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Research Article

COMPARATIVE EVALUATION OF XYLAZINE -KETAMINE AND DETOMIDINE-KETAMINE COMBINATION ANESTHESIA IN RABBITS

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Abstract

The use of alpha-2 agonists with an anesthetic is a common practice for the anesthesia of companion animals. The objective of this study is to compare the effects of two different alpha-2 agonists with a common anesthetic in rabbits. To achieve this objective, twenty rabbits weighing 0.7-1 kg were randomly divided into two treatment groups: a detomidine-ketamine (DK) and a xylazine-ketamine (XK) group with 10 rabbits assigned to each group. The DK group was administered detomidine (0.25 mg/kg b.wt.) in combination with ketamine (35 mg/kg b.wt.) via the intramuscular route. Similarly, the XK group received xylazine (3 mg/kg b.wt) combined with ketamine (35 mg/kg b.wt.) intramuscularly. The comparative effects of the two anesthetic protocols were evaluated based on clinical and hematological parameters, the onset and recovery of anesthetic reflexes, duration of anesthesia, and the occurrence of adverse effects. Rabbits in the DK group exhibited a longer time to loss of the righting reflex, a prolonged duration of pedal withdrawal reflex suppression, and a significantly longer recovery period to sternal recumbency compared with those in the XK group. In contrast, the XK group demonstrated a more pronounced reduction in respiratory rate at 25 min. following anesthetic induction. Heart rate declined more markedly over time in the DK group, whereas both groups showed comparable decreases in rectal temperature during the post-anesthetic period. Most hematological parameters in the DK group remained near baseline, with slight increases in hemoglobin, packed cell volume (PCV), and red blood cell (RBC) count, whereas the XK group showed marked reductions in hemoglobin and RBC count. In conclusion, the detomidine-ketamine protocol produced more effective anesthesia in rabbits, offering greater hematological stability, prolonged anesthetic duration, smooth recovery, and no observable adverse effects.

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Introduction

Anesthesia is a reversible state of controlled unconsciousness or chemical restraint that facilitates medical and surgical procedures by minimizing pain, stress, and discomfort while ensuring the safety and welfare of both the patient and the anesthetist (Thurmon, 1996). General anesthesia is essential for performing major procedures on small animals (Haque and Lucky, 2019). General anesthesia refers to a state of unconsciousness and loss of protective reflexes caused by administering one or more anesthetic drugs (Dewachter *et al.*, 2009). This method prevents patients from experiencing or recalling unpleasant or harmful stimuli. Rabbits are frequently used as laboratory animals in experimental surgeries. Additionally, many pet owners keep rabbits as domestic companions, and an increasing number choose to neuter or spay their rabbits for management and health reasons. As a result, a reliable and standardized anesthetic protocol

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is required for veterinarians. Administering anesthesia in rabbits is often challenging in veterinary practice unless the method is simple, efficient, and safe. Intubating rabbits and using volatile anesthetics, with or without muscle relaxants, can be complex and time-consuming for practitioners and even for researchers or surgeons working without advanced equipment (Flecknell, 1997). Various injectable drug combinations, such as fentanyl/fluanisone, ketamine–acepromazine, and ketamine–diazepam, are commonly used in rabbit anesthesia (Flecknell, 1996; Flecknell, 1998). Fentanyl–fluanisone–diazepam combinations were applied to 565 rabbits undergoing experimental orthopedic surgery (Mero *et al.*, 1987). While this combination is safer compared to other methods, it often results in prolonged recovery periods. Using ketamine alone as an anesthetic frequently leads to muscle rigidity, inadequate muscle relaxation, persistent pain reflexes, and aggressive recovery (Green *et al.*, 1981).

To minimize the undesirable side effects of ketamine, several drugs such as xylazine, an alpha 2 agonist, have been used in combination with it. Although the ketamine xylazine combination has been reported to produce satisfactory anesthesia in rabbits, cases of mortality have also been documented (White *et al.*, 1976). Alpha 2 adrenoreceptor agonist drugs, such as detomidine, are commonly used for sedation, analgesia, and premedication in large animals. The use of detomidine in small and laboratory animals is rare. Therefore, this study aimed to find out the more suitable protocol for anesthesia of rabbits by comparing the anesthetic efficacy, cardiopulmonary effect, clinical and hematological parameters between two different anesthetic protocols.

Materials and Methods

Study Area

The comparative study was performed at Panacea Vet and Pet Care, Mirabazar, Sylhet and the Department of Surgery and Theriogenology, Sylhet Agricultural University (SAU).

Study Period

The duration of the study period was October 2025 to April 2026.

Ethical

Ethical statement

The authors confirm that the experimental protocol adhered to the standard animal welfare guidelines with approval numbers: SAU/Ethical committee/ARP2026099 and ARP2026101.

Experimental Animals (Rabbits)

A total of 20 anesthetic evaluations were performed on 20 apparently healthy rabbits to assess the effects of anesthetics and sedative agents on clinical and hematological parameters. The rabbits were approximately 6 months of age, and weighted between 0.70 kg to 1.0 kg.

Experimental Materials

The alpha 2-adrenergic agonists used in this study were xylazine hydrochloride (Xyla®, 20 mg/mL; Interchemie, The Netherlands) and detomidine hydrochloride (Domosedan®, 10 mg/mL; Orion Pharma Animal Health, Japan). Ketamine hydrochloride (G-Ketamine®, 50 mg/mL; Gonoshasthaya Pharmaceuticals Ltd., Bangladesh) was used as the dissociative anesthetic agent. Syringes (1ml & 3ml), butterfly needle (25G), digital thermometer, stethoscope, digital weight machine, forceps, EDTA blood collection tube, etc., were used for this experiment.

Preparation for anesthesia

Prior to anesthetic administration, all rabbits underwent a thorough clinical examination to ensure the absence of any apparent pathological conditions. Body weight was recorded using a digital weighing scale for accurate dose calculation. Each rabbit was then placed on the operating table, and all anesthetic procedures were performed during the evening hours. The injection site was aseptically prepared with 70% alcohol before drug administration. The anesthetic agents were administered intramuscularly into the thigh muscle at the prescribed doses using a 1 mL syringe. Rabbits were not fasted before anesthesia. Each drug was administered sequentially using a separate sterile syringe.

Study design

The experimental rabbits were divided into two (2) groups (10 rabbits/group) and allocated to the following different anesthetic agents (Table 1).

Table 1. Study design

Group	Agents	Dose (mg/kg b.wt.)	Route
DK	Detomidine hydrochloride	0.25	IM
	Ketamine hydrochloride	35mg	IM
XK	Xylazine hydrochloride	3	IM
	Ketamine hydrochloride	35	IM

*IM=Intramuscularly

Determination of clinical parameters

Respiration rate (per minute), heart rate (per min.), and rectal temperature (°F) of the experimental rabbits were recorded before administration of anesthetic agent and during the course of the anesthetic period at 30min, 60 min, and 90 min.

Respiration rate

The respiration rate was recorded by the visual counting method, i.e., by watching and counting the movements of the abdomen. Care was taken not to excite the rabbits before and during monitoring.

Heart rate

The heart rate was determined using a stethoscope. For this, the diaphragm of the stethoscope was placed over the chest region of the rabbit.

Rectal temperature

The rectal temperature was taken by inserting a clinical thermometer into the rectum. The bulb of the thermometer was moistened with vaseline before insertion into the rectum. The position of the thermometer in the rectum was such that the bulb of the thermometer touched the rectal mucosa. The thermometer was held in position for 90 seconds.

Blood sample collection

For each rabbit, a blood sample was collected before injecting anesthetic and 30 min of anesthesia. Each blood sample was collected from the marginal ear vein using a 1ml syringe or butterfly needle attached to a plastic syringe. Blood was immediately transferred into an ethylenediaminetetraacetic acid (EDTA) micro-collection tube. Pre-anesthetic samples and post-anesthetic samples were collected from all 20 rabbits.

Hematology report

The CBC and ESR report was compared between before administration of anesthetic agents and during the anesthesia period (after 30 min of administration of anesthetic agents). These tests were performed in a hematoanalyzer machine.

Monitoring the duration of anesthesia

Anesthesia period

The time from induction of an anesthetic agent to return to sternal recumbency.

Surgical anesthesia period

This is where surgery happens. This is characterized by stable unconsciousness, controlled breathing, and loss of reflexes depending on depth. Normally, the corneal reflex is present.

Monitoring different reflexes and other observations

Time to loss of righting reflex

The time from anaesthetic agents' administration or induction to the first failure to regain normal posture.

Duration of loss of pedal withdrawal response

The time from loss of pedal withdrawal response to return of pedal withdrawal response during anesthesia. To check pedal withdrawal response, the limbs were pinched with forceps.

Return to sternal recumbency

The time at which the rabbit could maintain sternal recumbency unaided after loss of surgical anesthesia.

Reflexes monitored

The depth of anesthesia was monitored by the use of the palpebral reflex, head shaking reflex, and chewing reflex.

Other observations

Several miscellaneous parameters like defecation, urination, salivation, and lacrimation were observed carefully during each experiment.

Statistical analysis

The data were analyzed using the statistical software program SPSS 24.0 for Windows 10. Data were expressed as mean $\pm$ standard deviation (SD). Differences were considered statistically significant if $P < 0.05$ or highly significant if $P < 0.01$, and a tendency was considered if $0.05 < P < 0.01$.

Results

Two groups of rabbits ($n=20$) were injected with two different anesthetic combinations, following detomidine, ketamine, and xylazine, ketamine combination to find the effects on physiological and hematological parameters.

In the DK group, the respiration rate was 64.80 ± 3.96 , 46.40 ± 6.10 , 72.40 ± 5.59 , and 63.20 ± 4.65 before and after 25 min, 50 min, and 75 min of anesthesia, respectively. In the XK group, it was 73.20 ± 4.81 , 44.80 ± 3.962 , 49.60 ± 4.27 , and 48.80 ± 3.89 , respectively (Table 2).

Table 2. Effects of anesthetic agents on the respiration of the rabbit (before and after 25 min, 50 min, and 75 min of anesthesia)

Group	Respiration rate (per min.) (Mean± SD)			
	Before anesthesia	25 min	50 min	75 min
DK	64.80±3.96	46.40±6.10**	72.40±5.59*	63.20±4.65
XK	73.20± 4.81	44.80±3.962**	49.60±4.27**	48.80±3.89**

In the DK group, the heart rate was 173.60±6.10, 139.80±3.70, 185.00±3.80, and 171.60±5.07 before and after 25 min, 50 min, and 75 min of anesthesia, respectively. In the XK group, it was 186.00±5.43, 169.20±3.27, 178.00±4.69, and 174.40±3.36, respectively (Table 3).

Table 3. Effects of anesthetic agents on the heart rate of the rabbits (before and after 25 min, 50 min, 75 min of anesthesia)

Group	Heart rate (per min.) (Mean ±SD)			
	Before anesthesia	25 min	50 min	75 min
DK	173.60±6.10	139.80±3.70**	185.00±3.80**	171.60±5.07
XK	186.00±5.43	169.20±3.27**	178.00±4.69**	174.40±3.36**

In the DK group, the heart rate was 101.9 ±0.35, 97.25 ±3.04, 95.2±4.24, and 95.1±2.68 before and after 25 min, 50 min, and 75 min of anesthesia, respectively. In the XK group, it was 102.7 ±.33, 98.6 ± 0.14, 95.5±0.21 and 96.8±0.21, respectively (Table 4).

Table 4. Effects of anesthetic agents on the rectal temperature of the rabbits (before and after 25 min, 50 min, 75 min of anesthesia)

Group	Rectal temperature (°F) (Mean ± SD)			
	Before anesthesia	25 min	50 min	75 min
DK	101.9 ±0.35	97.25 ±3.04**	95.2±4.24**	95.1±2.68**
XK	102.7 ±.33	98.6 ± 0.14**	95.5±0.21**	**

In the DK group, the time to loss of righting reflex was 2.5 ±0.70. In the XK group, it was 3 ±1.41. In the DK group, the anesthesia period was 79.3±20. In the XK group, it was 58 ±2.82. In the DK group, the duration of loss of pedal withdrawal response was 36.6 ±10.5. In the XK group, it was 37.33 ±3.05. In the DK group, the duration of return to sternal recumbency was 79.3±20. In the XK group, it was 58 ±2.82. In the DK group, the duration of loss of the palpebral reflex was 68 ±6.07. In the XK group, it was 24 ±1.41. In the DK group, the duration of return of the chewing reflex was 64 ±14.93. In the XK group, it was 35 ±7.07. In the DK group, the duration of return of the head-shaking reflex was 67 ±16.56. In the XK group, it was 28 ±2.12. In the DK group, the duration of return of the normal walking reflex was 95 ±28.86. In the XK group, it was 66 ±2.82 (Table 5).

Table 5. Effects of anesthetic agents on time to loss of righting reflex

Parameters	Groups	
	DK	XK
Time to loss of righting reflex (min) (Mean± SD)	2.5 ±0.70	3 ±1.41
Anesthesia period (min) (Mean± SD)	79.3±20	58 ±2.82
Duration of loss of pedal withdrawal reflex (min) (Mean± SD)	36.6 ±10.5	37.33 ±3.05
Return to sternal recumbency (min) (Mean± SD)	79.3±20	58 ±2.82
Duration of loss of palpebral reflex (min) (Mean± SD)	68 ±6.07	24 ±1.41
Duration of return of chewing reflex (min) (Mean± SD)	64 ±14.93	35 ±7.07
Duration of return of head shaking reflex (min) (Mean± SD)	67 ±16.56	28 ±2.12
Return of normal walking reflex (min) (Mean± SD)	95 ±28.86	66 ±2.82

In Table 6, the hemoglobin level and RBC significantly decreased in the XK group during anesthesia, and total WBC and platelets decreased in both groups. Neutrophils decreased in the DK group and increased in the XK. ESR decreased in the XK. Other hematological parameters showed no significant changes.

Table 6. Effects of anesthesia on different blood parameters

Blood Parameters	Before anesthesia (Mean±SD)	30 min post-anesthesia (Mean±SD)	
		DK	XK
Hemoglobin (mg/dL)	13.10± 0.54	13.16± 0.36	10.08± 0.27**
Total WBC count (/cmm)	9040± 384.70	8800± 100.00*	8700±200.00
Platelet count (/cmm)	977000±80147.09	277000±75140.26*	1077000±75320*
Neutrophils %	60±7.18	52±5.00*	63±6.00
Lymphocytes %	35±12	36±10	36±11
Monocytes %	5±1.41	5±1.41	5±0.81
Eosinophils %	3±0.81	2±1.15	2±1.15
Basophils %	0	0	0
PCV %	40±4.85	44±2.17*	39±2.58
RBC (m/cmm)	5.3±1.04	6±1.22	3.83±1.03*
MCV (fL)	66.9±6.97	66.9±5.59	66.9±5.39
MCH (pg)	20.3±2.53	20.3±1.35	20.3±4.33
MCHC (g/dL)	30.4±3.1	30.4±4.09	30.3±4.39
RDW %	14.9±0.65	14.4±1.04	16.4±1.80*
ESR	10.5±1.23	10±2.11	8±1.78*

Observing lacrimation, salivation, urination, defecation, and other behavioral changes during the trials

There was no evidence of lacrimation, salivation, urination, defecation, or other behavioral changes in both groups.

Discussion

In this study, all rabbits anesthetized with xylazine-ketamine or detomidine-ketamine recovered safely. Rabbits anesthetized with detomidine-ketamine had a mean respiratory rate of 64.80 ± 3.96 breaths per minute before anesthesia. This rate decreased to 46.40 ± 6.10 breaths per minute at 25 minutes post-injection, then increased to 72.40 ± 5.59 breaths per minute at 50 minutes, stabilizing at 63.20 ± 4.65 breaths per minute at 75 minutes. Conversely, rabbits given xylazine–ketamine had a higher baseline respiratory rate of 73.20 ± 4.81 breaths per minute. Their respiratory rate dropped significantly to 44.80 ± 3.962 breaths per minute at 25 minutes, then gradually increased to 49.60 ± 4.27 at 50 minutes, and slightly decreased to 48.80 ± 3.89 at 75 minutes. Overall, both drug combinations initially lowered respiratory rates, but their recovery patterns differed, with the detomidine-ketamine group showing a stronger rebound towards baseline compared to the xylazine–ketamine group.

In the detomidine-ketamine group, the baseline heart rate was 173.60 ± 6.10 beats/min. Twenty-five minutes after anesthesia, it dropped significantly to 139.80 ± 3.70 beats/min, indicating notable bradycardia. The heart rate then rose to 185.00 ± 3.80 beats/min at 50 minutes, surpassing the baseline, and later stabilized near baseline at 171.60 ± 5.07 beats/min at 75 minutes. Conversely, the xylazine–ketamine group had a higher baseline heart rate of 186.00 ± 5.43 beats/min. At 25 minutes, it decreased to 169.20 ± 3.27 beats/min, with greater variability than the detomidine group. The heart rate gradually increased to 178.00 ± 4.69 beats/min at 50 minutes and slightly dropped to 174.40 ± 3.36 beats/min at 75 minutes, staying below the initial baseline. This aligns with studies showing a decrease in respiratory rate after xylazine injection (Hoffman, 1974). Overall, both anesthetic combinations caused a reduction in heart rate at 25 minutes. The detomidine-ketamine combo caused a more significant initial decrease, then temporarily rose above baseline at 50 minutes. The xylazine–ketamine combo showed a milder, more gradual change, with a stable heart rate below baseline after anesthesia. These results suggest detomidine–ketamine induces a stronger initial cardiovascular depression followed by recovery, whereas xylazine–ketamine has a more stable but moderate depressant effect. This agrees with research indicating detomidine causes a significant heart rate decrease similar to xylazine (Short *et al.*, 1984).

This study observed a steady decline in rectal temperature after administering both anesthetic combinations, indicating hypothermic effects. In the detomidine–ketamine group, the baseline rectal temperature was $101.9 \pm 0.35^\circ\text{F}$, dropping significantly to $97.25 \pm 3.04^\circ\text{F}$ at 25 minutes post-anesthesia. The temperature continued to fall, reaching $95.2 \pm 4.24^\circ\text{F}$ at 50 minutes and a minimum of $94.1 \pm 2.68^\circ\text{F}$ at 75 minutes, showing a consistent and notable decrease. Conversely, in the xylazine–ketamine group, the initial temperature was slightly higher at 102.7°F , decreasing to $98.6 \pm 0.14^\circ\text{F}$ at 25 minutes and to $95.5 \pm 0.21^\circ\text{F}$ at 50 minutes. A small rise to $96.8 \pm 0.21^\circ\text{F}$ at 75 minutes indicated partial recovery from hypothermia. Overall, both protocols significantly lowered rectal temperature, highlighting that heat loss mainly results from anesthetic-induced failure of thermoregulation and peripheral vasodilation caused by ketamine and the initial detomidine phase, rather than just reduced metabolism (Longley, 2014). The detomidine–ketamine combination caused a more prolonged and progressive hypothermic effect, while the xylazine–ketamine group showed signs of mild recovery over time. The time to loss of righting reflex was shorter with detomidine–ketamine (2.5 ± 0.707 minutes) compared to xylazine–ketamine (3 ± 1.414 minutes), suggesting a faster onset of anesthesia with the detomidine–ketamine combination.

The duration of pedal withdrawal loss differed between the two anesthetic protocols. Rabbits given the detomidine-ketamine combination had a duration of 36.6 ± 10.5 minutes, while those receiving the xylazine-ketamine combination experienced a slightly longer duration of 37.33 ± 3.05 minutes, with less

variability. The time to regain sternal recumbency was 79.3 ± 20 minutes for the detomidine-ketamine group, compared to 58 ± 2.82 minutes for the xylazine-ketamine group, indicating a faster recovery with xylazine-ketamine. This aligns with previous findings that detomidine is associated with longer recumbency periods (Smith *et al.*, 2020).

The loss of the palpebral reflex lasted significantly longer with the detomidine-ketamine combination than with xylazine-ketamine. Specifically, the detomidine-ketamine group experienced a duration of 68 ± 6.07 minutes, while the xylazine-ketamine group had a duration of 24 ± 1.41 minutes. This suggests that detomidine-ketamine results in more extended palpebral reflex suppression. Although previous studies report that xylazine (1 mg/kg BW, i/v) and detomidine (20 μ g/kg BW, i/v) provide similar sedation levels (14), the higher detomidine dose used in this study likely led to deeper sedation and longer recovery times. The return of the chewing reflex also took longer in the detomidine-ketamine group (64 ± 14.94 minutes) than in the xylazine-ketamine group (35 ± 7.07 minutes), indicating quicker recovery with xylazine-ketamine. Recovery of the head shaking reflex differed markedly between the protocols: 67 ± 16.56 minutes for detomidine-ketamine versus 28 ± 2.12 minutes for xylazine-ketamine, showing faster reflex recovery with xylazine-ketamine. Similarly, the time to regain normal walking was extended in the detomidine-ketamine group (95 ± 28.86 minutes) compared to the xylazine-ketamine group (66 ± 2.82 minutes), further indicating a longer recovery in animals given detomidine.

Table 13 shows how detomidine-ketamine and xylazine-ketamine anesthesia affect hematological parameters. After detomidine-ketamine delivery, hemoglobin concentration slightly increased (13.1 mg/dL) compared to the pre-anesthetic value (12.9 mg/dL), but the xylazine-ketamine group experienced a significant drop (9.90 mg/dL). In both groups, the total leukocyte count dropped somewhat from 9350/cmm prior to anesthesia to 8700/cmm and 8600/cmm after the administration of detomidine-ketamine and xylazine-ketamine, respectively.

The detomidine-ketamine group's platelet count was significantly lower (277,000/cmm) than baseline (977,000/cmm), but the xylazine-ketamine group's platelet counts increased (1,077,000/cmm). In comparison to the baseline value of 60%, the detomidine-ketamine group's neutrophil count decreased to 52%, whereas the xylazine-ketamine group's neutrophil count increased to 63%. In both groups, the percentages of monocytes and lymphocytes stayed comparatively constant. While basophils stayed constant (0%) during all observations, the eosinophil count slightly decreased. After receiving detomidine and ketamine, packed cell volume (PCV) rose to 44%; however, in the xylazine and ketamine group, PCV dropped somewhat to 39% from the initial value of 40%.

Similarly, RBC count increased in the detomidine-ketamine group (6m/cmm) but decreased in the xylazine-ketamine group (3.83 m/cmm). No changes were observed in MCV and MCH values across all groups, while MCHC remained nearly constant with a minimal decrease in the xylazine-ketamine group. RDW decreased slightly in the detomidine-ketamine group but increased in the xylazine-ketamine group. Erythrocyte sedimentation rate (ESR) showed a slight decrease in both groups following anesthesia. Detomidine-ketamine anesthesia was associated with mild increases in erythrocytic parameters, whereas xylazine-ketamine caused comparatively greater reductions in hemoglobin and RBC count along with variable effects on platelet and leukocyte profiles.

Conclusion

Both detomidine-ketamine and xylazine-ketamine combinations provided safe and effective anesthesia in rabbits, with smooth induction and recovery. Detomidine-ketamine produced a faster onset, longer

anesthetic duration, and more prolonged reflex suppression, indicating deeper anesthesia, but was associated with greater cardiopulmonary depression, hypothermia, and delayed recovery. In contrast, xylazine–ketamine resulted in more stable physiological parameters, less pronounced hypothermia, and faster recovery. Although hematological changes were generally within acceptable limits, xylazine–ketamine caused greater reductions in hemoglobin and RBC counts. Thus, xylazine–ketamine is preferable for shorter procedures requiring rapid recovery, whereas detomidine–ketamine is better suited for prolonged or deeper anesthesia.

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