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# The Philippine Journal of Veterinary Medicine

**Volume 58** **No. 1** **January – July 2021**

## CONTENTS

**Original Articles**

## Research Notes



## Case Report

**ORIGINAL ARTICLE**

# COMPARISON OF TILETAMINE-ZOLAZEPAM-XYLAZINE AND KETAMINE-XYLAZINE ANESTHESIA IN PHILIPPINE NATIVE GOATS UNDERGOING RUMENOTOMY

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## ABSTRACT

**Twelve Philippine native goats were used to compare two anesthetic combinations for rumenotomy. These were randomly assigned into treatment groups: TZX (3.5 mg/kg tiletamine – zolazepam + 1 mg/kg xylazine) and KX (10 mg/kg ketamine with 1 mg/kg xylazine). Vital signs, $SpO_2$, reflexes, induction time to recovery, serum cortisol levels, and ECG characteristics were monitored and compared. TZX had significantly longer duration of anesthesia, standing recovery time, and higher mean heart rate (MHR) at 45 minutes after induction. On the other hand, KX had significantly higher $SpO_2$ level at 30 minutes, lower cortisol during induction and after 30 minutes as well as shorter induction to sternal recovery time. There were no significant differences seen in temperature and respiratory rates at different time intervals, cortisol levels 30 minutes after recovery, induction until standing recovery time, mean time from obliteration to return of reflexes, and flank pain. In both groups, the common ECG abnormalities seen were atrial fibrillation, atrial flutter, and ventricular premature contractions. The KX combination produced better analgesia and maintained better oxygenation while TZX had a longer duration of anesthesia. Hence, TZX can be considered as an alternative anesthetic combination for long surgical procedures in goats.**

**Keywords:** *anesthesia, ketamine–xylazine, Philippine native goats, rumenotomy, tiletamine–zolazepam–xylazine*

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## INTRODUCTION

The use of single anesthetic agents usually require larger doses to maintain anesthesia resulting to more adverse effects (Lin and Walz, 2014). The practice of balanced anesthesia therefore makes use of a combination of two or more anesthetic agents to reduce the dose needed to induce anesthesia and minimize the adverse reactions associated with them. Ketamine, a commonly used dissociative anesthetic agent, provides analgesia from antagonism of neuro-muscular depolarizing agent (NMDA) receptors making it an anesthetic of choice for surgical procedures. However, it provides poor muscle relaxation thus, is often combined with other anesthetic drugs. Xylazine, an α–2 agonist sedative, as well as an anesthetic adjunct, is usually combined with ketamine for restraint to decrease the anesthetic requirements and produce a longer effect with additional analgesia (Grimm *et al.*, 2017). The combination of these anesthetics is commonly used in ruminant surgery (Lin and Walz, 2014). However, ruminants are up to 10 times more sensitive to the effects of xylazine compared to other species (Valverde and Doherty, 2008) thus, leading to cardiovascular and respiratory depression, rumen atony with bloat, hyperglycemia with resultant diuresis, and abortions in late gestation (Benson and Thurmon, 1986 ).

Tiletamine – zolazepam, a dissociative anesthetic, is the most locally available and used anesthetic agent in veterinary practice in the Philippines. The combination of tiletamine and

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and zolazepam have been shown to produce better muscle relaxation, analgesia, and duration of action than ketamine (Lin and Walz, 2014).

Goats are predisposed to foreign body ingestion from grazing in the pasture. Rumenotomy can be used to manage acute bloat (Das and Behera, 2011) and ruminal impaction (Dharmaceelan *et al*., 2017) in goats. Surgery triggers stress response that affects the vital signs such as the heart rate, respiratory rate, and temperature. This activates the autonomic nervous system to secrete cortisol (Desborough, 2000). Analgesia is important to prevent the development of hypersensitization during surgery and results to reduced post–operative pain (Clarke *et al.*, 2014). Goats have a low tolerance to pain even with minor procedures thus, anesthesia with good analgesic properties should be administered to them to prevent shock during any surgical procedure (Hendrickson and Baird, 2013).

There is limited access to ketamine in the Philippines as it has been classified as a Schedule II drug under the Philippine Comprehensive Dangerous Drugs Act of 2002. Hence, if gas anesthesia is not available, the use of an alternative anesthetic combination for animals undergoing long surgical procedure is being considered. This study was made to compare tiletamine – zolazepam – xylazine and ketamine – xylazine anesthesia in Philippine native goats undergoing rumenotomy through vital signs, $SpO_2$ level, reflexes, induction time to recovery, serum cortisol levels, and ECG abnormalities.

## MATERIALS AND METHODS

Twelve 1 – 2 year – old female Philippine native goats weighing 6.7 – 12.7 kg with a mean body condition score (BCS) of 2.5/5 were used in this study. The procedures were previously approved by the Institutional Animal Care and Use Committee (IACUC) of the College of Veterinary Medicine, University of the Philippines Los Baños (Protocol No. 2015-0071). They were randomly housed in pairs and acclimatized for two weeks. Vitamins ADE and ivermectin were given prior to the onset of the study. The goats were randomly assigned to two groups: TZX (tiletamine – zolazepam 50 mg/mL at 3.5 mg/kg – optimal dose acquired from Abalos *et al*. (2016) mixed with 2% xylazine at 0.1mg/kg) and KX (ketamine 100 mg/mL at 10 mg/kg dose combined with xylazine at 0.1 mg/kg).

Complete blood count was done to ensure that the animals were fit for surgery and fasted for 24 hours. The baseline values for vital signs and 5 ml blood for serum cortisol were obtained prior to surgery. Half of the computed bolus anesthesia was administered rapidly with the rest given slow IV via the external jugular vein using a pre–placed IV catheter.

Standard rumenotomy procedure was done as described by Hendrickson and Baird (2013) with the rumen left open for five minutes prior to closure to simulate exploration time of the rumen in an actual rumenotomy.

The vital signs (heart rate, respiratory rate, and rectal temperature), $SpO_2$, ECG and reflexes (palpebral, pupillary, corneal, swallowing, pedal and anal reflexes, flank pain, and leg tremors) were assessed every 15 minutes from the start of surgery until the goat reached standing recovery. A patient monitor (SurgiVet® V34041, Smiths Medical 5200 Upper Metro Place, Suite 200 Dublin, OH 43017 U.S.A.) was used to obtain the heart rate, temperature, and $SpO_2$. The respiratory rate and the reflexes were manually monitored. A 6 – lead ECG was recorded using an ECG machine (ECG Machine Single Channel ECG2301G, China).

Intraoperative and post–operative stress were assessed using cortisol assay with 5 ml of blood collected via the IV catheter 30 minutes before anesthetic induction, immediately after induction, 30 minutes after induction, and 30 minutes after standing recovery using an evacuated serum (non–anticoagulated) tube. The blood was allowed to clot prior to centrifugation for collection of serum which was stored in a freezer for a maximum of 5 days before being sent to a diagnostic laboratory where ELISA test for serum cortisol levels were performed.

The results for vital signs, reflexes, $SpO_2$, and cortisol level were analyzed using the unpaired Student's T–test to compare groups. ECG abnormalities were analyzed using Chi–square test. The statistical analysis used had 95% level of confidence.

## RESULTS AND DISCUSSION

All the 12 goats used in the study were adequately anesthetized, rumenotomy was successful, and recovery was uneventful. Mean heart rate in KX and TZX treatment are shown in Table 1. A significant difference at 45 minutes after induction was observed with KX (57.3 ± 10.86 bpm) showing a significantly lower mean heart rate than TZX (72.3 ± 10.50 bpm). Ketamine stimulates increased sympathetic outflow resulting to elevated heart rate and arterial pressures. However, combination with an α – 2 adrenergic agonist would suppress the cardiovascular–stimulating effects of ketamine

Table 1. Mean ± SD of heart rate (beats per minutes), respiratory rate (breaths per minute), body temperature (°C), and $SpO_2$ (%) of goats anesthetized with Tiletamine – Zolazepam – Xylazine (TZX) and Ketamine – Xylazine (KX) at different time periods.

| | Heart rate (bpm) | | Respiratory rate (bpm) | | Temperature (°C) | | $SpO_2$ (%) | |
|---|---|---|---|---|---|---|---|---|
| | TZX | KX | TZX | KX | TZX | KX | TZX | KX |
| Baseline | 91.8 ± 15.18 (76 – 112) | 72.0 ± 16.00 (60 – 104) | 33.2 ± 5.08 (27 – 40) | 33.3 ± 9.69 (28 – 52) | 37.8 ± 0.80 (36.7 – 38.7) | 37.7 ± 0.48 (37.1 – 38.3) | 82.8 ± 10.72 (69 – 96) | 75.5 ± 4.37 (69 – 82) |
| 0 min | 70.7 ± 18.77 (49 – 101) | 61.5 ± 9.05 (52 – 73) | 42.5 ± 39.44 (8 – 115) | 26.8 ± 11.70 (12 – 44) | 37.9 ± 0.83 (36.8 – 39) | 37.4 ± 0.26 (36.9 – 37.7) | 80.2 ± 13.14 (55 – 92) | 84.7 ± 6.06 (74 – 91) |
| 15 mins | 59.8 ± 14.08 (38 – 81) | 60.5 ± 10.54 (50 – 74) | 21.2 ± 11.14 (8 – 40) | 25.5 ± 17.18 (16 – 60) | 36.5 ± 2.00 (33.2 – 38.4) | 36.9 ± 0.33 (36.4 – 37.3) | 82.8 ± 7.22 (71 – 92) | 89.8 ± 5.19 (84 – 98) |
| 30 mins | 68.5 ± 15.71 (57 – 99) | 54.3 ± 5.01 (47 – 61) | 53.7 ± 51.50 (8 – 126) | 37.0 ± 26.71 (16 – 88) | 35.5 ± 2.30 (31.7 – 37.6) | 36.5 ± 0.31 (36.2 – 36.9) | 69.2 ± 11.48[a] (58 – 87) | 85.8 ± 6.71[b] (73 – 93) |
| 45 mins | 72.3 ± 10.50[a] (56 – 87) | 57.3 ± 10.86[b] (48 – 73) | 29.3 ± 27.12 (4 – 72) | 27.7 ± 26.55 (8 – 80) | 36.7 ± 0.78 (35.7 – 37.7) | 36.0 ± 0.63 (34.9 – 36.8) | 85.3 ± 10.52 (69 – 99) | 81.2 ± 9.99 (67 – 90) |
| 60 mins | 96.3 ± 54.86 (53 – 189) | 58.7 ± 12.88 (42 –76) | 28.3 ± 18.81 (4 – 72) | 26.5 ± 15.41 (8 – 80) | 36.6 ± 0.80 (35.6 – 37.4) | 35.9 ± 0.28 (35.5 – 36.3) | 77.2 ± 15.90 (61 – 96) | 90.5 ± 4.72 (84 – 98) |
| 75 mins | 84.0 ± 41.67 (51 – 151) | 52.3 ± 9.83 (46 – 62) | 18.8 ± 8.67 (4 – 57) | 16.8 ± 10.55 (12 – 51) | 35.9 ± 1.03 (34.8 – 36.8) | 35.6 ± 0.39 (35.2 –36.1) | 88.0 ± 16.49 (59 – 99) | 91.3 ± 6.95 (79 – 98) |
| 90 mins | 80.0 ± 41.49 (53 – 153) | 52.0 ± 5.66 (43 – 56) | 18.8 ± 5.93 (4 – 26) | 17.2 ± 7.60 (8 – 33) | 35.5 ± 1.46 (33.8 – 36.5) | 35.48 ± 0.34 (34.9 – 35.9) | 75.0 ± 18.07 (48 – 86) | 86.5 ± 14.29 (66 – 99) |

Means with different superscripts among rows are statistically different ($P < 0.05$).

(Lin and Walz, 2014). The TZX group exhibited significant decrease in heart rate from baseline to induction. Lin and Walz (Lin and Walz, 2014) also observed a transient decrease in heart rate in calves administered tiletamine – zolazepam at 4 mg/kg IV that is associated with the negative inotropic and chronotropic effect of tiletamine. Tiletamine – zolazepam combination has been shown to preserve cardiovascular capacity thus giving a steady heart rate through its sympathetic action on myocardium (Saha *et al*., 2007).

The $SpO_2$ levels of TZX 30 minutes post induction (69.2 ± 11.48%) was lower than baseline values while that of KX (85.8 ± 6.71%) was higher than baseline values. Results indicate that mean $SpO_2$ levels for KX were above baseline values for the duration of surgery while those for TZX were more variable. The values for TZX were within the published intraoperative range obtained for $SpO_2$ of 80 to 100% (Lin and Walz, 2014) while $SpO_2$ values for TZX tended to go lower. $SpO_2$ levels are an indicator of peripheral tissue perfusion as $SpO_2$ levels of above 90% correlate with arterial systolic pressures of at least 60 mmHg which is the level believed to indicate adequate tissue oxygenation (Thomas and Lerche, 2010). However, hypotension, hypothermia. and vasoconstriction can also affect pulse oximeter readings (Lin and Walz, 2014). Mild hypothermia was found in this study, as well as that of Cistola *et al*. (2004). Still, $SpO_2$ levels detected using a pulse oximeter provides reliable estimation of the oxygen saturation (Lin and Walz, 2014).

No significant differences in the mean respiratory rate between TZX and KX were observed (Table 1). Within treatment comparison have shown significant difference from 15 to 45 minutes post induction in TZX producing depression in the respiratory rate. Tiletamine – zolazepam and ketamine tend to produce dose–dependent respiratory depression (Maddison *et al*., 2008). The decrease may be associated to xylazine's α – 2 adrenergic effect and tiletamine's sympathetic effect have stimulated bronchodilation (Frandson *et al*., 2009) leading to apneustic breathing.

There were no significant differences in the mean temperature of KX and TZX as shown in Table 1. Both TZX and KX showed decrease in temperature after induction. Mild hypothermia, temperature from 32 to 37.8 °C, was observed in both TZX and KX. Hypothermia was observed in goats given with TZX that may be associated with profound muscle relaxation caused by tiletamine – zolazepam leading to hypothermia (Lin and Walz, 2014).

A significant difference in the time of obliteration of pedal reflex between TZX (18.0 ± 6.71) and KX (42.5 ± 22.08) is shown in Table 2. Absence of pedal reflex indicates surgical plane of anesthesia and withdrawal of the limbs indicates a light plane anesthesia. Presence of palpebral and corneal reflex was observed throughout the surgical procedure using TZX and KX. According to Muir *et al*. (1995), the ocular, pharyngeal and laryngeal reflexes are depressed while the corneal reflex is maintained with tiletamine – zolazepam or ketamine, while xylazine depresses the pharyngeal and laryngeal reflexes. KX produces longer obliteration of the reflexes.

The use of TZX demonstrated a significantly longer duration of anesthesia from induction to standing recovery as shown in Table 3. The addition of xylazine with

Table 2. Mean time (minutes) (mean ± SD) from obliteration, to return of reflexes and flank pain with goats anesthetized with Tiletamine – Zolazepam – Xylazine (TZX) and Ketamine – Xylazine (KX).

| Reflexes | TZX | KX |
|---|---|---|
| Palpebral | 0.0 ± 0.00 | 0.0 ± 0.00 |
| Corneal | 0.0 ± 0.00 | 0.0 ± 0.00 |
| Pupillary | 3.0 ± 6.71 (0 – 15) | 5.0 ± 11.18 (0 – 30) |
| Swallowing | 12.0 ± 19.56 (0 – 45) | 22.5 ± 12.55 (0 – 30) |
| Anal | 27.0 ± 19.56 (0 – 45) | 27.5 ± 32.05 (0 – 90) |
| Pedal | 18.0 ± 6.71[a] (15 – 30) | 42.5 ± 22.08[b] (15 – 75) |
| Flank pain | 60.0 ± 41.08 (15 – 120) | 65.0 ± 15.49 (45 – 90) |

Means with different superscripts among rows are statistically different ($P < 0.05$).

Table 3. Duration (minutes) (mean ± SD) from induction of anesthesia until standing recovery in goats anesthetized with Tiletamine – Zolazepam – Xylazine (TZX) and Ketamine – Xylazine (KX).

| Duration | TZX | KX |
|---|---|---|
| Duration of Anesthesia | 100.83 ± 43.37[a] (38 – 170) | 95.17 ± 12.32[b] (84-119) |
| Standing Recovery | 197.67 ± 113.74[a] (90 – 413) | 117.83 ± 36.86[b] (51-158) |

Means with different superscripts among rows are statistically different ($P < 0.05$).

tiletamine – zolazepam prolonged the duration of anesthesia (Wang *et al*., 2017). The effect of xylazine involved the nitric oxide (NO) and cyclic guanosine monophosphate pathways affecting the N–methyl–D–aspartic acid (NMDA) and M cholinergic receptors (Wang *et al*., 2017). This blocks NO production and decreases available excitatory neurotransmitters reducing pain (Wang *et al*., 2017) and possibly influencing level of anesthesia. Furthermore, the addition of xylazine with other analgesic and depressant drugs can enhance level of analgesia and anesthesia. On the other hand, KX had shorter duration of anesthesia and standing recovery time compared to TZX. In a similar study involving disbudding of goats, the use of these combinations was not enough and did not produce good quality anesthesia and analgesia (Wagmann *et al*., 2018).

Table 4 shows the cortisol levels for both TZX and KX. KX was observed to have lower cortisol levels at induction of anesthesia and 30 minutes after sternal recovery compared to TZX. Cortisol levels below normal cortisol levels (14 – 18 ng/mL) indicate good analgesic effect (Saidu *et al*., 2016). Ketamine has a strong analgesic property due to the blockade of spinoreticular tract, depression of lamina in the spinal cord, activates CNS and spinal cord opiate receptors and NMDA receptor antagonist. NMDA receptors are associated with nociceptive response from tissue injury (Lin and Walz, 2014). These can control α2 – adrenergic receptors which are responsible for analgesia, muscle relaxation and sedation (Wang *et al*., 2017).

The ECG abnormalities exhibited by the goats anesthetized with TZX and KX are shown in Table 5. The most common abnormality noted is atrial flutter in both groups. Other ECG abnormalities observed in this experiment include atrial fibrillation, ventricular premature complex, 2nd degree atrioventricular block, and 3rd degree atrioventricular block. The occurrence of cardiac arrhythmias (Table 5) was more frequent with TZX than KX. Second degree AV block occurrence with TZX was significantly frequent (50%). Ketamine and tiletamine have a negative inotropic effect that blocks the sympathetic system predisposing to the occurrence of cardiac arrhythmias (Plumb, 2015). Tiletamine – zolazepam has an arrhythmogenic effect due to the release of epinephrine (Maddison *et al*., 2008). On the other hand, xylazine can produce 2nd degree AV block and other cardiac arrhythmias (Plumb, 2015). Cardiac abnormalities affect oxygen transport to tissues and promote further tissue damage during surgery (Lin and Walz, 2014).

Table 4. Cortisol level (ng/mL) (mean ± SD) of goats anesthetized with Tiletamine – Zolazepam – Xylazine (TZX) and Ketamine – Xylazine (KZ) at different time periods.

| Period | TZX | KX |
|---|---|---|
| 30 minutes before induction | 8.58 ± 5.86 (4.2 – 18.2) | 3.43 ± 3.19 (1.2 – 9.5) |
| During induction | 9.50 ± 4.32[a] (2.8 – 14) | 4.22 ± 3.36[b] (1.3 – 9.1) |
| 30 minutes after induction | 8.17 ± 3.81[a] (3.7 – 12.5) | 3.23 ± 2.29[b] (1.1 – 7.5) |
| 30 minutes after recovery | 12.15 ± 7.54 (2.2 – 21) | 5.42 ± 4.88 (1.4 – 13.6) |

Means with different superscripts among rows are statistically different ($P < 0.05$).

Table 5. Number of goats anesthetized with Tiletamine – Zolazepam – Xylazine (TZX) and Ketamine – Xylazine (KX) which exhibited ECG abnormalities.

| ECG Abnormalities | TZX N = 6 | KX N = 6 |
|---|---|---|
| Ventricular Premature Contraction | 3 (50%) | 3 (50%) |
| Atrial Fibrillation | 4 (67%) | 4 (67 %) |
| Atrial Flutter | 5 (83%) | 4 (67%) |
| 2nd degree AV Block | 3[a] (50%) | 0[b] (0%) |
| 3rd degree AV Block | 0 (0%) | 2 (33%) |

Means with different superscripts among rows are statistically different ($P < 0.05$)

The use of KX combination had better analgesic effect, provided better arterial oxygenation, prolonged obliteration of reflexes and lesser cardiac arrhythmias making it the anesthetic of choice for rumenotomy. On the other hand, TZX has shown to produce enough pre–emptive analgesia, maintenance of the cardiopulmonary activity, and longer anesthetic effect from induction to recovery making it an acceptable alternative for prolonged surgeries in Philippine native goats.

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## STATEMENT ON COMPETING INTEREST

The authors declare no conflict of interest.

## AUTHOR'S CONTRIBUTION

Authors KRG and JHA Conceptualization, Investigation, Methodology, Data Analysis, Funding acquisition, Resources, Administration, Manuscript writing. Authors MJA and AMGP Investigation Methodology, Data Analysis, Manuscript writing.

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