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THESIS

COMPARATIVE EFFICACY OF TILETAMINE HCl – ZOLAZEPAM (ZOLETIL®) AND KETAMINE – DIAZEPAM FOR INDUCTION ANESTHESIA IN 4 – 6 MONTH OLD FOALS

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The study was designed to compare the drug combinations effect of xylazine – zoletil® (XZ group) and xylazine – ketamine – diazepam (XKD group). Both of drugs groups were administered to six foals, age range 4 to 6 months and body weight between 107 to 125 kg in a crossover design. Measured variables were heart rate, respiratory rate, body temperature, blood glucose, systolic and diastolic blood pressure, mean arterial blood pressure, blood gas variables (pH, PaO_2, $PaCO_2$, HCO_3^-, TCO_2, BE, and SaO_2). All parameters were evaluated at 5 minutes before and 7 minutes after xylazine administered and were also measured at 5, 10, 15 and 20 minutes after anesthetic drugs administration. Quality of induction and recovery, quality of mouth opening and intubation, number of attempts to regain sternal recumbency, standing position and duration of anesthetic effects were measured. There were no significant differences in any variables (p value < 0.05) suggested that xylazine – zoletil® combination was safe for induction in the 4 to 6 month old foals.

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Suphannika Phutthachalee

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LIST OF ABBREVIATIONS

CEPEF	=	Confidential Enquiry into Perioperative Equine Fatalities
TIVA	=	Total Intravenous Anesthetic Technique
HR	=	heart Rate
RR	=	respiratory Rate
BT	=	body Temperature
CRT	=	capillary refill time
mm	=	mucous membrane color
bpm	=	beat per minute
PaCO2	=	arterial carbon dioxide partial pressure
PaO2	=	arterial oxygen partial pressure
Beef, BE	=	base excess
HCO_3^-	=	bicarbonate
TCO_2	=	total concentration of carbon dioxide
SaO_2	=	saturated with oxygen
pH	=	arterial pH
CNS	=	central nervous system
BW	=	body weight
mmHg	=	millimeter mercury
mg/kg	=	milligram per kilogram
CSU	=	Colorado State University
IV	=	intravenous
GABA	=	gamma – aminobutyric acid
WBC	=	total white blood cell count
RBC	=	total red blood cell count
Hb	=	hemoglobin
Hct	=	hematocrit

LIST OF ABBREVIATIONS (Continuted)

MCV	=	mean corpuscular volum
MCH	=	mean corpuscular hemoglobin
MCHC	=	mean corpuscular hemoglobin concentration
RDW	=	red cell distribution width
PLT	=	platelets
MPV	=	mean platelet volume
nRBC	=	normal red blood cells
Band	=	band neutrophils
Seg.	=	segment neutrophils
Lymph.	=	lymphocytes
Mono.	=	monocytes
Eos.	=	eosinophils
Baso.	=	basopphils
PP	=	plasma protein
BP	=	blood pressure
MAP	=	mean arterial blood pressure
BUN	=	blood urea nitrogen
AST	=	aspartate aminotransferase
GGT	=	gamma-glutamyl transferase
XZ	=	xylazine/Zoletil
XDK	=	xylazine/diazepam and ketamine
Nyst.	=	Nystagmus
Palpeb.	=	Palpebral
Bl.	=	Blood

COMPARATIVE EFFICACY OF TILETAMINE HCl – ZOLAZEPAM (ZOLETIL®) AND KETAMINE – DIAZEPAM FOR INDUCTION ANESTHESIA IN 4 – 6 MONTH OLD FOALS

INTRODUCTION

In veterinary practice, anesthesia is used to reduce pain and to immobilize the animal for medical treatment or surgery procedures. The beginning of equine practice anesthesia was focused on physical restraint for immobilization during middle 1970s and it continues to be an important tool for detailing and describing drugs, anesthetic techniques, equipment and monitor under general anesthesia and for reducing complications from pre-anesthetic, anesthetic, and post-anesthetic periods (Muir and Hubbell, 1991; Garcia *et al*., 2002). However, equine anesthesia is usaully associated with a higher mortality rate than that applied to other species and humans (Flaherty *et al*., 1996; Staffieri and Driessen, 2007). The anatomic and physiologic dimensions of horses are specific. Horses are characterized by heavy weight, high height, nervous breed, big muscles, long neck and oral cavity length, and large thoracic cavity. The lung volume of the horse can be decreased during recumbency because of the weight of the visceral organs pressing on the diaphragm. The consequences of decreasing lung volume for the horse during anesthetic period are: respiratory or ventilation insufficiency, arterial hypotension, hypoperfusion, cardiac arrhythmias, hyperthermia, acute air way obstruction, myopathy-neuropathy syndrome, excitation, pain, and post anesthetic colic (Garcia *et al*., 2002; Caukett, 2007).

Confidential Enquiry into Perioperative Equine Fatalities [CEPEF] (2002) concluded that the choice of the anesthetic technique has a relatively high risk mortality rate, a 3% rate if only inhalant agents are used compared to 0.3% of total intravenous anesthetic (TIVA) technique. The induction with injectable agents followed by maintenance with anesthetic for the maintenance of prolong anesthesia in horses, can cause the perioperative inhalation mortality rate under anesthesia. The mortality rate in foals aged less than 6 months and less than 1 month are at higher risk with a 1.1% and 1.5 % of mortality respectively for studied cases (Johnston *et al*., 2002). One third of the deaths were caused by cardiac arrest, another third from

fractures and myopathies, and the rest of the deaths from other causes (Marntell, 2004).

For the above reasons, a successful selection of the applied anesthetic techniques and anesthetic drugs requires of easily recumbency, rapidly surgical procedures without changing cardiovascular or respiratory functions while producing good muscle relaxation, avoiding movement of the horses and smooth recovery (Garcia *et al*., 2002; Staffieri and Driessen, 2007).

The selection of sedation and anesthetics in foal is particularly difficult for the equine practitioner because the immature physiology of neonatal foals and small body size. In addition, low fat and glycogen storage in the body of foals creates heat loss as a consequence of the high surface area relative to body weight and lack of cutaneous fat. The hypoglycemia is due to very small energy reservation and a higher metabolic rate compared with adult horses, particularly if the foals are ill foal, premature or very young. Furthermore, foal may easily pass into hypoxemia, hypercapnia, and acidosis because of anesthetic agents that can induce cardiovascular depression. Therefore we should carefully examine the characteristics of anesthetic drugs before we can apply them to foals.

The most popular sedative drug used in foals is benzodiazepine because of its minimal cardiovascular and respiratory side effects. Other drugs such as phenothiazine and alpha-2 adrenoceptor agonist are typically avoided in foals of less than 6 weeks of age or ill foals because their administration is associated with hypotension, bradycardia, and decreasing cardiac output effects. Xylazine is excellent sedative and analgesics (Garcia *et al*., 2002; Aubin and Mama, 2002) In the older foals (6 weeks up to 6 months of age), which already have a mature metabolic, circulatory and respiratory pathway, Xylazine can be used similarly to adult horses (Tranquilli and Thurmon, 1990). The most popular anesthetic drug for producing short-term general anesthesia in horses is ketamine because it has low effect on cardiovascular and respiratory depression. However this drug is controlled by Thai authorities due its abuse by human in Thailand, therefore it is not easy to obtain for equine practitioner living in this country. Other drugs used for anesthesia such as

propofol, thiopental, pentobarbital create depression of cardiovascular and respiratory system of the foal. Zoletil® (Virbac Laboratories, France) is a commercial and easily available drug that combines tiletamine and zolazepam and is usually used for producing short-term chemical restraint and induction to inhalation anesthesia in horses (Muir and Hubbell, 1991; Hubbell, 1999; Staffieri and Driessen, 2007).

The hypotheses of my thesis are:

1. Zoletil® can be used instead of ketamine and diazepam combination for anesthetic induction in 4 – 6 month old foals.

2. Zoletil® is safety as anesthetic induction drug in foal 4 – 6 months of age.

OBJECTIVES

1. To compare drugs efficacy between Zoletil® and ketamine-diazepam via an evaluation of the physiologic changes [vital signs (heart rate, respiratory rate, body temperature), blood gas analysis ($PaCO_2$, PaO_2, Beef, HCO_3, TCO_2, and SaO_2), blood glucose, arterial blood pressure] after anesthetic induction in 4 to 6 months old foals.

2. To compare the quality of anesthetic induction and recovery period between Zoletil® and ketamine - diazepam in 4 to 6 months old foals.

LITERATURE REVIEW

The knowledge of normal physiological values in the healthy foal is necessary to avoid high anesthetic risk and to estimate the undergoing anesthetic impact since the physiology of foals is different.

Important factors to consider when planning anesthesia in foals include: the dosage of administration, the plasma albumin level, the relative distribution of cardiac output to vessel organ, the extracellular fluid volume, the receptor site for drug redistribution, and the level of hepatic metabolism and renal excretion. The aforementioned factors can cause an alteration difference in the response to distribution, metabolism and excretion from drug in foals (Dunlop, 1994; Mama *et al*., 1996) when compared with adult horses.

In 2004, Knottenbelt and co-workers separated foals into two groups depending on the relatively differences of adaptive period and organ immaturity: neonatal foal (0 to 2 weeks of age) and pediatric foal (2 weeks to 6 months of age). However, other authors (VaaLa, 1985; Klein, 1985; Dunlop, 1994) divided foals into three groups, neonatal foal (0 to 2 weeks of age), younger foal (less than 6 weeks of age), and older foal (6 weeks up to 6 months of age). The older foal group was considered to have a mature metabolic partway, circulatory and respiratory function that could be treated similarly to the adult horses (Tranquilli and Thurmon,1990).

Physiological considerations

Cardiovascular system

The changes of the new born foal circulation occur immediately after birth through the closure of the ductus arteriosus and foramen ovale. However cardiac murmur is probably normal and the arterial oxygen value is lower than expected value of healthy foals around 3 to 5 days of age due to the common patent ductus arteriosus and foramen ovale (Dunlop, 1994; Taylor and Clarke, 1999). The low vascular resistance or low vasomotor tone resulting in low blood pressure in foal is originated

from the immature sympathetic nervous system of foal that usaully occurs until the foal is around 1 month after birth (Dunlop, 1994; Knottenbelt *et al*., 2004). Anesthesia should be carefully performed in foal less than 3 to 5 days of age because anesthetic drugs can decrease cardiac output and vascular tone consequently, the foal develops hypoxemia and metabolic acidosis. Basically, foals have centralized circulation, so they have great ratio of their cardiac output being delivered to the brain. Nevertheless, the blood brain barrier of foal is highly permeable for the first month of age allowing drug access to the central nervous system (CNS). Therefore, less blood perfusion of muscle and other peripheral tissue, as well as smaller muscle mass can limit drug redistribution in foals (Dunlop, 1994; Knottenbelt *et al*., 2004).

Respiratory system

At birth foals have immature lungs which have relatively low arterial oxygen pressure (PaO_2). However PaO_2 is rapidly increased in the first week of age. The number and size of alveoli, as well as the metabolic function of foals continues to develop until 6 weeks of age, when they can response to the anesthetic condition similarly to adult horses. The tone of respiratory muscle (intercostal and diaphragm) is commonly reduced and easily fatigued when foals are anesthetized, especially in the recumbency posture, which probably increases the chances to have alveolar collapse (Dunlop, 1994; Knottenbelt *et al*., 2004). Therefore, the anesthetic drug selection should consider avoiding the depressant effect to the respiratory system.

Thermoregulation

The anesthetized foal produces a hypothermia condition because of its small body size, large surface area to body mass ratio and little body fat storage. The total body fat of a neonatal foal (2-3% of body weight) is lesser than that of an adult horse (5% of body weight) (Baggot, 1994). The anesthetic drugs can interfere heat regulation, making the foal not able to preserve heat through various ways such as depression of the central control mechanism, dilatation of peripheral blood vessels, and reduction of the muscle activity and tone. The consequences of hypothermia, which is easily developed from foals of less than 6 weeks of age, are peripheral blood

vasoconstriction, bradycardia, decreased cardiac output, decreased tissue perfusion, severe hypoxemia and metabolic acidosis. The final changes of a hypothermic foal can be slow during drug metabolism and excretion and can create a prolonged anesthetic recovery period (Klein, 1985; Tranquilli and Thurmon, 1990; Dunlop, 1994; Taylor and Clarke, 1999; Knottenbelt *et al*., 2004).

Glucose homeostasis

Foals could acquire hypoglycemia because their fat storage is very limited. The new born foals are so highly metabolic that they do not need to be starved from suckling milk. The under 2-3 month-old-foals do not need the withholding time for suckling milk and concentrate food as well. After 2-6 months of age, foals should be starved from concentrate food around 4 to 8 hours before anesthetic drugs administration but not withhold suckling (Taylor and Clarke, 1999). Those foals older than 6 months should be starved for 12 hours prior to be anesthetized (Dunlop, 1994). Regurgitation or vomiting during anesthesia is uncommon in foals (Taylor and Clarke, 1999).

Distribution

The neonatal foals have higher total body water, 70 to 75% of body weight, compared with those, 50 to 60% of body weight, in adult horses (VaaLa, 1985). Extracellular fluid volume of the 1-week, 3-week of age foal accounts for 43% and 34% of body weight respectively. However, the volume of extracellular fluid in foal of up to 1 month of age, 35 to 40% of body weight, is much higher than that of the 20 to 25% of body weight of adult horses (Kami *et al*., 1984; Baggot, 1994; Conny, 2005). As the neonatal foal has much of extracellular fluid volume, the volume of non-protein bound or minimal bound drugs (i.e. Ketamine) distribution of the neonatal foal is greater than that of the older foal and adult horse (Tranquilli and Thurmon, 1990). The amounts of total serum protein and albumin in healthy foals are within the normal quantity as in adult horses. Therefore, the bioavailability, altered by protein bound drugs, of foals and adult horses is similar (Dunlop, 1994).

Metabolism

The immaturity of the hepatic function is an important factor responsible for sedative and anesthetic drugs because the liver is the main site of drug metabolism (VaaLa, 1985). The metabolism pathway of lipid soluble nonpolar drugs (i.e. barbiturates) includes hepatic microsomal oxidative reaction and glucoronide conjugation for reduction and hydrolysis of such drugs (Tranquilli and Thurmon, 1990). decreased pharmacologic activity or inactive and easily excreted in the urine (Baggot, 1994). The foals of around a day of age many drugs (i.e. phenobarbital) and have prolonged half-lifes because of the low activity of these metabolic pathway is well developed in foals of 3 to 4 weeks of age and in adults by 2 to 3 months of age. The glucoronide synthesis is rapidly developed within the first week of age (VaaLa, 1985; Baggot, 1994). There is a prolongation of effects that requires redistribution in fat or clearance by the liver or kidneys (i.e. all injectable tranquillizers and anesthetics and most neuromuscular blocking agents).

Excretion

Renal function is an important factor for excretion of many kinds of drugs. Drug elimination occurrs through glomerular filtration of drug molecules being free in the plasma and through tubular secretion of certain polar organic compounds, this is the primary route of elimination for polar and ionized drugs (VaaLa, 1985). Glomerular filtration and effective renal plasma flow is well developed in the foals from 1 to 10 days of age, which is already similar to adult horses (Holdstock *et al.,* 1998). In the horse, the renal function is relatively mature at the age of 1 to 2 weeks. The low urinary pH in foals could delay excretion of weak organic acids (bases), reduce the reabsorbing of weak bases, whereas the organic acids may be increased (VaaLa, 1985; Baggot, 1994).

Anesthetic drugs for older foal

Anesthetized 1 week of age foals have slow drug metabolism and excretion until around 1 month of age, already similarly to adult horses (Dunlop, 1994). Therefore, the foal age information is crucial for decision making of foal anesthesia in order to facilitate the surgical procedure. Basically, the group of foal can be categorized by the age period, which has different kind of abnormalities to be treated by surgical correction. The 1-2 weeks of age foal abnormalities are rupture bladder, patent urachus, umbilical remnant, gastrointestinal defects (such as severe impaction or intussusceptions), musculoskeletal injury and septic arthritis. The most frequent abnormalities of the foal between 1 to 3 months of age are angular limb deformities, musculoskeletal injury and septic arthritis. For the group of foals between 4 to 6 months of age, the common abnormalities are umbilical hernia repair and laceration repair, which can be compatible with general anesthesia for diagnosis procedures (Dunlop, 1994).

Principally, intravenous anesthesia is the method of choice for performing equine anesthesia for short term procedures under field condition. Intravenous anesthesia technically can use the combination of the sedative drugs (alpha-2 adrenoceptor; xylazine) and dissociative agents (i.e. ketamine, tiletamine in Telazol® or Zoletil®), or the combination of centrally active muscle relaxants (guaifenesin or benzodiazepine agents; diazepam, midazolam) (Mama, 2000; Staffieri and Driessen, 2007).

Xylazine

Xylazine is an excellent sedative and analgesic drug that produces a summit peak effect of sedation within 3 to 5 minutes after intravenous administration (Garcia *et al*., 2002; Mama *et al*., 1996). The full onset of sedation and duration of this drug effect depends on dosage and route of administration (Benson and Thurmon, 1990).

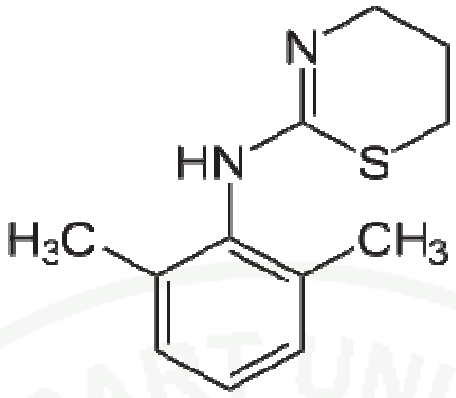

Figure 1 Xylazine: *N*-(2,6 – dimethylphenyl)-5,6-dihydro-4*H*-1,3-thiazin-2-amine

Alpha-2 adrenoceptors include xylazine, detomidine and romifidine. The mechanism of action of alpha-2 adrenoceptor is an activation of central alpha-2 receptors located both presynaptically and postsynaptically in the peripheral and central nervous system. The presynaptic alpha-2 receptors generally have an inhibitory effect on the releasing of transmitter from the synaptic nerve endings i.e. norepinephrine, dopamine, serotonin and acetylcholine (Benson and Thurmon, 1990; Aubin and Mama, 2002; Adarsh, 2007)

The sympathetic blockage and vagal stimulation are involved in baroreceptor activation, peripheral vasoconstriction, bradycardia, sinu-arterial arrest and first and second degree artrioventricular blocks (Garcia *et al*., 2002; Aubin and Mama, 2002; Frias *et al*., 2003; Marntell, 2004; Adarsh, 2007). The analgesic effect of alpha-2 receptors are also found in the spinal cord (Adarsh, 2007) resulting in bradycardia, arrhythmias, decreasing in cardiac output, and low blood pressure. However, mean arterial pressure does not drop below 60 mmHg (Tranquilli and Thurmon, 1990; Frias *et al*., 2003). Additionally, there is also initial hypertension followed by prolonged hypotension causing raised pulmonary pressure and body temperature was reduced (VaaLa,1985; Tranquilli and Thurmon, 1990; Hubbell, 1999; Aubin and Mama, 2002; Marntell, 2004). Alpha-2 adrenoceptors are very effective for reducing muscle hypertonicity and excitement from dissociative agents that were often used to induce anesthesia (Aubin and Mama, 2002). Xylazine has a rapid metabolism (around 20 minutes in rat) with several metabolized and the half-life of xylazine is 45.5 minutes

after intravenous administration of a single dose in horses. The dosage of xylazine for older foals (over 2 month of age) is 0.3 – 1.0 mg/kg intravenous. The researchers from the Colorado State University (CSU) studied the drug use of xylazine (dose 0.3 mg/kg IV administration) in 8 foals and found that all foals decreased heart rate, cardiac output, and reduced of oxygen tissue perfusion.

Dissociative anesthetics

Dissociative anesthetics are phencyclidine, ketamine and tiletamine. These anesthetics are popular for producing short-term general anesthesia in horses because they have a significant analgesic activity for anesthesia and immobility without a lack of cardiopulmonary depressant effects. (Muil and Hubbell, 1991; Bettschart-Wolfensberger and Larenza, 2007)

Ketamine

Ketamine is an intravenous anesthetic drug that can depress the central nervous system (CNS) by electrophysiological dissociation (disconnection) of thalamo – neocortical areas from limbic and other subcortical structure in the brain. Consequently, the consciousness is lost and the limbic system is activated (Staffieri and Driessen, 2007; Bettschart-Wolfensberger and Larenza, 2007). The frequently accompany effects of ketamine are dysphoria, hallucinations, derilium, and excitement with the undesirable catatonic response (i.e. clonic – tonic muscle activity) (Benson and Thurmon, 1990).

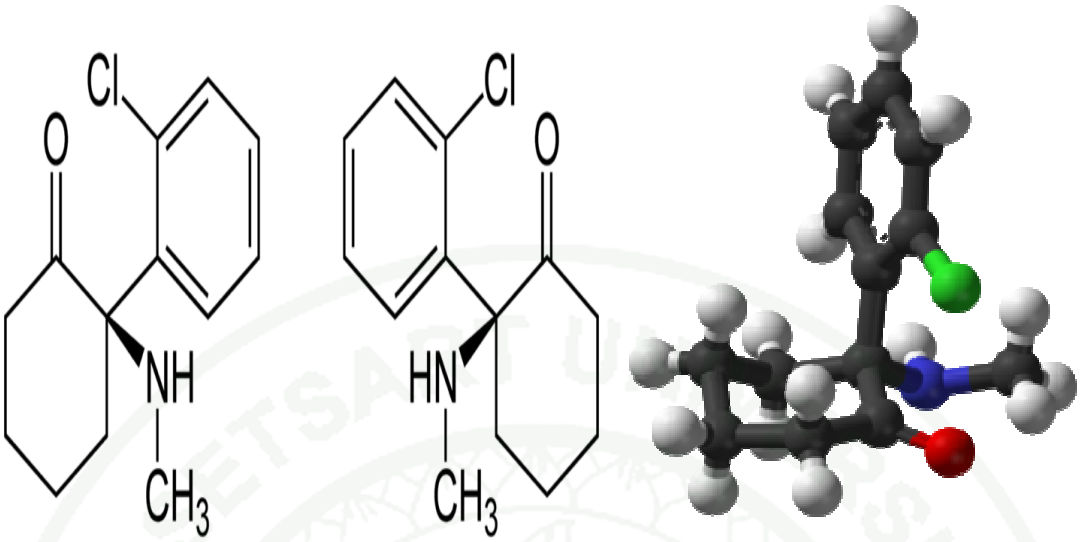

Figure 2 Ketamine: (*RS*)-2-(2-chlorophenyl)-2-methylamino-cyclohexan-1-one

Ketamine inhibits gamma – aminobutyric acid [GABA], and also blocks serotonin, norepinephrin and dopamine in the CNS by interfering and interaction with several centrally acting neurotransmitters. Ketamine can increase serotonin and dopamine concentration in the brain producing excitement and increasing motor activity in horses. Furthermore, ketamine also produce poor muscle relaxation and retention of muscle tonus during the induction phase causing the difficulty to open the horse's mouth for intubation (Muil and Hubbell, 1991; Staffieri and Driessen, 2007).

Ketamine has sympathomimatic effects on the cardiovascular system that can increase heart rate, myocardial contractility, cardiac output, mean arterial pressure, pulmonary artery pressure, and central venous pressure (Benson and Thurmon, 1990). In addition, ketamine can stimulate the sympathetic system and counteract some of the vagotonic effects from the alpha-2 adrenoceptor. Ketamine has a minimal effect on respiratory depression that can induce an apneutic respiratory pattern with mild hypoventilation characterized by hypoxemia and mild hypercapnia when the horse breathes room air (Benson and Thurmon, 1990; Bettschart-Wolfensberger and Larenza, 2007).

The horse being sedated with xylazine and followed with ketamine for induction will lay down in lateral recumbency within 1-3 minutes. The anesthetized

horse first will raise head around 10 to 30 minutes after induction and usually will stand at the first attempt having mild to moderate ataxia (Staffieri and Driessen, 2007).

Ketamine is distributed into all body tissue rapidly and the highest level is found in the brain, liver, lung and fat. The level of ketamine-plasma protein binding in the horses is 50% (Muir and Hubbell, 1991). The duration of action of ketamine is directly related to redistribution of ketamine to muscle tissue and to hepatic metabolism. Approximately 60 % of ketamine in the body of horse is metabolized by the liver and remaining 40% is eliminated unchanged in the urine (Benson and Thurmon, 1990).

Telazol® or Zoletil®

Zoletil® is a combination of dissociative anesthetic agent, tiletamine and a tranquilizer, zolazepam.

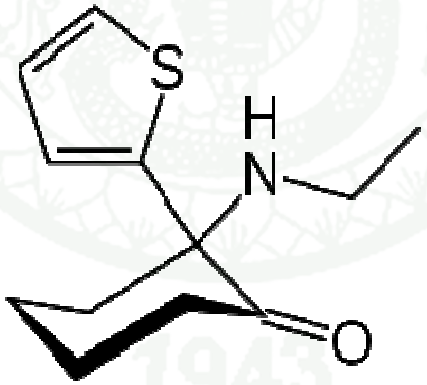

Figure 3 Tiletamine: 2-ethylamino-2-(2-thienyl) cyclohexenone

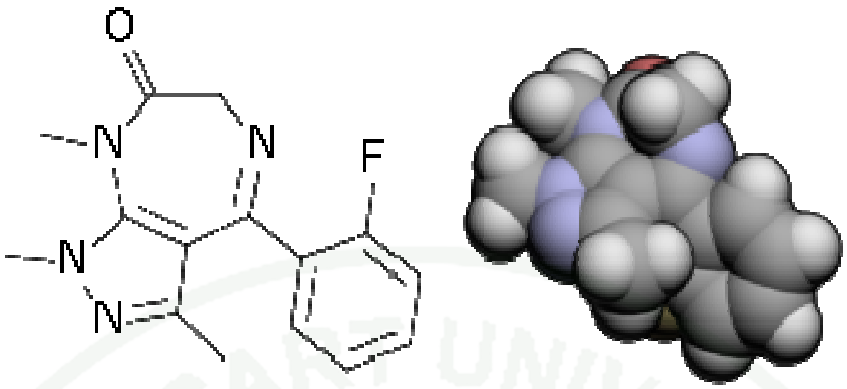

Figure 4 Zolazepam:4-(2-fluorophenyl)-1,3,8-trimethyl-6,8-dihydropyrazolo [3,4-e][1,4] diazepin-7(1*H*)-one

Tiletamine is usually used for producing short term chemical restraint and induction of anesthesia in horses (Muir and Hubbell, 1991; Hubbell, 1999; Staffieri and Driessen, 2007). The basic pharmacology of tiletamine is similar to ketamine. Similarly to diazepam, zolazepam is a benzodiazepine derivative tranquilizer having central muscle relaxant effect and anticonvulsant activity.

The Zoletil® effects on cardiovascular system are the incremen of heart rate and cardiac output, and reduction of arterial blood pressure, systemic vascular resistance and myocardial contractility. However, Zoletil® does not have an effect in central venous and pulmonary vascular pressure (Benson and Thurmon, 1990).

The tiletamine has longer duration of action time, greater analgesia effect and muscle relaxation than ketamine (Benson and Thurmon, 1990; Muir *et al*., 1991; Aubin and Mama, 2002; Marntell *et al*., 2006; Staffieri and Driessen, 2007). When using xylazine for sedation, the quality of induction anesthesia in horse from tiletamine is smooth and occurs approximately 35 seconds after intravenous induction administration, the horse remains in lateral recumbency for an average of 45 minutes. However, the anesthetized horse is assumed to roll for sternal recumbency at 30 to 39 minutes and would stand up within 32 to 45 minutes after induction. In addition, the duration of anesthesia is related to the dosage of Zoletil® (Benson and Thurmon, 1990; Mama, 2002). The quality of recovery should be clam without excitation

(Marntell, 2004; Marntell *et al*., 2006) and stand on the first attempt. The Telazol® has been combined with xylazine to induce a short period of anesthesia in adult horses and similar actions are expected in the older foals (Benson and Thurmon, 1990).

Diazepam

Diazepam, a benzodiazepine group drug, is a centrally acting muscle relaxant drug, being of common use in veterinary practice. Diazepam can be used for treating seizures, enhancing the quality of anesthesia when used with dissociative anesthetics and sedative analgesics. Additionally, diazepam enhances muscle relaxation by reducing the degree of tonic-clonic twitching. However, the analgesic duration of diazepam is not increased for short – term anesthesia (Benson and Thurmon, 1990; Muir *et al*., 1991; Muir and Hubbell, 1991; Marntell, 2004; Staffieri and Driessen, 2007). The mechanism of action of diazepam is the depression of the subcortical levels (primarily limbic, thalamic and hypothalamic) of the CNS. The benzodiazepine specific receptor sites have been located within the CNS. Basically the benzodiazepine receptors potentiate the action of GABA, being generally an inhibitory neurotransmitter of the brain, thus this drug produces anxiolytic, sedative, skeletal muscle relaxant and anticonvulsant effects (Bettschart-Wolfensberger and Larenza, 2007). The muscle relaxation effect from diazepam due to central nervous system (CNS) in origin, although some of this action is attributable to direct activity at neuromuscular junction (Hubbell, 1999). The cardiovascular depressant effect from low dose diazepam is not so important for horse and the effect of diazepam to the respiratory system is very rare (Adarsh, 2007). Garcia (2002) concluded that diazepam could be used as an ansiolytics in foals and could produce a very good sedation and muscle relaxation.

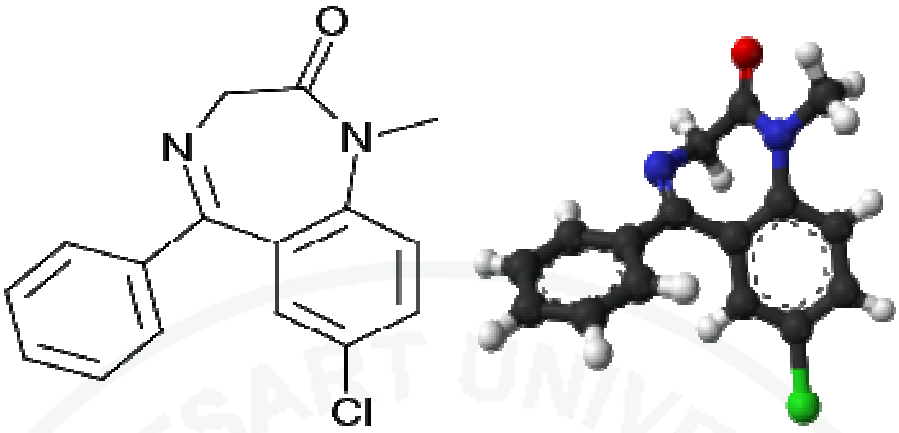

Figure 5 Diazepam: 7-Chloro-1,3dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepine-2-one

Diazepam is a highly lipid soluble substance that can be widely distributed throughout the body and can vastly bound (99%) to plasma protein (Bettschart-Wolfensberger and Larenza, 2007) and metabolized in the liver. Diazepam in the body is eventually conjugated with glucoronide and eliminated primarily in the urine.

Norman and co-workers (1997) studied diazepam via intravenous administration (dosage 0.25 mg/kg) at different of foal age (4, 21, 42 and 84 days) and found that diazepam was highly lipophilic. The age related increase in diazepam volume of distribution most likely reflects an increasing in fat to water ratio. In such study, the diazepam volume distribution of the 4-day old foal was lower than that of the 21 to 84 day old foal. However, the diazepam volume distribution of foals from 21 to 84 days of age from Norman *et al.,* study is similar to previous ones reported from adult horses (Muir *et al*., 1982). Since the maturation of the hepatic enzyme system of horse appears to progress rapidly over the first 3 weeks of life and then approaches to adult status, the neonatal foal has lower hepatic oxidative capacity for diazepam clearance than that of older foals or adult horses.

Monitoring of Foal Anesthesia

Monitoring means continuous surveillance of the anesthetized horses. The aim of monitoring during anesthesia is to observe the depth of anesthesia for the safest anesthetic practice and to decrease the risk of the anesthetic complications. The foal anesthetic monitoring depends on the patient, age, physical status, and the duration of the surgical procedure (Dunlop, 1994)

Monitoring can be divided into subjective (qualitative) and objective (quantitative) data. Qualitative data or physical monitoring methods generally are techniques that require visual, tactile and auditory skills. The anesthetist has to assess the quality of induction and recovery of horse, ocular reflexes, ocular movement, mucous membrane color and snoring. Quantitative data are dependent of technological monitoring methods classified as indirect and direct. Indirect methods are related to monitor the horse patient or direct methods, which are recorded as a numerical value (Riebold, 1990; Muir and Hubbell, 2009). Equine anesthetic monitoring has focused on particular three organ systems: central nervous system, cardiovascular and respiratory systems. The usual frequency for monitoring variables is a 5-minute interval (Riebold, 1990; Muir and Hubbell, 2009).

Central nervous system (CNS) and depth of anesthesia

The level of consciousness or depth of anesthesia is of high concern during the general anesthesia of horse. Ideally, the horse should not move in response to painful stimuli during anesthesia. If the horse is at the too light depth of anesthesia, the horse will probably respond to surgical stimulation resulting in excessive stress, movement inducing contamination of the surgical site and injury to the horse and helper. Conversely, if the depth of equine anesthesia is too deep, the horse cardiovascular, respiratory and central nervous system will be depressed (Taylor and Clarke, 1999; Muir and Hubbell, 2009).

The eye signs, for instance nystagmus, tearing and blink, can be used to identify the depth of anesthesia. Generally, the nystagmus, tearing and blink occur

during light planes of equine anesthesia. The eyeball may rotate forwards or ventromedial during the early stage of anesthesia and the eyeball may return to a central position of the globe as the level of anesthesia is deep. Muir and Hubbell (2009) have developed the guidelines for monitoring the depth of equine anesthesia by eye signs as shown in the Table 1.

Table 1 Monitoring of anesthesia depth

Stage	**Pupil position/size**	**eye reflex**
One (analgesia)	Central/small	Palpebral/corneal active
Two (delirium)	Central/small	Palpebral/corneal active
Three		
Plane 1 (light)	Ventromedial/small	Palpebral mildly depressed Corneal active
Plane 2 (medium)	Ventromedial/medium	Palpebral depressed Corneal mildlydepressed
Plane 3 (medium-deep)	Central/medium	Palpebral depressed Corneal depressed
Plane 4 (deep)	Central/large	Palpabral absent Corneal markedly depressed
Four (overdose)	Central full dilation	Palpebral/corneal absent

The central nervous system can be monitored by observation of the ocular reflexes and used to evaluate the depth anesthesia. The ocular reflexes are palpebral reflex, nystagmus, and the corneal reflex. The palpebral reflex is the ability of horse for closure of the eyelids. During normal anesthesia, the horse show absence or slow eyelid closure when the eyelids or cilia are stimulated (Riebold, 1990). Anesthetic drugs, for example ketamine or tiletamine, usually maintain active palpebral reflex (Muir and Hubbell, 2009). The presence of nystagmus usually indicates the light anesthetic plane and an insufficient anesthetic drug effect to prevent movement (Riebold, 1990). The corneal reflex, being always present during anesthesia, is evaluated by closure of the eyelids when digital pressure is applied on the cornea. The absent of corneal reflex indicates that the horse is at too deep of anesthetic depth and

has central nervous system depression during anesthesia (Riebold, 1990; Muir and Hubbell, 2009).

Cardiovascular system

The primary goal of equine anesthesia is to maintain adequate perfusion and delivery of blood oxygen to vital organ and peripheral tissue. The parameters used to monitor and record the cardiovascular alteration are heart rate, pulse strength, arterial blood pressure, color of mucous membrane and capillary refill time (Riebold, 1990; Taylor and Clarke, 1999).

Heart rate

Normal heart rate of foals varies with age. In 1967, Rossdale reported that heart rate of the immediate newborn Thoroughbred foals ranges from 30 to 90 bpm. At 15 to 60 minutes after birth the range of heart rate is between 75 to 200 bpm and from 10 hours to 43 hours after birth is between 70 to 90 bpm. The variation of heart rate depends on the level of foal activity, for example, in young foals have heart rate between 60 to 90 bpm, but it is decreased as they become older foals (Riebold, 1990). Heart rate may be increased at the beginning of anesthesia because of excitement stage or hypotension effect associated with induction. However, heart rate is usually at the normal range within 10 to 20 minutes after induction administration (Riebold, 1990).

Pulse and arterial blood pressure

Superficial artery, located underneath the skin, is suitable for pulse measurement by digit or direct arterial pressure instruments (e.g., arterial catheter placement). These superficial arteries are facial, transverse facial, great metatarsal, metacarpal and digital arteries (Taylor and Clarke, 1999). Digital palpation of a peripheral artery pulse is a method for determining heart rate and rhythm in the recumbent horses. The pulse should be strong and regularly on digital palpation. Pulse pressure can be used to indicate changes of anesthetic depth. In the equine operation,

sharp increase of arterial blood pressure of the horse is probably the response of horse to light anesthesia while the surgical procedure is going on. During anesthesia the neonatal foals have lower systemic blood pressure, especially arterial blood pressure, than that of adult horses. The mean arterial blood pressure of neonatal foal should be maintained at more than 50 mmHg (Klein, 1985) and in older foals and adult horses above 70 mmHg (75 to 100) (Riebold, 1990; Taylor and Clarke, 1999).

Pulse pressure can be measured by direct arterial pressure (invasive) and indirect arterial pressure (noninvasive). The direct arterial catheterization is the direct arterial pressure measurement method using percutaneous inserted catheters or butterfly needles, connected to a transducer or aneroid manometer in the superficial artery. In foals, the direct arterial pressure measurement is difficult because their arteries are smaller, more fragile and more mobile than those of adult horses (Dunlop, 1994). The indirect arterial pressure measurements of foal can be done by evaluation of ultrasound blood flow or vessel wall motion detection technique. This noninvasive technique uses a pneumatic cuff placed on the tail or on the middle coccygeal artery of foal. Then, blood pressure is detected by the cuff and transmitted to a transducer (Klien, 1985; Dunlop, 1994; Nout *et al*., 2002).

Mucous membranes

Color of mucous membranes of normal horse should be pink and capillary refill time should be 1 to 2 seconds. The mucous membrane and capillary refill time give an indication of oxygenation and tissue perfusion as well as peripheral vascular tone. Pale mucous membranes and prolonged capillary refill time always occur by excessive depth of anesthesia, prolonged anesthesia, vasoconstriction affected by premedication drugs administered (e.g., xylazine, detomidine) and inadequate perfusion from low cardiac output. Brick-red (congested) mucous membranes are associated with endotoxic shock or poor gas exchange (Riebold, 1990; Taylor and Clarke, 1999; Muir and Hubbell, 2009).

Respiratory system

Respiration

Respiratory rate can be monitored by watching the movement at the chest and abdominal wall, rebreathing bag and the passage of air at the nostrils. The respiratory rate of immediate after birth foal is higher than 60 bpm (60 – 80 bpm) and declines to about 30 bpm (20 – 40 bpm) within 1 to 2 hours (Beech, 1985; Knottenbelt *et al*., 2004). Normally, the respiratory rate during anesthesia of the adult horse and the foal are usually 6 to 10 bpm and 10 to 20 bpm respectively (Riebold, 1990). Low respiratory rate or apnea can occur from some anesthetic administration (e.g. ketamine, tiletamine) and over dosage of anesthetic drug inducing excessive anesthesia depth (Muir and Hubbell, 2009).

Pulse oximetry

Pulse oximetry is a simple and noninvasive technique for measuring blood oxygen. This technique calculates, hemoglobin saturation (SaO_2) by evaluating the degree of absorbance of emitted light through tissue. The light from the Oxymeter probes is differentially absorbed by saturated and unsaturated hemoglobin (Dunlop, 1994; Hubbell, 1999; Taylor and Clarke, 1999). Oxymeter probes are always clipped on any non-pigmented area where light can be transmitted through the tissue, for example tongue, non-pigmented lips, and the nasal septum (Taylor and Clarke, 1999).

Blood gas analysis

Arterial blood gas analysis is used to determine of blood hemoglobin concentration, arterial pH, and blood gas tensions. Arterial blood gas analysis is also the standard method of evaluating adequacy of ventilation (PaO_2, $PaCO_2$), acid–base status, and pulmonary gas exchange (Riebold, 1990; Muir and Hubbell, 2009). The normal values of arterial pH values range from 7.30 to 7.45. The optimal arterial pH is important for tissue metabolism and cellular homeostasis.

The arterial blood carbon dioxide tension ($PaCO_2$) is used for assessment of the breathing condition (hypoventilation, hyperventilation). The $PaCO_2$ is an essential value for adjustment the balance between the metabolic production of carbon dioxide and its elimination by the lungs or removal of carbon dioxide. The normal range of $PaCO_2$ values of a normal horse is 37 to 49 mmHg or 40 to 60 mmHg in anesthetized horses (Table 2).

Table 2 The relationship between $PaCO_2$ values with physiological response

$PaCO_2$	**Indication**
Increases	Decrease in alveolar ventilation (Hypoventilation)
Decreases	Hyperventilation
Moderate increases (50 – 70 mmHg)	Cardiac output and tissue blood flow via vasodilatation and epinephrine release
Severe increase (> 70 – 80 mmHg)	Increases arterial blood pressures

The arterial blood oxygen tension (PaO_2) is used for determining oxygen delivery. The normal tension of PaO_2 is 89 to 115 mmHg. However the PaO_2 value of anesthetized horses is below 60 mmHg (Muir and Hubbell, 2009). Occasionally, the pH and HCO_3^- levels of the horse are decreased with normal $PaCO_2$level indicating metabolic acidosis. Muir and Hubbell (2009) proposed a guideline for evaluation of blood gas analysis as shown in Table 3.

Table 3 The relationship between acid–base and pH, $PaCO_2$ and HCO_3^- changes

	pH	**$PaCO_2$**	**HCO_3^-**
Uncompensated			
Metabolic acidosis	↓	N	↓↓
Metabolic alkalosis	↑	N	↑↑
Respiratory acidosis	↓	↑↑	N
Respiratory alkalosis	↑	↓↓	N
Compensated			
Metabolic acidosis	↓	↓	↓↓
Metabolic alkalosis	↑	↑	↑↑
Respiratory acidosis	↓	↑↑	↑
Respiratory alkalosis	↑	↓↓	↓

N = normal, ↓ = slightly decrease, ↑ = slightly increase, ↓↓ = decrease, ↑↑ = increase

The anesthetic record

The information we need to record when performing anesthesia should include patient identification, a brief surgical history and medical care, pre-anesthetic physical examination (laboratory data), and the anesthetic agents administered (type, dosage, route and time of administration). The recorded variables at regular intervals should be the heart rate, respiratory rate, systolic and diastolic blood pressure, mean arterial blood pressure, ocular reflexes, color of mucous membrane, capillary refill time, body temperature, the administration of other drugs (antibiotic, emergency drugs), the type and quantity of intravenous fluid administration and the other record such as blood gas analysis (Hubbell, 1991; Muir and Hubbell, 2009).

MATERIALS AND METHODS

Animals

Six healthy Thoroughbred-crossbred foals, five male and one female, aged range from 4 to 6 months (4.5 ± 0.5; mean ± SD) and body weight between 107 and 125 kg (118.3±7.2; mean ± SD) were used in this study. The foals were clinically healthy based complete physical examination (HR, RR, CRT, mm, lung sound, gut sound, and body temperature), complete blood count (WBC, RBC, Hb, Hct., MCV, MCH, MCHC, RDW, PLT, MPV, nRBC, Band, Seg., Lymph., Mono., Eos., Baso., PP, and BP), and blood chemistry (BUN, Creatinine, AST, GGT) for one week before the experiment. All foals were starved for 8 hours prior to each anesthesia but water and suckling were not withheld prior to anesthesia. This study used foals between these ranges of age, because if there is not an emergency anesthesia (e.g., repair of ruptured bladder, patent urachus, gastrointestinal surgery, or musculoskeletal repair) the foal with an age of more than 6 weeks does not present problems with anesthesia (1 – 6 months) of age (Dunlop, 1994).

Experimental design

In this study we used a crossover design; six foals were divided into two groups. Group 1: XZ was tiletamine – zolazepam (1 mg/kg BW: Zoletil®, Virbac Laboratories, France), and Group 2: XKD was ketamine (2.0 mg/kg BW: Calypsol, Gedeon Richter Ltd., Hungary) – diazepam (0.1 mg/kg BW: Ropam injection®, L.B.S. Laboratory Ltd., Part., Thailand). The Xylazine (1 mg/kg BW: X – zine®, L.B.S. Laboratory Ltd., Part., Thailand) was used as the sedative for both groups. Each foal was anesthetized twice for 1 week apart. For the first week, the first anesthetized 3 foals were treated with tiletamine – zolazepam (XZ), and the remained 3 foals were treated with ketamine – diazepam (XKD). For the second week, the first 3 foals were anesthetized with ketamine – diazepam (XKD) and the rested foal were treated with tiletamine – zolazepam (XZ). All six foals were randomly blind anesthetized. Both groups of anesthetic combination were administered via jugular vein injection.

Experimental procedure

All foals were anesthetized under field conditions. Before foal sedation, the mare was sedated with acepromazine maleate (0.04 mg/kg BW: Combistress, Phoenix Pharmaceuticals N.V. Antwerp, Belgium), was separated from its foal, and kept the mare at the adjacent stall. 5 minutes before the foal was sedated, an indirect blood pressure monitoring cuff (IW1, Omron Healthcare CO. Ltd., Japan) was placed at the base of the foal tail (middle coccygeal artery) for recording the systolic and diastolic blood pressure. Collection of arterial blood sample (facial arteries, transverse facial arteries, or dorsal metatarsal arteries) for blood gas analysis: pH, PaO_2, $PaCO_2$, HCO_3, TCO_2, BE, SO_2 (i - Stat® G3+ Cartridge, Portable Clinical Analyzer, Abbott Laboratories Inc., U.S.A.), HR (heart rate), RR (respiratory rate), BT (body temperature), CRT (capillary refill time), mm (mucus membrane color) were also recorded. Five minutes after sedation with xylazine, all these parameters were again recorded. Seven minutes after xylazine administration, an induction with XZ (xylazine/Zoletil: Group 1) or XDK (xylazine/diazepam and ketamine: group 2). The observers were blinded to the combination of induction drugs used in each study. During induction and recovery phase foals were observed without help for record induction and recovery scores. After induction, the foal was in lateral recumbency and an endotracheal tube, No.12, 15.6 mm. internal diameter cuffed, (KRUUSE, Denmark) was intubated. The ease of mouth opening and intubation were evaluated (Mama et al., 1996) and recorded on a 1 to 3 scale; 1 = difficult: more than three attempts for intubation; 2 = moderate: two or three attempts and 3 = easy, intubation made at the first attempt. A 18 G, 1 ¼ inch catheter (NIPRO Corporation Limited, Thailand) was inserted into the jugular vein for collection of blood samples and blood glucose analysis. A 20 G, 1 inch catheter (NIPRO Corporation Limited, Thailand) was inserted into the facial artery or transverse facial artery and/or dorsal metatarsal artery for measurement of blood gas analysis. We also collected the color of mucous membranes, capillary refill time and ocular reflex (blink, palpebral, and corneal reflex). Data were recorded at 5, 10, 15, and 20 minutes after induction via intravenous administration. After administration of anesthetic induction drugs, the following times were recorded.

The number of attempts made to sternal recumbency and standing position was also recorded.

The anesthetic record system

The record system included the anesthetic record form (see appendix, table 1), the anesthetic induction quality and recovery record (see appendix, table 2), mouth opening and intubation record and number of attempts to regain sternal recumbency and standing position (see appendix, table 3), and time table in minute (see appendix, table 4).

Measurements of blood glucose

Collection of venous blood samples were taken from the jugular vein at 5 minutes before sedation, 5 minutes after being sedated, and after induction intravenous administration at 5, 10, 15, and 20 minutes. Blood samples for glucose determination were collected into sterile evacuated tube Vacvette® 2 ml containing FX Sodium fluoride/Potassium Oxalate (greiner bio-one) and stored on ice, Plasma was extracted by centrifugation of 5 minutes at 2,500 round per minute and stored plasma at – 80 ºC until analyzed by spectophotometer method with the use of commercially available test kit (Biotech Reagent, Biotechnical Co., Ltd., Bangkok, Thailand).

Measurement of arterial blood pressure

a IW1 is Automatic Blood Pressure Monitor (Omron Healthcare CO. Ltd., Japan) uses the oscillometric method of blood pressure measurement was applied to the indirect blood pressure was determined using a blood pressure monitoring cuff placed at the base of the tail (middle coccygeal artery) (Figure 6) and the monitor detects the pulse wave vibrations in the artery and converts the oscillations into a digital reading for recorded the systolic and diastolic blood pressure.

Mean arterial blood pressure (MAP) can be calculated from the formula described below:

MAP (mmHg) = diastolic + [1/3 (systolic - diastolic)]

Diastolic = diastolic blood pressure (mmHg)
Systolic = systolic blood pressure (mmHg)

Figure 6 The picture show the measurement of arterial blood pressure by the non-invasive oscillometric technique at the head tail of the foal as well as the monitoring of the rectal body temperature (C°) by the digital thermometer.

The quality of anesthetic induction and recovery assessment

The quality of anesthetic induction and recovery score were divided in a 1 to 5 scale score as described by Mama et al., (1996): 1 = poor; 2 = fair; 3 = fairly good; 4 = good; 5 = excellent (Table 4)

Table 4 Quality of induction anesthetic and recovery score

Score	Induction	Recovery
5 (excellent)	Very smooth induction, quiet and instant lie down and lateral recumbency, good muscle relaxation no twitching after induction of drugs	Excellent; smooth to stand with minimal or no ataxia, one attempt to stand
4 (good)	Smooth induction instant lie down and lateral recumbency but head or limb twitching and movement after induction of drugs	Good; one attempt to stand, mild ataxia
3 (fairly good)	A slightly delay in time to lie down and lateral recumbency, not good muscle relaxation with muscle spasm or rigidity or limbs movement	Calm recovery; but more than one attempt to stand (2 to 3 attempts)
2 (fair)	Increased muscular activity, movement with mild signs of excitement prior, attempts to stand or any other situation during the transition from standing to lateral recumbency	Excited; several attempts to stand considerable ataxia present with or without minor injury (wound laceration)
1 (poor)	Failed to recumbency, poor muscle relaxation does not become recumbent or assumes recumbency briefly	Bad recovery; several weak attempts to stand with high risk of fetal injury

Source: Mama *et al*. (1996)

Measurement of arterial blood gas analysis

Collection of arterial blood sample (facial arteries, transverse facial arteries, or dorsal metatarsal arteries) (Figure 7, 8) was made at 5 minutes before xylazine intravenous administration, at 5 minutes after premedication with xylazine, and at 5, 10, 15 and 20 minutes after anesthetic induction. The variables for blood gas analysis were pH, PaO_2, $PaCO_2$, HCO_3^-, TCO_2, BE, SaO_2 (i - Stat® G3+ Cartridge, Portable Clinical Analyzer, Abbott Laboratories Inc., U.S.A.).

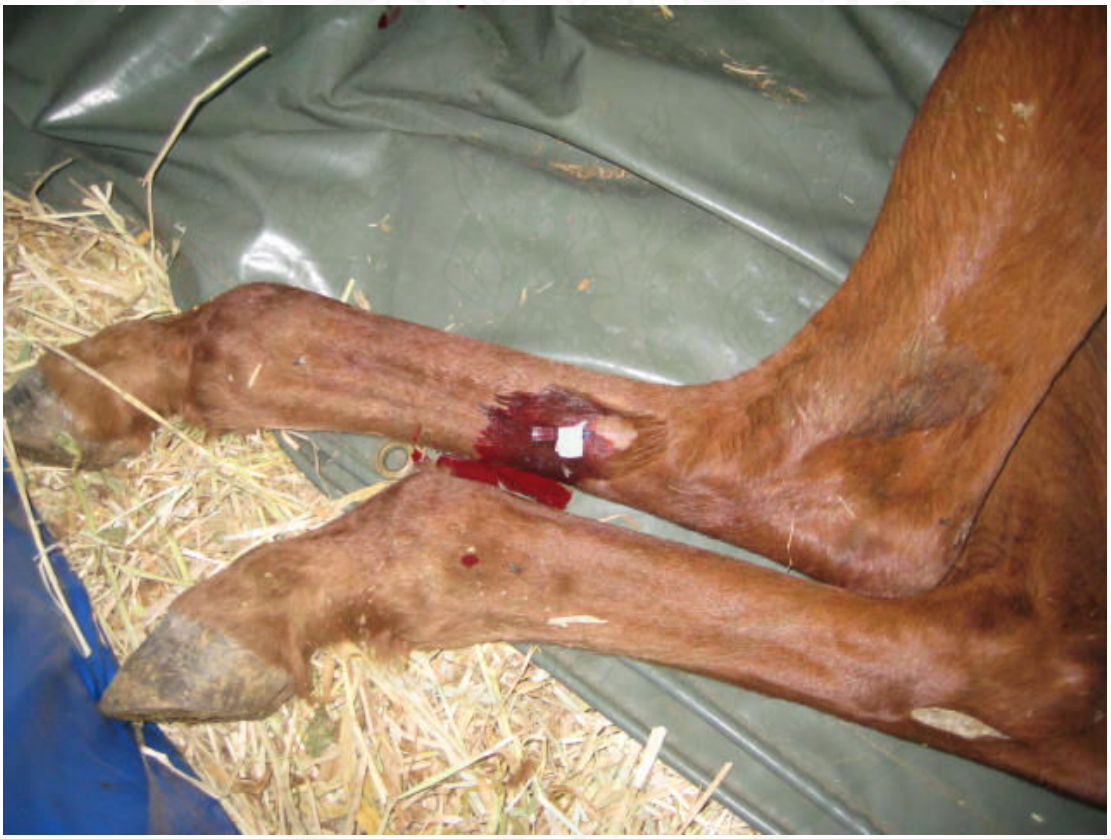

Figure 7 Catheterization of the dorsal metatarsal artery

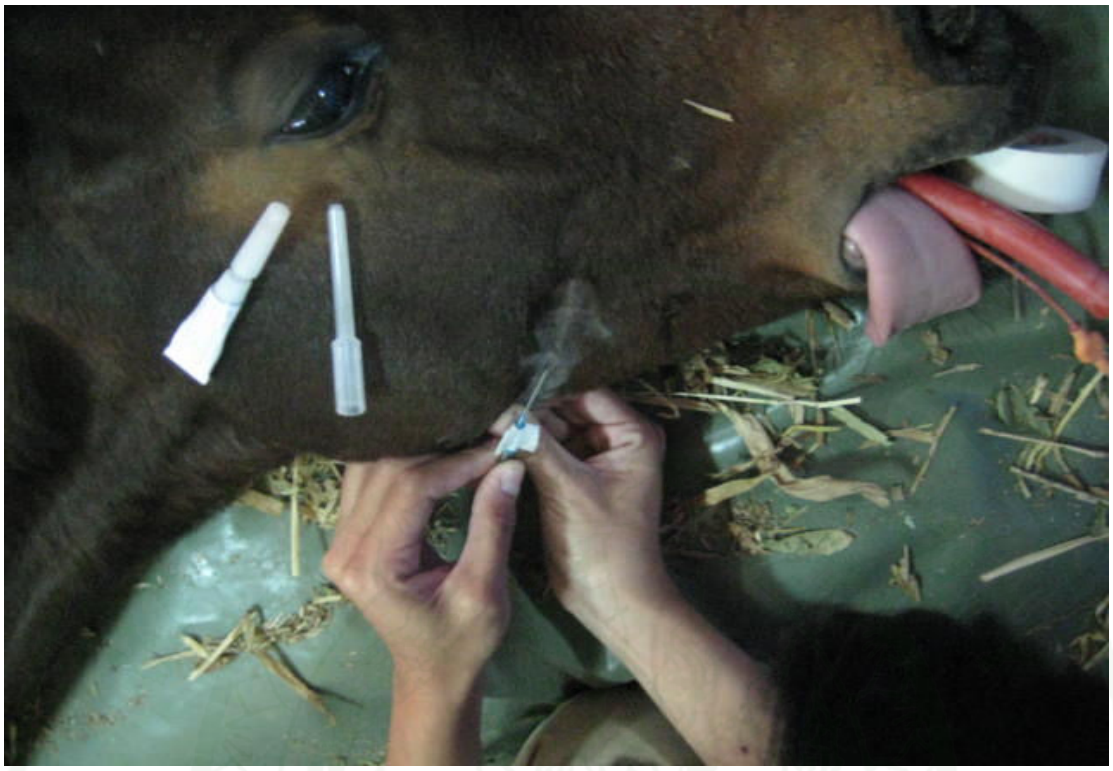

Figure 8 Catheterization of the facial artery

The quality of intubation assessment

The endotracheal tube can be passed through the mouth into the pharynx and gently manipulated into the larynx after lateral recumbency (Figure 9).

The ease of mouth opening and intubation were evaluated (Mama et al, 1996) and recorded on a 1 to 3 scale:

1 = difficult, intubation more than third attempt
2 = moderate, intubation two or three attempt and
3 = easy, intubation at first attempt

The foals were extubated when they displayed vigorous chewing and coughing or resistance to the endotracheal tube.

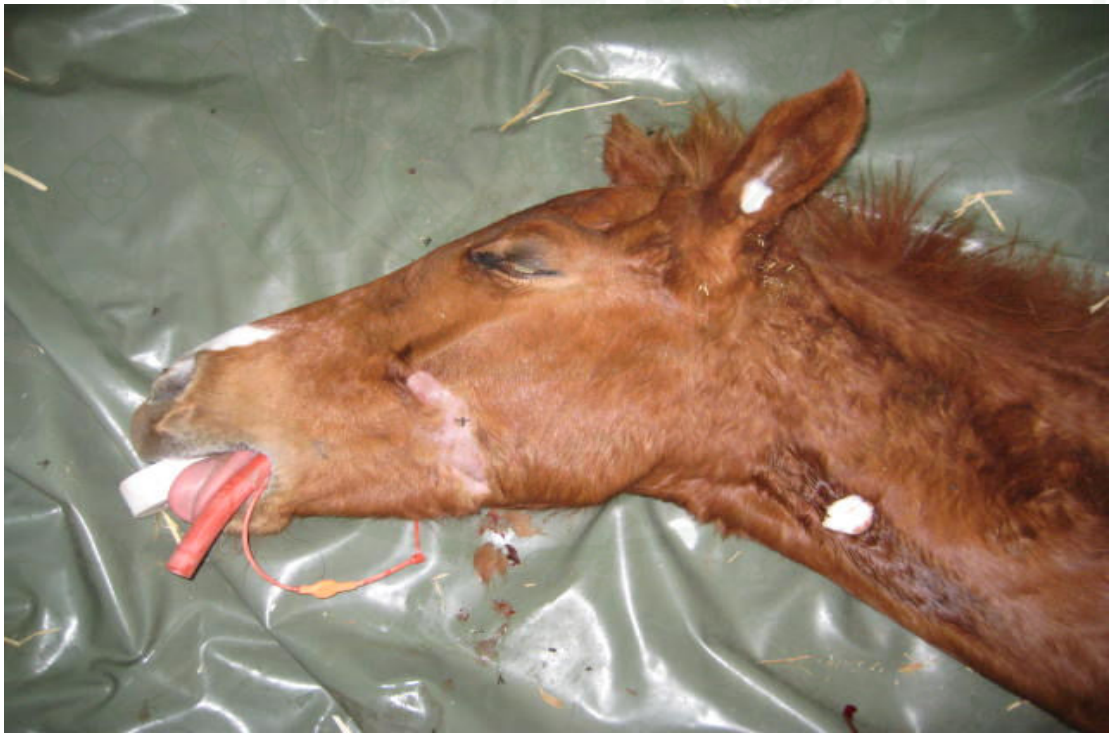

Figure 9 Orotracheal tube is inserted into the mouth and advanced into the pharynx

Measurement of attempt to sternal and standing position

The number of foal attempts to sternal recumbency and standing position were recorded at recovery period.

Time measurement

After administration of anesthetic induction drugs, the following times were recorded:

T*effect*	Time from inducing agent injection to lateral recumbency
T*intubation*	Time from inducing agent injection to loss of swallow reflex
T*swallowing*	Time from inducing agent injection to raise of swallow reflex
T*sternal*	Time from inducing agent injection to sternal recumbency
T*standing*	Time from inducing agent injection to standing
T*locomotion*	Time from standing to no ataxia on walk
T*recovery*	Time from inducing agent injection to no ataxia on movement

Statistical Analysis:

The repeated measured analysis of variance was used for evaluation the difference of blood gas values (pH, PaO_2, $PaCO_2$, HCO_3, TCO_2, Beef, SaO_2), blood pressure (systolic, diastolic and mean arterial blood pressure; MAP), HR, RR, BT and blood glucose between two groups (XZ and XKD) and time effect during the experiment (T1-T6). The differences between times after administration of anesthetic induction drugs, number of attempts to sternal recumbency and standing position, the quality of induction and recovery score, and mouth opening and intubation score were analyzed for normally and compared using Wilcoxon scores (Rank sums) test. Significant differences between drug groups and times were taken if p-value < 0.05.

Place of experiment

The study was carried out at the Veterinary Remount Department, Kanchanaburi province (Thailand) in January 2009. Mean air temperature (ºC) during study period was 24.2 ºC (the deviation of the mean air temperature is 1.4 ºC) and the relative humidity (RH) ranged from 70 – 80 %.

Duration of experiment

September, 2008 – September, 2009

RESULTS

Cardiovascular and respiratory effects

The experiment during anesthetic intravenous administration (Table 5) resulted in no statistically significant differences between the experiment groups. Xylazine caused the condition bradycardia (heart rate decrease below baseline values) within 5 minutes after intravenous administration and 5 minutes after induction in both group heart rate slightly increased. In group 1 heart rate quietly increased at 15 and 20 minutes after injection, but remained lower than base line. Group 2 heart rate was increased at 20 minutes after injection and was higher than base line (Figure 10).

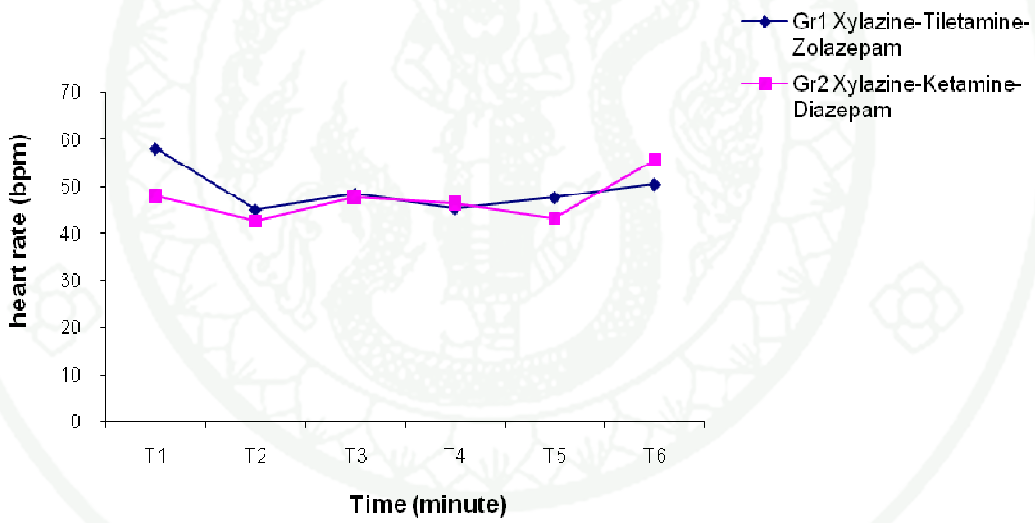

Figure 10 The mean values of HR (bpm) from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

Respiratory rate was decreased after 5 minutes xylazine administration and encourage decreased during the first 5 minutes after induction drugs administration in both group and remained slowly than base line until 20 minutes after injection (Figure 11). The time effect was found with RR for both groups (XZ and XKD) during the experiment. For both groups, the RR values of T3 and T5 were significantly lower from T1 ($p < 0.05$).

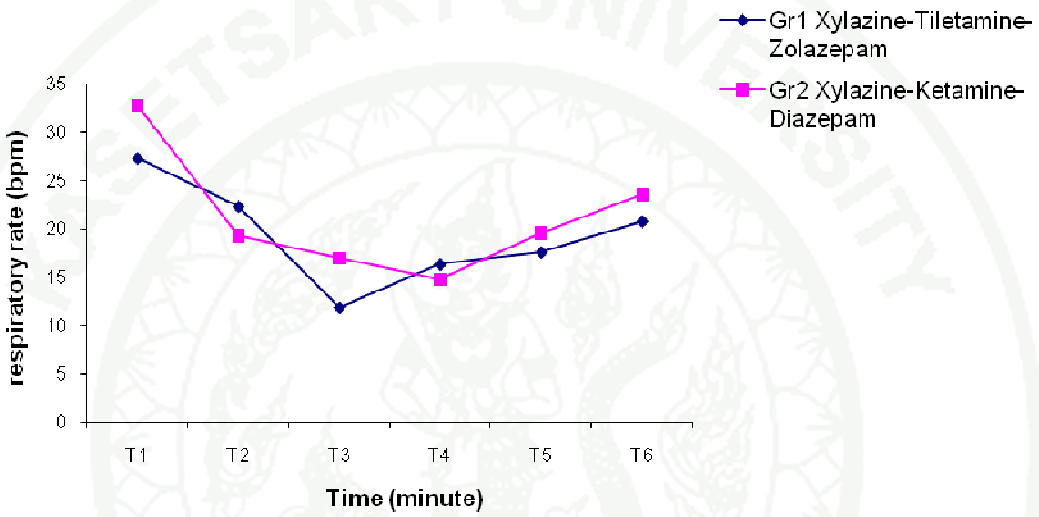

Figure 11 The mean values of RR (bpm) from the foal between the XZ and XKD group from T1 to T6..

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

Body temperature slightly increased from base line at 5 minutes after injection of xylazine and decreased during at 5, 10, 15 and 20 minutes after induction of drugs administered. Body temperature was lower than base line at 10, 15 and 20 minutes for both of the experiment groups (Figure 12).

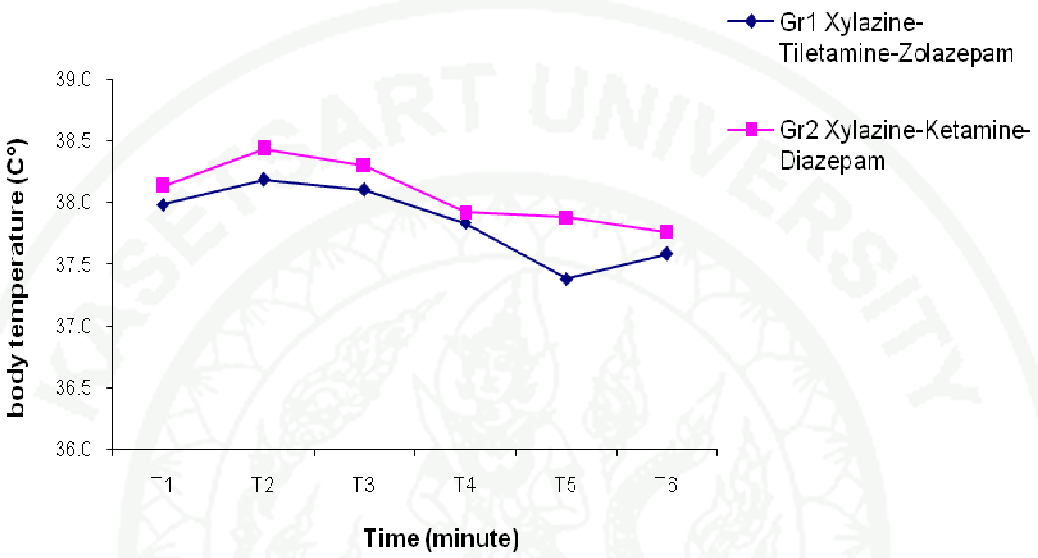

Figure 12 The mean values of BT (C°)from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

Mean arterial blood pressure (Table 5) was increased from base line at 5 minutes after xylazine was administered. In group 1, after 5 minutes induction drug injection, MAP increased, but subsequently decreased at 10, 15 and 20 minutes. In group 2, after 5, 10, 15 minutes induction drug injection, MAP decreased, but increased at 20 minutes after injection.

Systolic blood pressure (Figure 13) increased from base line at 5 minutes after injection of xylazine and still increased at 5 minutes after induction drugs administered. After that, its values went down at 10, 15 and 20 minutes. These values were higher than base line in group 1, and not in group 2, which showed this difference at 20 minutes that tend slightly increased.

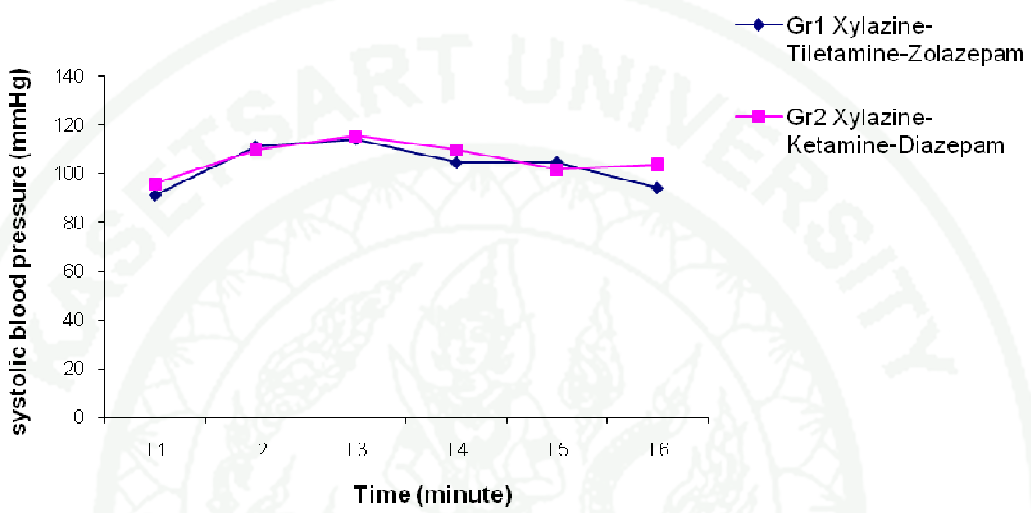

Figure 13 The mean values of systolic blood pressure (mmHg) from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

Diastolic blood pressure (Figure 14) increased from base line at 5 minutes after injection of xylazine. In group 1 diastolic blood pressure increased during the first 5 minutes after drug injection, but it decreased in group 2. It continued decreasing at 10, 15 and 20 minutes in group 1. However, in group 2 increased at 20 minutes.

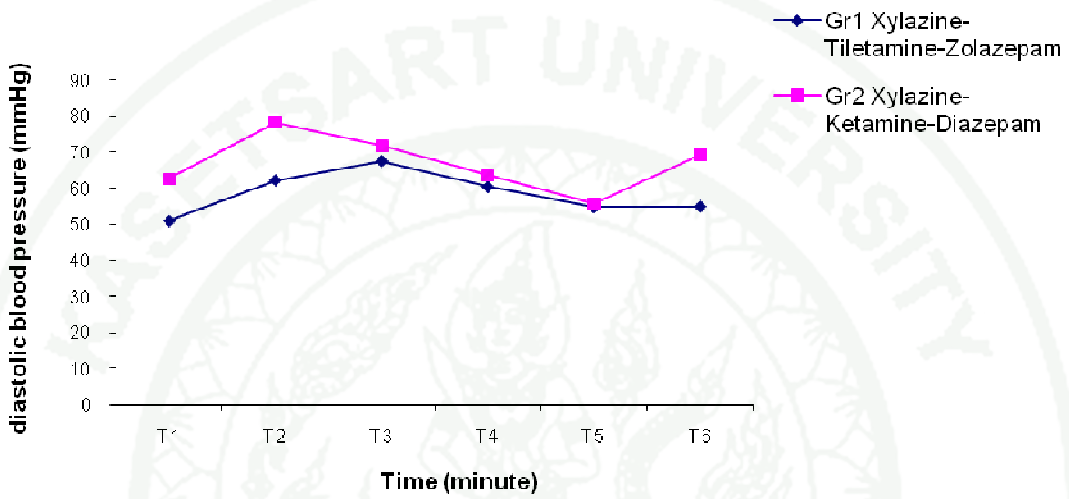

Figure 14 The mean values of diastolic blood pressure (mmHg) from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

Table 5 Cardiovascular and respiratory parameters during anesthetic administration in six older foals.

				After anesthetic drug administration			
	Group	Time 0	After xylazine	5 min	10 min	15 min	20min
Heart rate	XZ	58.0 ± 12.0	44.0 ± 8.0	48.0 ± 7.0	45.0 ± 10.0	48.0 ± 8.0[#]	50.0 ± 9.0[#]
(bpm)	XKD	48.0 ± 7.0	43.0 ± 6.0	48.0 ± 7.0	46.0 ± 5.0[*]	43.0 ± 11.0[*]	56.0 ± 9.0[*]
Resp. rate	XZ	27.0 ± 5.0	22.0 ± 4.0	12.0 ± 5.0	16.0 ± 11.0	18.0 ± 5.0[#]	21.0 ± 3.0[#]
(bpm)	XKD	33.0 ± 8.0	19.0 ± 2.0	17.0 ± 8.0	15.0 ± 6.0[*]	20.0 ± 5.0[*]	24.0 ± 8.0[*]
Temperature	XZ	38.0 ± 0.3	38.2 ± 0.3	38.1 ± 0.3	37.8 ± 0.6	37.4 ± 0.5[#]	37.6 ± 0.4[#]
(ºC)	XKD	38.1 ± 0.4	38.4 ± 0.4	38.3 ± 0.5	37.9 ± 0.5[*]	37.9 ± 0.4[*]	37.8 ± 0.3[*]
MAP	XZ	65.0 ± 4.4	78.6 ± 21.1	83.2 ± 11.5	75.2 ± 14.6	71.5 ± 10.1[#]	68.1 ± 15.0[#]
(mmHg)	XKD	73.3 ± 19.8	88.9 ± 25.2	86.3 ± 15.3	78.9 ± 16.4[*]	71.1 ± 17.9[*]	80.8 ± 24.1[*]
Systolic BP	XZ	91.3 ± 5.0	111.2 ± 22.8	114.2 ± 11.5	104.5 ± 15.6	104.8 ± 11.5[#]	94.2 ± 18.9[#]
(mmHg)	XKD	95.8 ± 14.5	109.8 ± 22.4	115.3 ± 17.5	109.6 ± 19.6[*]	101.6 ± 23.1[*]	103.6 ± 20.7[*]
Diastolic BP	XZ	51.0 ± 4.3	62.3 ± 21.5	67.7 ± 11.7	60.5 ± 14.3	54.8 ± 9.8[#]	55.0 ± 13.3[#]
(mmHg)	XKD	62.7 ± 22.9	78.3 ± 27.0	71.8 ± 15.3	63.6 ± 15.5[*]	55.8 ± 15.9[*]	69.4 ± 26.4[*]

Data are expressed as mean ± SD

XZ = xylazine–Zoletil®; XKD = xylazine–ketamine–diazepam.

n= 6 unless labeled otherwise

[*]= number of foals equals 3

[#] = number of foals equals 4

Blood gas Analysis

Analysis of blood gas parameters included arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2), base excess (BE/beef), pH, HCO_3^-, TCO_2, SaO_2 and blood glucose. None of these parameters showed a significant differences between groups (Table 6).

After xylazine intravenous administration pH values decreased from base line and they tended to be increase only during the first 5 minutes after induction drugs administration in all experiment groups. In group 1 pH increased at 10 and 15 minutes and decreased at 20 minutes after injection, but in group 2 pH values were irregular. In all groups, pH values when foals were anesthetized were lower than base line value (Figure 15).

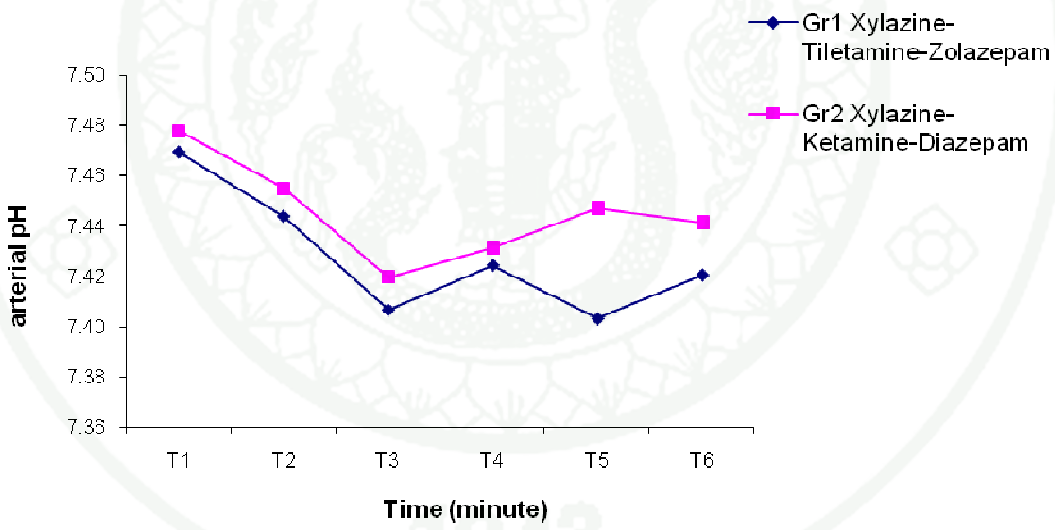

Figure 15 The mean arterial pH values from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

PaO_2 values after 5 minutes induction drugs administration PaO_2 decreased in both experiment groups. In group 1 PaO_2 increased at 10, 15 and 20 minutes after injection, but remained lower than base line value and in group 2 which values continued decreasing at 10, 15 and 20 minutes, lower than base line too (Figure 16).

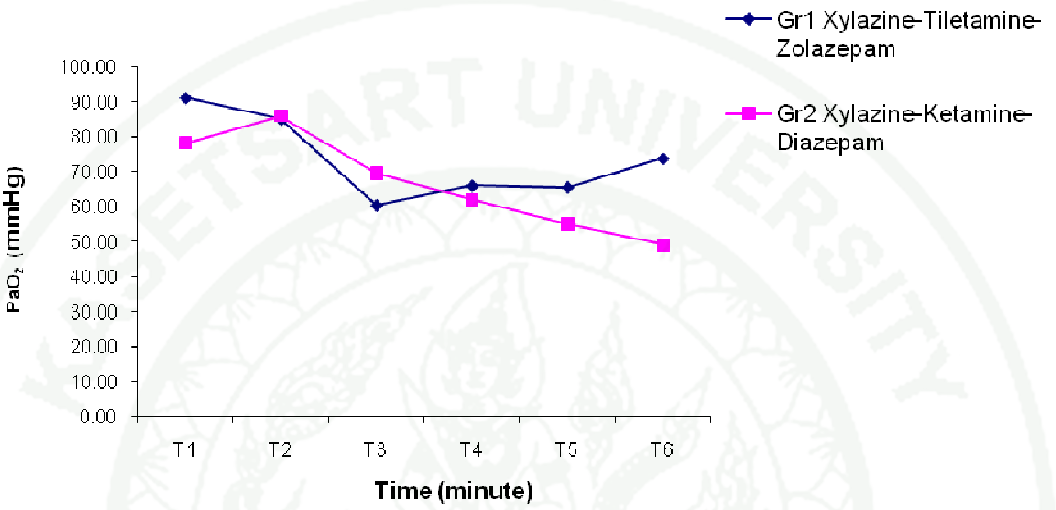

Figure 16 The mean arterial oxygen partial pressure (mmHg) from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

$PaCO_2$ values (Figure 17) increased after premedication with xylazine and subsequently increased at 5 minutes after induction. In group 1 and group 2 values were higher than base line.

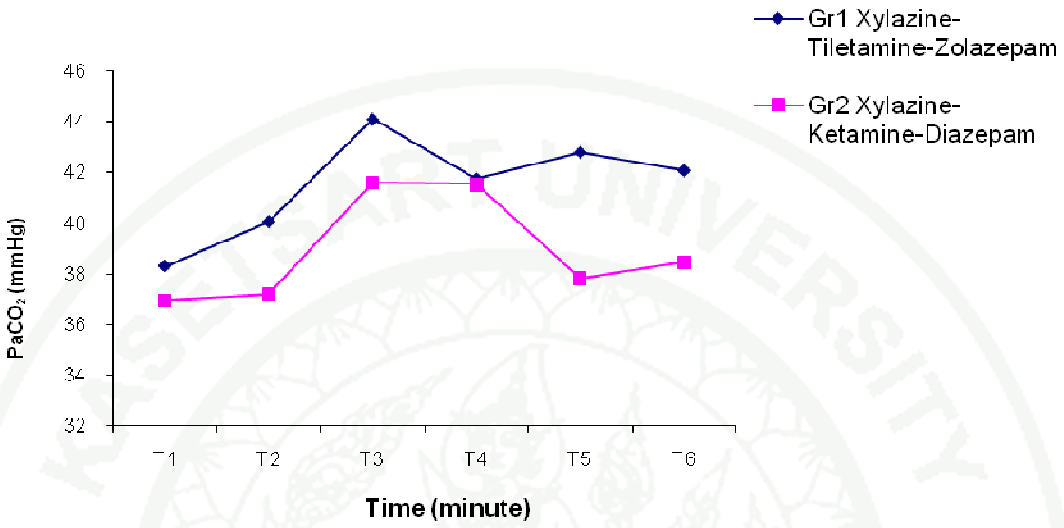

Figure 17 The mean arterial carbon dioxide partial pressure (mmHg) from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

HCO_3^- value (Figure 18) decreased after xylazine injection at 5 minutes. In group 1 and group 2, these values slightly increased from premedication at 5 minutes, but they were lower than base line value. These values decreased at 10, 15 minutes and increased at 20 minutes and were lower than base line value in both groups.

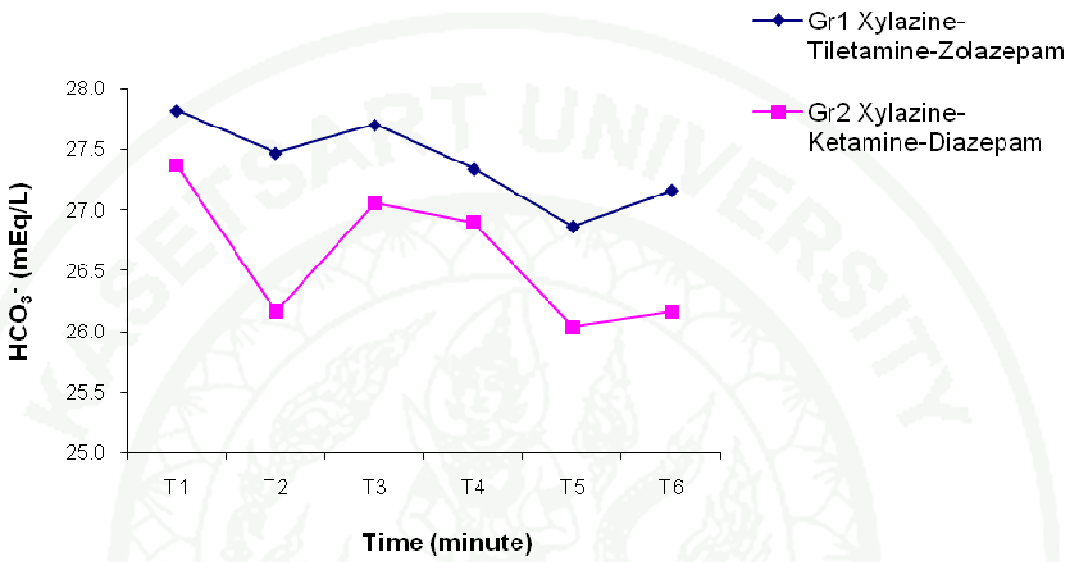

Figure 18 The mean bicarbonate (mEq/L) values from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

At 5 minutes after premedication TCO_2 value decreased (Figure 19). In group 1, TCO_2 increased at 5 minutes after induction and decreased at 10 and 15 minutes, and increased again at 20 minutes. After induction at 5 and 10 minutes TCO_2 values increased in Group 2. However, group 2 values decreased again at 15, 20 minutes. TCO_2 values when foals anesthetized were lower than awake foals in both groups.

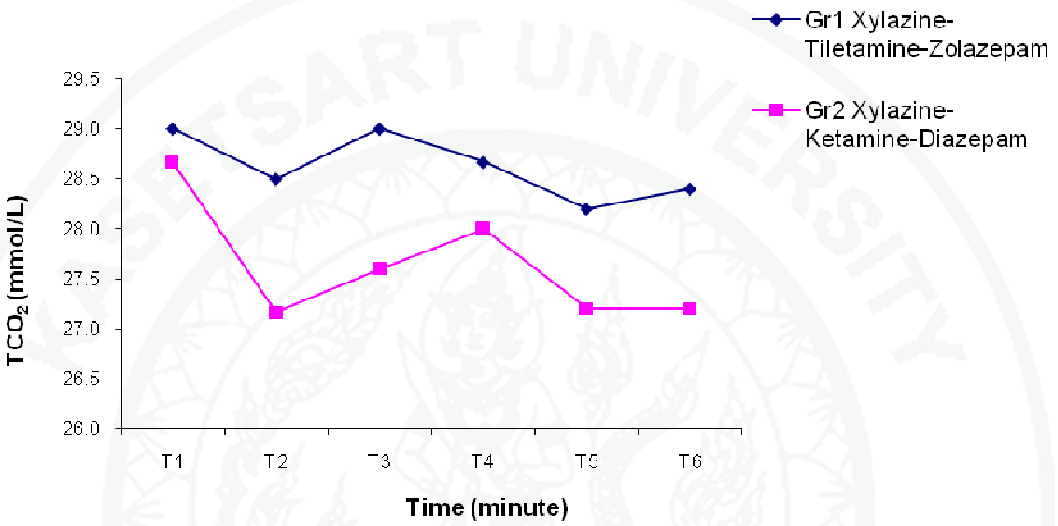

Figure 19 The mean total concentration of carbon dioxide (mmol/L) from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

Base excess after xylazine administration decreased (Figure 20). Group 1 Beef decreased from base line and xylazine at 5, 10, 15 and slightly increased again at 20 minutes. Values decreased in group 2 from base line, but slightly increased at 5 minutes after induction and turned to decreased at 10, 15 and 20 minutes. Beef values in foals anesthetized were lower than in awake foals.

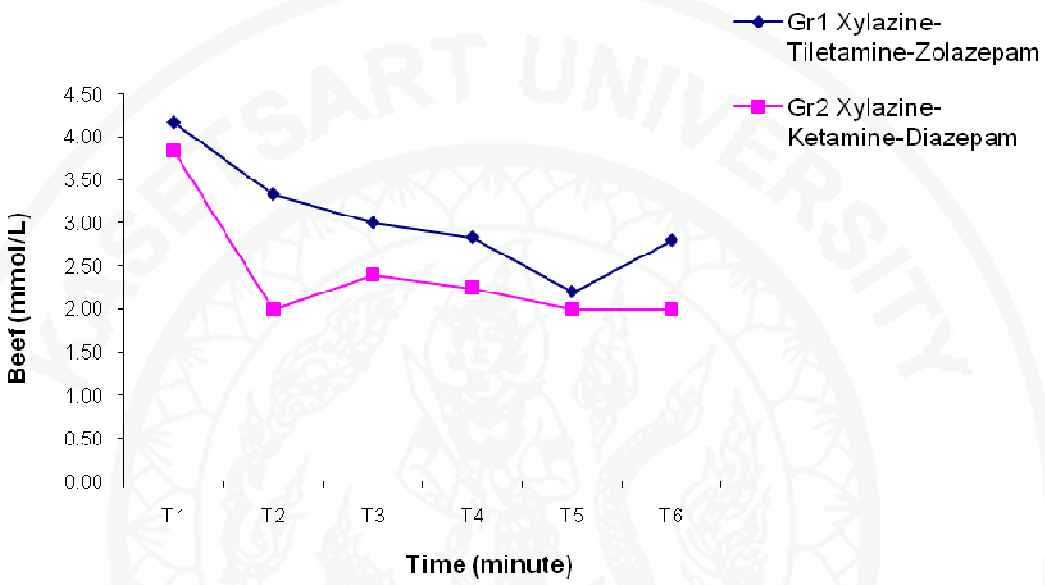

Figure 20 The mean base excess values (mmol/L) from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

SaO_2 values in group 1 decreased at 5 minutes after induction and slightly increased at 10 minutes and maintained this increment until at 20 minutes. All SaO_2 values decreased in group 2 after 5, 10, 15 and 20 minutes after induction (Figure 21).

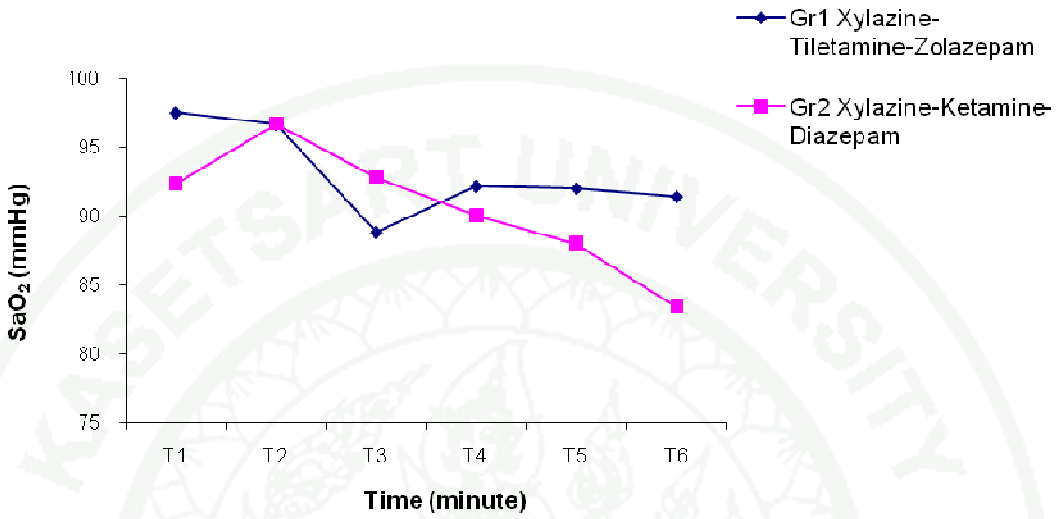

Figure 21 The mean SaO_2 values (mmHg) from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

After premedication with xylazine blood glucose levels slightly decreased, but increased again at 5 and 10 minutes after induction in group 1. In group 2, blood glucose levels decreased at 20 minutes after that. In both groups blood glucose levels were higher than base line value (Figure 22). The time effect was found for blood glucose concentration for both groups (XZ and XKD). The blood glucose concentration of both groups at T4 was significantly higher than that of T1 ($p<0.05$).

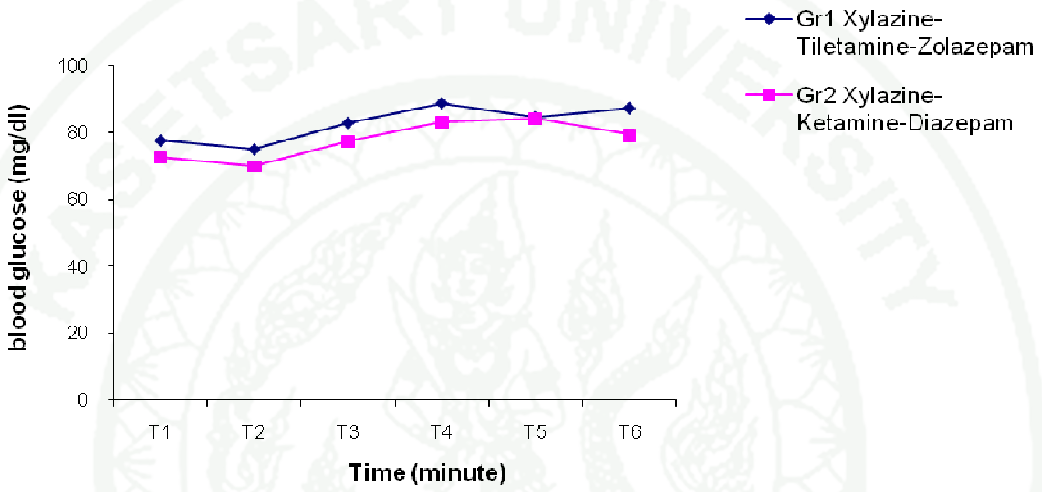

Figure 22 The mean blood glucose concentration (mg/dl) from the foal between the XZ and XKD group from T1 to T6.

Time: T1 = 5 minutes before xylazine administration (base line: Time 0), T2 = 5 minutes after xylazine administration, T3 = 5 minutes after induction drugs administration, T4 = 10 minutes after induction drugs administration, T5 = 15 minutes after induction drugs administration, T6 = 20 minutes after induction drugs administration.

Table 6 Blood gas analysis (pH, PaO_2, $PaCO_2$, HCO_3, TCO_2, BE, sO_2) and blood glucose concentration

	Group	Time 0	After xylazine	After anesthetic drugs administration 5 min	10 min	15 min	20 min
pH	XZ	7.47 ± 0.02	7.44 ± 0.02	7.41 ± 0.04†	7.43 ± 0.03	7.40 ± 0.02†	7.42 ± 0.02†
	XKD	7.48 ± 0.03	7.45 ± 0.02	7.42 ± 0.04†	7.43 ± 0.05#	7.45 ± 0.03†	7.44 ± 0.04†
PaO_2(mmHg)	XZ	91.2 ± 9.8	85.0 ± 8.3	60.4 ± 11.8†	66.0 ± 11.9	65.6 ± 11.2†	73.8 ± 27.1†
	XKD	78.2 ± 24.0	85.8 ± 8.9	69.6 ± 14.5†	62.0 ± 14.2#	55.0 ± 11.7†	49.2 ± 13.0†
$PaCO_2$(mmHg)	XZ	38.3 ± 3.2	40.1 ± 1.9	44.1 ± 3.7†	41.8 ± 4.0	42.8 ± 2.6†	42.1 ± 3.1†
	XKD	36.9 ± 3.7	37.2 ± 3.4	41.6 ± 4.2†	41.5 ± 5.1#	37.8 ± 5.6†	38.4 ± 5.1†
HCO_3(mmol/L)	XZ	27.8 ± 2.2	27.5 ± 1.9	27.7 ± 1.9†	27.3 ± 2.1	26.9 ± 1.9†	27.2 ± 1.9†
	XKD	26.7 ± 3.2	25.9 ± 2.7	26.8 ± 2.8†	27.2 ± 3.1#	25.8 ± 3.6†	25.9 ± 3.3†
TCO_2(mmol/L)	XZ	29.0 ± 2.4	28.5 ± 1.9	29.0 ± 1.9†	28.7 ± 2.1	28.2 ± 1.9†	28.4 ± 1.9†
	XKD	28.0 ± 3.5	27.0 ± 2.8	27.2 ± 3.2†	28.3 ± 2.9#	26.8 ± 3.8†	27.0 ± 3.4†
BE(mmol/L)	XZ	4.2 ± 2.3	3.3 ± 2.2	3.0 ± 2.4†	2.8 ± 2.4	2.2 ± 2.2†	2.8 ± 2.3†
	XKD	3.8 ± 2.6	2.0 ± 2.8	2.4 ± 2.9†	2.3 ± 3.8#	2.0 ± 3.4†	2.0 ± 3.5†
sO_2(%)	XZ	97.5 ± 0.8	96.7 ± 1.2	88.8 ± 7.7†	92.2 ± 5.6	92.0 ± 4.1†	91.4 ± 9.6†
	XKD	97.3 ± 0.8	96.5 ± 0.8	93.4 ± 4.9†	90.0 ± 7.7#	89.2 ± 6.6†	85.0 ± 10.0†
Glucose(mg/ml)	XZ	77.6 ± 7.1	74.9 ± 5.2	82.8 ± 7.95	88.7 ± 6.7	84.6 ± 6.3	87.2 ± 8.3
	XKD	72.4 ± 13.6	69.7 ± 9.9	77.3 ± 12.4	83.0 ± 11.9	84.1 ± 8.6	79.2 ± 2.5

Data are expressed as a mean ± SD
XZ = xylazine–Zoletil®; XKD = xylazine–ketamine–diazepam
n=6 unless labeled otherwise
† = number of foal is equally 5
# = number of foal is equally

Quality of anesthesia

In group 1, the quality of induction score between 3 to 4 by 2 foals were grade 3 and 4 foals were grade 4 (3.7 ± 0.5) and group 2 have 1 foal was grade 1 and another foals were grade 4 of induction score (3.8 ± 1.2) (Table 7).

Quality of recovery score has an average of grade mean ± SD was 3.2 ±1.5 (Table 11) in group 1. In group 2 the mean was 2, 1 foal was grade 3, 2 foals were grade 4 and 2 foals were grade 5 (3.8 ± 1.2).

Mouth opening and intubation in group 1 have 4 foals were grade 2 and 2 foals grade 3 (2.3±0.5) and group 2

Table 7 The number of foal in each score level and the mean score (1-5 level) of the : quality (for induction, recovery, mouth opening and intubation) and number of attempts (to sternal recumbency and standing position) (n=6)

	XZ group						XKD group					
Score level / mean	1	2	3	4	5	**mean**	1	2	3	4	5	**mean**
Quality												
Induction	0	0	2	4	0	**3.7**	0	0	1	5	0	**3.8**
Recovery	1	1	1	2	1	**3.2**	0	1	1	2	2	**3.8**
Mouth opening and intubation	0	4	2	0	0	**2.3**	2	2	2	0	0	**2.0**
Number of attempts												
Sternal recumbency	5	1	0	0	0	**1.2**	2	1	1	0	2	**2.8**
Standing position	1	5	0	0	0	**1.8**	3	3	0	0	0	**1.5**

XZ = xylazine–Zoletil®; XKD = xylazine–ketamine–diazepam

Duration of anesthetic effects

Analysis of the time from induction to recovery showed no difference between Group. The mean time (± SD) duration of the T*effect* or to knockdown was less than 1 minute in group 1 and 1.17 ± 0.41 in group 2 (Table 8). The time from induction to loss of the swallowing reflex and intubation, to sternal and standing position in group 1 was faster than group 2. The time from induction to swallowing reflex, the time from stood up to no evidence of ataxia on walking, and the time from induction to no evidence of ataxia on locomotion in group 1 was longer than group 2.

Table 8 The duration of time parameters (mean±SD) : T*effect* , T*intubation*, T*swallowing*, T*sternal*, T*standing*, T*locomotion* and T*recovery* in six foals pre-medicated with xylazine (1.1 mg/kg) and anesthetized with Zoletil®(1 mg/kg) or diazepam (0.1 mg/kg) and ketamine (2 mg/kg)

Time (min)	XZ group	XKD group
T*effect*	1.0 ± 0.0	1.2 ± 0.4
T*intubation*	1.0 ± 0.5	2.0 ± 0.9
T*swallowing*	21.2 ± 7.6	19.2 ± 7.1
T*sternal*	24.2 ± 7.1	24.8 ± 8.6
T*standing*	25.2 ± 7.1	26.3 ± 9.0
T*locomotion*	17.3 ± 6.4	15.8 ± 6.2
T*recovery*	42.3 ± 10.5	42.2 ± 8.4

XZ = xylazine–Zoletil®; XKD = xylazine–ketamine–diazepam

DISCUSSION

At 5 minutes before xylazine administration (base line: T1) HR, RR, and blood glucose concentration were slightly increased. This is probably due to the foals were excited, fear, or stress form restraint during the data record. The arterial blood pressure was slightly below form normal level which, in this experiment, may came from the movement of the foal or using of indirect blood pressure measurement which were consistently lower of systolic, diastolic, and mean than direct measurement (Nout *et al*., 2002, and Hubbell and Muir, 2009).

After administration of xylazine, all studied foals had bradycardia and depressed respiratory system. Body temperature of foals slightly increased from base line because xylazine contains alpha-2 adrenoceptors agonist. The mechanism of action is the activation of central alpha-2 receptors. The alpha-2 receptors are located both presynaptically and postsynaptically in the peripheral and central nervous system; the presynaptic alpha-2 receptors are actions that generally have an inhibitory on the release of transmitter from the synaptic nerve endings i.e. norepinephrine, dopamine, serotonin, acetylcholine (Benson and Thurmon, 1990; Aubin and Mama, 2002) and the sympathetic block and vagal stimulation are involved in baroreceptor activation, peripheral vasoconstriction, bradycardia, sinu-arterial arrest, and first and second degree artrioventricular blocks (Garcia *et al*., 2002; Aubin and Mama, 2002; Frias *et al*., 2003; Marntell, 2004). These resulted of bradycardia, arrhythmias and blood pressure are decreased, but the mean arterial pressure did not drop below 60 mmHg (Tranquilli and Thurmon, 1990; Frias *et al*., 2003). The decreasing in cardiac output and initial hypertension followed by prolonged hypotension increased pulmonary pressure but body temperature was reduced (VaaLa,1985; Tranquilli and Thurmon, 1990; Hubbell, 1999; Aubin and Mama, 2002; Marntell, 2004). More effectiveness in the muscle hypertonicity and excitement associated with dissociative drugs are often used to induce anesthesia (Aubin and Mama, 2002). The Colorado State University (CSU) studied 8 foals by using a xylazine dose 0.3 mg/kg IV administration and found that it created a reduction of heart rate and cardiac output, as well as oxygen tissue perfusion (Dunlop, 1994).

During induction anesthesia by Zoletil® or ketamine and diazepam in our study, there was not a statistically significant difference in any of the measured variables. No differences are because the basic pharmacology of tiletamine is similarly to that of ketamine and zolazepam are benzodiazepine tranquilizers with central muscle relaxant and anticonvulsant activity similarly to diazepam. The tiletamine effects on cardiovascular are increased heart rate and cardiac output, decreased arterial blood pressure, systemic vascular resistance and myocardial contractility but do not affect central venous and pulmonary vascular pressure (Benson and Thurmon, 1990). Both groups induced hypoventilation resulting in increased in $PaCO_2$, but decreased PaO_2, arterial pH, and HCO_3^-. This is similar to a previous study in horses (Hubbell *et al*., 1989). Base excess and SaO_2 concentration were found slightly decreased from base line. However if there is longer duration of anesthesia the foals may develop hypoxemia, hypercapnia, or acidosis.

Blood glucose concentration was found slightly increased from base line but the concentration level was within normal range. This is probably the effect of xylazine which can stimulate the α_2- adrenoreceptors locating on pancreatic β-cell, resulting in inhibition of insulin secretion. The consequences are the decreasing of insulin and increasing glucose concentration in serum (Muir, 2009).

The mouth opening and orotracheal tube intubation or jaw tone relaxation in this study remained quite relaxation and easy for intubation as previously reported (Short *et al*., 1989).

The quality of the induction anesthesia using xylazine for sedation in both groups were smooth with excellent muscle relaxation similarly to previously report (Matthews *et al.,* 1991). However, the quality of the recovery period in both groups were vary, score scale form 1 – 5, which may came from the side effect of dissociative agent, ketamine or tiletamine. Basically the dissociative agent can cause excitement or delirium during the recovery phase. Subsequently, the foals were stimulated via sympathetic activation during the recovery phase under subconscious form loud noise, light, fear, stress, and mare (Muir, 2009).

In this study XZ group has longer duration of T*effect* to T*swollow* (21.2 ± 7.6 min.) than that of XKD group (19.2 ± 7.1 min.) which is similar to the previous studies (Benson and Thurmon, 1990; Aubin and Mama, 2002; Marntell *et al*., 2006; Staffieri and Driessen, 2007) demonstrating that the tiletamine has a longer duration of action, greater analgesia effect, and muscle relaxation than ketamine. Normally, horses remain in lateral recumbency for an average 45 minutes after finishing anesthesia or roll to sternal recumbency in 30 to 39 minutes and stood up within 32 to 45 minutes, and the duration of anesthesia is related to the dose of Zoletil® (Benson and Thurmon, 1990).

Ketamine inhibits gamma–aminobutyric acid [GABA], and also may block serotonin, norepinephrin, and dopamine in the CNS by interfering and interacting with several centrally acting neurotransmitters, This can cause an increase of serotonin and dopamine concentration in the brain, which produces excitement and increase of motor activity in horses and probably poor muscle relaxation or retention of muscle tonus during the induction phase (Muir, 1991; Staffieri and Driessen, 2007). Therefore, the relaxation of the jaw muscle is poor, making difficult to open the mouth for intubation (Staffieri and Driessen, 2007). Ketamine stimulates sympathomimatic effects on the cardiovascular system including increased heart rate, myocardial contractility, cardiac output, mean arterial pressure, pulmonary artery pressure and central venous pressure (Benson and Thurmon, 1990). Ketamine is also a sympathetic stimulation and counteracts some of vagotonic effects of the alpha-2 adrenoceptor and a minimal effect of respiratory depression inducing an apneutic respiratory pattern with mild hypoventilation characterized by hypoxemia and mild hypercapnia when the horse breathes room air (Benson and Thurmon, 1990; Bettschart-Wolfensberger and Larenza, 2007). Diazepam is the centrally acting muscle relaxant. Benzodiazepine is the most commonly used in veterinary practice for treated seizures and is given combination with dissociative anesthetics and sedative analgesics to improve the quality of anesthesia and enhance muscle relaxation for reducing the degree of tonic–clonic twitching but duration and analgesia are often not increased for short–term anesthesia (Benson and Thurmon, 1990; Muir and Hubbell, 1991; Marntell, 2004; Staffieri and Driessen, 2007). The mechanism of action of diazepam is depression at the subcortical levels (primarily limbic, thalamic and

hypothalamic) of the CNS. Benzodiazepine specific receptor sites have been located within the CNS, these receptors potentiate the action of GABA activity which is generally an inhibitory neurotransmitter of the brain, thus producing the anxiolytic, sedative, skeletal muscle relaxant, and anticonvulsant effects (Bettschart-Wolfensberger and Larenza, 2007). The effects of producing good muscle relaxation are may be central in origin although some of this action is attributable to direct activity at neuromuscular junction (Hubbell, 1999). Garcia (2002) concluded that used the anxiolytics in foals produced a very good sedative effect and muscle relaxation.

CONCLUSION

This study showed no significantly difference of all parameters between XZ group and XKD group. In all drug combinations, we observed a produced relatively safe anesthesia of varying duration in all six foals. Therefore, Zoletil® similarly effects of Ketamine and Diazepam combination, could be used as the safe field anesthetic for induction in the 4-6 month old foal.

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APPENDIX

Appendix Table A1 Anesthesia record

Case No._____ Date of Admission _____
Foal's Name_____ Mare's Name _____
Date of Birth _____ Breed _____ Sex _____
Bodyweight of foal: _____kg

Sedation/Pre-medication:	Xylazine	Dose	1.0mg/kgBW	Total	_____ml	Time_____
Induction:	Zoletil	Dose	1.0mg/kgBW	Total	_____ml	Time_____
	Ketamine	Dose	2.0 mg/kgBW	Total	_____ml	Time_____
	Diazepam	Dose	0.1mg/kgBW	Total	_____ml	Time_____

	Time	HR bpm	RR bpm	BT ℃	CRT Sec	MM color	Nyst. reflex	Blink reflex	Palpeb. reflex	Cor. reflex	BP mmHg	Bl.glu mg/dl	PH	Pa CO_2	PO_2	Be ef	HC O_3	TC O_2	Sa O_2
Xylazine (X-5)																			
Xylazine (X+5)																			
Induction (I+5)																			
Induction (I+10)																			
Induction (I+15)																			
Induction (I+20)																			
Induction score		Recovery score				No. sternal			No. standing			mount opening & intubation							

Appendix Table A2 Anesthetic induction quality and recovery record

Case No.	Score induction					Score recovery				
	1	2	3	4	5	1	2	3	4	5
N1										
N2										
N3										
N4										
N5										
N6										
N7										
N8										
N9										
N10										
N11										
N12										

SCORE: 1 = poor 2 = marginal 3 = fair 4 = good 5 = excellent

Appendix Table A3 Mount opening and intubation record and number of attempts to regain sternal recumbency and standing position

Case No.	Mount opening & intubation Score			No. of attempts									
				Sternal recumbency					Standing position				
	1	2	3	1	2	3	4	5	1	2	3	4	5
N1													
N2													
N3													
N4													
N5													
N6													
N7													
N8													
N9													
N10													
N11													
N12													

SCORE: 1 = difficult, intubation accomplished after third attempt
2 = moderate, intubation accomplished at second or third attempt
3 = easy, intubation accomplished at first attempt

Appendix Table A4 Time table (in minutes)

Time	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11	N12
T*effect*												
T*intubation*												
T*swallowing*												
T*sternal*												
T*standing*												
T*locomotion*												
T*recovery*												

T*effect* induction – lateral recumbency
T*intubation* induction – loss of the swallowing reflex, intubation
T*swallowing* induction – swallowing reflex
T*sternal* induction – reached sternal recumbency
T*standing* induction – reached the standing position
T*locomotion* stood up – no evidence of ataxia on walking
T*recovery* induction – no evidence of ataxia on locomotion

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