anesthetics, tranquillizers and opioid analgesics. In: Equine clinical pharmacology. 1sted Bertone JJ and Horspool LJI (ed) China Elsevier p. 267-301.

Matsubara LM, LS Oliva VN, Gabas DT, Oliverira GCV and Cassetari ML 2009. Effect of lidocaine on the minimum alveolar concentration of sevoflurane in dogs. Vet Anaesth Analg. 36(5): 407-413.

Muir WW and Sams R 1992. Effects of ketamine infusion on halothane minimal alveolar concentration in horses. Am J Vet Res. 53(10): 1802-1806.

Nóbrega NPI, Luna SP, Queiroz-Williams P, Mama KR, Steffey EP and Carregaro AB 2013. Cardiorespiratory and antinociceptive effects of two different doses of lidocaine administered to horses during a constant intravenous infusion of xylazine and ketamine. BMC Vet Res. 9: 199.

Pöppel N, Hopster K, Geburek F and Kastner S 2014. Influence of ketamine or xylazine supplementation on isoflurane ananesthetized horses- a controlled clinical trial. Vet Anaesth Analg. 42(1): 30-38.

Rezende ML, Wagner AE, Mama KR, Ferreira TH and Steffey EP 2011. Effects of intravenous administration of lidocaine on the minimum alveolar concentration of sevoflurane in horses. Am J Vet Res. 72(4): 446-451.

Ringer SK, Kalchofner K, Boller J, Furst A and Bettschart-Wolfensberger R 2007. A clinical comparison of ananesthesia protocols using lidocaine ormedetomidine in horses. Vet Anaesth Analg. 34(4): 257-268.

Santos M, Fuente M, Garcia-Iturralde P, Herran R, Lopez-Sanroman J and Tendillo FJ 2003. Effects of alpha-2 adrenoceptor agonists during recovery from isoflurane anaesthesia in horses. Equine Vet J. 35(2): 170-175.

Senior JM 2013. Morbidity, Mortality, and Risk of general anesthesia in horses. Vet Clin North Am Equine Pract. 29(1): 1-18.

Spadavecchia C, Levionnois O, Kronen P and Andersen OK 2010. The effects of isoflurane minimum alveolar concentration on withdrawal reflex activity evoked by repeated transcutaneous electrical stimulation in ponies. Vet J. 183(3): 337-344.

Steffey EP, Howland D, Giri S and Eger EI 1977. Enflurane, halothane and isoflurane potency in the horse. Am J Vet Res. 38(7): 1037-1039.

Steffey EP, Hodgson DS, Dunlop CI, Miller MF, Woliner MJ, Heath RB and Grandy J 1987. Cardiopulmonary function during 5 hours of constant-dose isoflurane in laterally recumbent, spontaneously breathing horses. J Vet Pharmacol Ther. 10(4): 290-297.

Steffey EP, Pascoe PJ, Woliner MJ and Berryman ER 2000. Effects of xylazine hydrochloride during isoflurane-induced anesthesia in horses. Am J Vet Res. 61(10): 1225-1231.

Teixeira Neto FJ, Mcdonell WN, Black WD, Durongphongtorn S 2004. Effects of glycopyrrolate on cardiorespiratory function in horses anesthestized with halothane and xylazine. Am J Vet Res. 65(4): 456-463.

Valverde A, Doherty TL, Hernandez J and Davis W 2004. Effect of lidocaine on the minimum alveolar concentration of isoflurane in dogs. Vet Anaesth Analg. 31(4): 264-271.

Valverde A, Gunkelt C, Doherty TJ, Giguère S and Pollak AS 2005. Effects of a constant rate infusion of lidocaine on the quality of recovery from sevoflurane or isoflurane general anaesthesia in horses.Equine Vet J. 37(6): 559-564.

Valverde A 2013. Balanced anesthesia and constant-rate infusions in horses. Vet Clin North Am Equine Pract. 29(1): 89-122.

Vesal N, Spadavecchia C, Steiner A, Kirscher F, Levionnois OL 2011. Evaluation of the isoflurane-sparing effects of lidocaine infusion during umbilical surgery in calves. Vet Anaesth Analg. 38(5): 451-460.

Villalba M, Santiago I and Gomezde Segura IA 2011. Effects of constant rate infusion of lidocaine and ketamine, with or without morphine, on isoflurane MAC in horses. Equine Vet J. 43(6): 721-726.

บทคัดย่อ

การประเมินทางคลินิกการใช้ไซลาซีนร่วมกับลิโดเคนและเคตามีนที่ให้ผ่านเส้นเลือดดำอย่างต่อเนื่องเพื่อลดการใช้ไอโซฟลูเรนในม้าพื้นเมืองไทย

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การวางยาสลบแบบใช้ยาร่วมกันหลายชนิดช่วยลดอัตราการตายเนื่องจากการวางยาสลบในม้าได้ ยาซึม ยาสลบ และยาลดปวดมีใช้อย่างแพร่หลายในงานรักษาม้าในประเทศไทย เช่น ไซลาซีน เคตามีน ไอโซฟลูเรน และลิโดเคน อย่างไรก็ตามยังไม่มีรายงานผลของการใช้ยาเหล่านี้ร่วมกัน การศึกษานี้มีวัตถุประสงค์เพื่อประเมินค่าความเข้มข้นของไอโซฟลูเรนในถุงลมปอดที่ต่ำที่สุด (MAC) และค่าทางคลินิกในม้าพื้นเมืองไทยที่อยู่ภายใต้ยาสลบ สุ่มเลือกม้าจำนวน 6 ตัวและทำการทดลองสลับจนครบ 4 กลุ่มตามชนิดของยาคงการสลบแบบฉีดผ่านเส้นเลือดดำ ได้แก่ กลุ่มที่คงการสลบด้วยไอโซฟลูเรน (I) ไอโซฟลูเรนร่วมกับลิโดเคน (IL) ไอโซฟลูเรนร่วมกับไซลาซีนและเคตามีน (IXK) และไอโซฟลูเรนร่วมกับไซลาซีน ลิโดเคน และเคตามีน (IXKL) นำสลบม้าทุกตัวด้วยอะซีโปรมาซีน (0.04 มิลลิกรัมต่อกิโลกรัม เข้าเส้นเลือดดำ) และไซลาซีน (0.8 มิลลิกรัมต่อกิโลกรัม เข้าเส้นเลือดดำ) ชักนำสลบด้วยเคตามีน (2 มิลลิกรัมต่อกิโลกรัม เข้าเส้นเลือดดำ) และไดอะซีแพม (0.1 มิลลิกรัมต่อกิโลกรัม เข้าเส้นเลือดดำ) และคงการสลบด้วยการดมไอโซฟลูเรนร่วมกับให้ยาสลบแบบฉีดผ่านเส้นเลือดดำ ค่าพารามิเตอร์ที่วัดประกอบด้วยอัตราการเต้นของหัวใจ อัตราการหายใจ ความดันเลือดเฉลี่ย ค่าก๊าซในเลือด ความเข้มข้นของไอโซฟลูเรนในลมหายใจออก ความเข้มข้นของคาร์บอนไดออกไซด์ในลมหายใจออก ค่าความเข้มข้นของไอโซฟลูเรนในถุงลมปอดที่ต่ำที่สุด และคะแนนคุณภาพการฟื้นตัว ค่าความเข้มข้นของไอโซฟลูเรนในถุงลมปอดที่ต่ำที่สุด (ค่าเฉลี่ยบวกลบส่วนเบี่ยงเบนมาตรฐาน) ในกลุ่ม I IL IXK และ IXKL เท่ากับ 0.74±0.2% 0.67±0.2% 0.45±0.2% และ 0.16±0.1% ตามลำดับ โดยพบความแตกต่างกัน (78 เปอร์เซ็นต์) อย่างมีนัยสำคัญทางสถิติระหว่างกลุ่ม I และ IXKL ($p<0.05$) แต่ไม่พบความแตกต่างของค่าก๊าซในเลือดและคะแนนคุณภาพการฟื้นตัวในทุกกลุ่ม สรุปได้ว่า การให้ไซลาซีนขนาดเริ่มต้น 0.8 มิลลิกรัมต่อกิโลกรัม ตามด้วยขนาด 0.5 มิลลิกรัมต่อกิโลกรัมต่อชั่วโมงผ่านเส้นเลือดดำ การให้เคตามีนขนาดเริ่มต้น 2 มิลลิกรัมต่อกิโลกรัมตามด้วยขนาด 1 มิลลิกรัมต่อกิโลกรัมต่อชั่วโมงผ่านเส้นเลือดดำ และการให้ลิโดเคนขนาดเริ่มต้น 1.5 มิลลิกรัมต่อกิโลกรัม ภายใน 15 นาที ตามด้วยขนาด 50 ไมโครกรัมต่อกิโลกรัมต่อนาทีผ่านเส้นเลือดดำ ร่วมกับการดมไอโซฟลูเรนสามารถลดปริมาณการใช้ไอโซฟลูเรนในม้าพื้นเมืองไทย อีกทั้งยังทำให้ม้ามีคุณภาพการฟื้นตัวที่ดี

คำสำคัญ: ไซลาซีน ลิโดเคน เคตามีน ม้าพื้นเมืองไทย MAC

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