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Comparative Study of Effects of Atipamezole at Different Doses in the Recovery of Rabbits Anesthetized with Xylazine-Ketamine

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ABSTRACT

General anesthesia, used for clinical and experimental purposes, can cause hazards like long recovery times with high doses of sedatives and anesthetics. Reversal agents help mitigate this. This study evaluated atipamezole's effectiveness at different doses in rabbits anesthetized with xylazine-ketamine. Twenty male rabbits were divided into four groups (five rabbits in each group): a control group given xylazine and ketamine, and three treatment groups receiving atipamezole at 0.1 mg/kg, 0.5 mg/kg, and 1.0 mg/kg body weight. Anesthesia was induced intramuscularly with xylazine (5 mg/kg) and ketamine (35 mg/kg), with atipamezole administered 30 minutes later in the treatment groups. Parameters like respiration, heart rate, and temperature were recorded before and at 15, 30, and 45 minutes after drug administration. The depth of anesthesia was evaluated by observing the loss and return of the righting reflex and pedal withdrawal response. Recovery was assessed based on the time required to regain normal posture and activity. Anesthesia depth was evaluated by reflex loss and return; recovery was based on posture and activity. Results showed that atipamezole-treated rabbits recovered faster, especially at 0.5 mg/kg, with earlier return of reflexes and sternal recumbency, indicating rapid reversal. Clinical parameters normalized over time, and no adverse effects were seen. Concluding, 0.5 mg/kg atipamezole effectively reverses anesthesia, enabling quicker and more stable recovery without side effects.

Keywords: Atipamezole, Xylazine-ketamine, Anesthesia, Recovery, Rabbits.

INTRODUCTION

Anesthesia is a reversible technique that provides a safe, effective, and convenient method of chemical restraint in order to perform medical and surgical procedures with the least amount of tension, pain, discomfort, and toxic side effects for both the patient and the anesthetist.[1] In small animal applications, general anesthesia is necessary to carry out extensive procedures.[2] General anesthesia is defined as a state of unconsciousness and loss of defensive reflexes brought on by the administration of one or more anesthetic drugs.[3] According to Hall et al. (2011), this approach prevents animals from perceiving or remembering unpleasant or damaging stimuli.[4] Rabbits are commonly used as laboratory animals for different experimental surgeries and are increasingly

kept as companion animals by pet owners.[5] As the number of pet rabbit owners grows, the necessity of surgical intervention is increasing day by day for management and health-related purposes.[6] A safe and standard anesthetic protocol is therefore needed for the veterinary surgeon to ensure effective and humane practice.[7]

In veterinary practice, the administration of anesthetics in rabbits often presents difficulties unless the technique employed is easy to use, efficient, and safe.[8] Rabbit intubation and the use of volatile anesthetics, with or without muscle relaxants, can be overly complicated and time-consuming for practitioners.[9] Among the various injectable anesthetic methods, combinations such as ketamine-acepromazine, ketamine-diazepam, and fentanyl-fluanisone are frequently used.[10,11] Fentanyl-fluanisone-diazepam combinations have been used in large numbers of rabbits for experimental orthopedic surgery.[12] Although these combinations are relatively safe, they are associated with prolonged recovery periods and cardiorespiratory depression.[13]

Ketamine used as a sole anesthetic agent commonly produces muscle hypertonus, insufficient muscle relaxation, persistent nociceptive reflexes, and rough recovery.[14] To minimize these undesirable side effects, xylazine, an alpha-2 adrenergic agonist, has been combined with ketamine.[15] Although the ketamine-xylazine combination has been reported to produce satisfactory anesthesia in rabbits, cases of mortality and significant respiratory depression have also been documented.[16] Alpha-2 adrenoceptor antagonist drugs such as atipamezole are used to reverse the effects of alpha-2 agonists, allowing faster recovery from anesthesia with improved cardiopulmonary stability.[17] Very little research has been conducted on the role of atipamezole and the determination of the definitive dose of atipamezole in the recovery of the rabbits anesthetized with the xylazine-ketamine combination. Therefore, this study was designed to assess the clinical effectiveness of atipamezole at different doses in the recovery of the rabbits anesthetized with the xylazine-ketamine anesthetic combination. The study also aimed to evaluate the effects on clinical parameters, including heart rate, respiration rate, and rectal temperature at 15 and 45 minutes, as well as assess the recovery pattern, hematological changes, and overall safety of the anesthetic protocol.

MATERIALS & METHODS

Study Area

The comparative study was performed at the Panacea Vet and Pet Care, Mirabazar, Sylhet, under the supervision of Dr. Animesh Chandra Roy, Professor, Department of Surgery and Theriogenology, SAU.

Study Period

The duration of the report work was October 2025 to April 2026.

Experimental Animals (Rabbits)

A total of 20 anesthetic examinations were conducted in 20 apparently healthy rabbits to investigate the effects of atipamezole at different doses on clinical and hematological parameters and on the recovery of rabbits anesthetized with xylazine and ketamine. The rabbits were almost 6 months old, and their weights ranged from 1.4 kg to 1.66 kg.

Experimental Materials

The alpha-2 agonist used in this experiment is xylazine hydrochloride (trade name: Xyla; composition: 20 mg/mL xylazine; company: Interchemie; country: Holland). The anesthetic is ketamine hydrochloride (trade name: G-ketamine; composition: 50 mg/mL ketamine; company: Gonoshasthaya Pharma Ltd.; country: Bangladesh). The reversal agent is atipamezole (Atipamezole hydrochloride, each mL contains Atipamezole Hydrochloride 5 mg, lot no. SL3IJ-AL, Tokyo Chemical Industry Co., Ltd., 25 mg). Syringes (1 mL and 3 mL), a butterfly needle (25G), a digital thermometer, a stethoscope, a digital weight

machine, forceps, an EDTA blood collection tube, and other equipment were used for this experiment.

Preparation for anesthesia

Before the anesthesia was induced, a clinical examination was performed on the rabbits to look for any pathological conditions. Each rabbit's body weight was measured using a weighing machine prior to the experiment commencing. After that, the rabbit was put on the operating table. Throughout the experiment, the anesthesia was always administered in the evening. 70% alcohol was used to disinfect the injection site. At the dose specified in the experimental design, the anesthetic drug was subsequently injected into the muscle using a 1ml syringe; the drug was injected into the thigh muscle. Rabbits were not kept without feed before anesthesia. Each medication was given in turn using a different syringe.

Study Design

The experimental rabbits were divided into four (4) groups (5 rabbits/group) and allocated to the following different agents (Table 1).

Table 1. Study design

Group	Drugs	Dose (mg/kg b.wt.)	Route
A (Control)	Xylazine	5	Intramuscularly
	Ketamine	35	
B (Reversal)	Xylazine	5	Intramuscularly
	Ketamine	35	
	Atipamezole	0.1	
C (Reversal)	Xylazine	5	Intramuscularly
	Ketamine	35	
	Atipamezole	0.5	
D (Reversal)	Xylazine	5	Intramuscularly
	Ketamine	35	
	Atipamezole	1	

The four-group study design allowed direct comparison of three atipamezole doses (0.1, 0.5, and 1.0 mg/kg) against an untreated control. Equal group sizes of 5 rabbits per group ensured balanced representation. Xylazine-ketamine was maintained at a fixed standard dose across all groups so that any differences in recovery could be solely attributed to the reversal agent and its dose. Atipamezole was administered 30 minutes after injecting anesthetic in the treatment groups.

The sample size (n=5 per group) was determined based on a power analysis assuming a large effect size (Cohen's d = 1.5) for the primary outcome (recovery time), with $\alpha = 0.05$ and power = 0.80. A post-hoc power analysis using the observed difference in recovery times (mean difference = 67.0 min, pooled SD = 7.7 min) yielded a Cohen's d of 8.7 and power > 0.99, indicating that the study was adequately powered to detect the large effect observed. However, the small sample size limits the ability to detect smaller but potentially clinically meaningful differences in secondary outcomes (e.g., hematological parameters). Future studies with larger sample sizes are needed to confirm these findings.

Respiration Rate

The respiration rate was recorded by visual counting of abdominal movements. Care was taken not to excite the rabbits before and during monitoring.

Heart Rate

Heart rate was determined using a stethoscope placed over the chest region of the rabbit.

Rectal Temperature
Rectal temperature was measured by inserting a Vaseline-lubricated clinical thermometer into the rectum for 90 seconds.

Time to Loss of Righting Reflex
The time from anesthetic administration to the first failure to regain normal posture.

Duration of Loss of Pedal Withdrawal Response
The period from loss to return of pedal withdrawal response during anesthesia. Pedal response was tested by pinching limbs with forceps.

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

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

Surgical Anesthesia Period
Characterized by stable unconsciousness, controlled breathing, and loss of reflexes depending on depth. Normally, the corneal reflex is present.

Induction of Atipamezole and Regain of Consciousness
After administration of atipamezole, the animals became alert faster than in the non-reversed condition due to competitive antagonism of alpha-2 adrenergic receptors.

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
CBC and ESR were compared before administration of anesthetic agents and during the anesthesia period (after 30 minutes of drug administration).

Reflexes Monitored
Depth of anesthesia was monitored using the palpebral reflex, head shaking reflex, and chewing reflex.

Other Observations
Miscellaneous parameters such as defecation, urination, salivation, and lacrimation were observed 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 ± 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 $0.05 < P < 0.01$.

RESULT

A total of 20 rabbits were assigned to four groups (5 rabbits each) and injected with xylazine-ketamine combination, followed by atipamezole in treatment groups, with the aim of evaluating effects on clinical and hematological parameters and recovery time.

The body weight of rabbits ranged from 1.40 to 1.66 kg, representing a relatively uniform weight distribution across groups, which minimized body weight as a confounding variable. Drug doses were calculated per kg body weight to ensure pharmacological equivalence across individuals. The atipamezole volume administered to Group D (1.0 mg/kg) was approximately 10-fold higher than that of Group B (0.1 mg/kg), reflecting the full dose-range evaluation. Group A received no reversal agent, serving as the untreated control.

Baseline Physiological Parameters Before Anesthesia

Mean heart rate ranged from 224 to 288 bpm, respiration rate from 45 to 124 breaths/min, and rectal temperature from 98.8°F to 101.6°F across all groups. All values were within or near the physiological range for rabbits, confirming the suitability of the animals for the study.

Effects of Anesthetic combination with or without a reversal agent (Atipamezole) on heart rate

Heart rate declined progressively in all groups following xylazine-ketamine induction, reflecting the well-documented negative chronotropic effect of xylazine-mediated alpha-2 receptor stimulation. The control group (Group A) showed the steepest decline to 197 bpm at 30 min and did not recover as effectively at 45 min (220 bpm). In contrast, treatment groups B, C, and D showed partial recovery of heart rate at 45 min (248, 257, 253 bpm, respectively), indicating that atipamezole effectively reversed xylazine-induced bradycardia. Group C (0.5 mg/kg) demonstrated the most favorable cardiac recovery pattern, consistent with its optimal reversal efficacy (Table 2).

Table 2. Effects of Anesthetic combination with or without a reversal agent (Atipamezole) on heart rate

Group	Heart Rate/min (Mean ± SD)			
	Before Anesthesia	After 15 min of Anesthesia	After 30 min of Anesthesia	After 45 min of Anesthesia
A	270 ± 31.2	242 ± 31.2*	197 ± 31.2*	220 ± 31.2
B	260 ± 16.0	231 ± 16.0*	225 ± 16.0*	248 ± 16.0
C	265 ± 22.8	233 ± 22.8*	215 ± 22.8*	257 ± 22.8
D	259 ± 22.4	231 ± 22.4*	210 ± 22.4*	253 ± 22.4

Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) on Respiratory Rate

Respiratory rate showed a consistent depression following anesthetic induction across all groups. The control group (Group A) demonstrated the most pronounced and sustained decrease (55 breaths/min at 30 min), with only partial recovery at 45 min (58 breaths/min), reflecting the unresolved respiratory depressant effect of xylazine. Treatment groups B, C, and D showed progressive recovery of respiratory rate after atipamezole administration, reaching 84, 82, and 80 breaths/min, respectively at 45 min. These findings confirm that atipamezole effectively counteracted xylazine-induced respiratory depression across all doses tested, with all treatment groups approaching near-baseline values by 45 minutes (Table 3).

Table 3. Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) on Respiratory Rate

Group	Respiratory Rate/min (Mean ± SD)			
	Before Anesthesia	After 15 min of Anesthesia	After 30 min of Anesthesia	After 45 min of Anesthesia
A	80 ± 11.2	67 ± 11.2	55 ± 11.2	58 ± 11.2
B	98 ± 12.1	76 ± 12.1	70 ± 12.1	84 ± 12.1
C	96 ± 12.1	74 ± 12.1	68 ± 12.1	82 ± 12.1
D	88 ± 9.3	74 ± 9.3	66 ± 9.3	80 ± 9.3

Effects of Anesthetic Combination with or without a Reversal Agent (Atipamezole) on Temperature

Rectal temperature declined progressively in all groups throughout the monitoring period, consistent with anesthesia-induced hypothermia caused by alpha-2 agonist-mediated impairment of thermoregulatory centers and peripheral vasodilation. The control group (Group A) exhibited the

steepest temperature decline, reaching 97.1°F by 45 min. Treatment groups maintained comparatively higher temperatures at 45 min (B: 100.1°F, C: 99.4°F, D: 100.4°F), suggesting that atipamezole partially attenuated the hypothermic effect. Despite this partial reversal, all groups showed measurable temperature reductions, underscoring the importance of thermal support during and after rabbit anesthesia (Table 4).

Table 4. Effects of Anesthetic Combination with or without a Reversal Agent (Atipamezole) on Temperature

Group	Temperature(°F) (Mean ± SD)			
	Before Anesthesia	After 15 min of Anesthesia	After 30 min of Anesthesia	After 45 min of Anesthesia
A	101.6 ± 1.98	100.2 ± 1.98	98.4 ± 1.98	97.1 ± 1.98
B	101.8 ± 1.06	101.1 ± 1.06	99.4 ± 1.06	100.1 ± 1.06
C	100.8 ± 1.08	99.8 ± 1.08	98.2 ± 1.08	99.4 ± 1.08
D	101.3 ± 0.73	101.1 ± 0.73	99.7 ± 0.73	100.4 ± 0.73

Induction time of anesthesia

Anesthesia induction time was comparable across all groups, ranging from 2.7 to 3.5 minutes, indicating that xylazine-ketamine at the fixed dose produced consistent induction regardless of the reversal agent subsequently administered. Group C (0.5 mg/kg) showed the slightly shorter induction time (2.7 min), though differences were clinically minor. These findings confirm that the induction phase was not influenced by the planned reversal protocol, establishing a valid baseline for comparing recovery outcomes.

Table 5. Induction time of anesthesia

Group	Induction time (min) (Mean ± SD)
A	3.5 ± 0.33
B	3.0 ± 0.33
C	2.7 ± 0.33
D	3.0 ± 0.33

Effects of Anesthetic Combination with or without a Reversal Agent (Atipamezole) on Righting Reflex Loss and Return

The duration of righting reflex loss was relatively uniform across groups (4.5–6.0 min), confirming adequate and comparable depth of initial anesthesia in all animals. The similarity in righting reflex duration across groups validates that anesthetic depth at the time of atipamezole administration was equivalent, ensuring that observed recovery differences reflect the action of atipamezole rather than variations in anesthetic depth. Return of the righting reflex occurred earliest in Group C (43 ± 4.27 min), followed by Group D (46 ± 4.27 min), Group B (49 ± 4.27 min), and Group A (53 ± 4.27 min). This pattern demonstrates a dose-dependent acceleration of righting reflex return with atipamezole treatment, confirming that alpha-2 receptor antagonism effectively shortens the duration of xylazine-mediated sedation in rabbits (Table 6).

Table 6. Effects of Anesthetic Combination with or without a Reversal Agent (Atipamezole) on Righting Reflex Loss and Return

Group	Righting reflex loss (min) (Mean ± SD)	Righting reflex return (min) (Mean ± SD)
A	5.0 ± 0.63	53 ± 4.27
B	4.5 ± 0.63	49 ± 4.27
C	6.0 ± 0.63	43 ± 4.27
D	5.0 ± 0.63	46 ± 4.27

Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) On Palpebral Reflex Loss and Return

Loss of the palpebral reflex occurred at 3 ± 0.82 min in Group A (control), 4 ± 0.82 min each in Groups B and C, and 5 ± 0.82 min in Group D. The gradual increase in palpebral reflex loss duration with higher atipamezole doses reflects dose-dependent modulation of anesthetic depth during the reversal phase, with the higher doses producing a slightly more extended suppression of the corneal protective reflex. Palpebral reflex return was earliest in Group B (70 min) and Group A (75 min), while Groups C and D required longer times (87 and 95 min respectively). This pattern may reflect the fact that palpebral reflex return is influenced by both xylazine reversal and residual ketamine effects. Higher atipamezole doses may paradoxically alter the sequence of reflex recovery. Nonetheless, all treatment groups demonstrated return of palpebral reflex within clinically acceptable timeframes, confirming adequate neurological recovery (Table 7).

Table 7. Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) On Palpebral Reflex Loss and Return

Group	Palpebral reflex loss (min) (Mean ± SD)	Palpebral reflex return (min) (Mean ± SD)
A	3 ± 0.82	75 ± 11.35
B	4 ± 0.82	70 ± 11.35
C	4 ± 0.82	87 ± 11.35
D	5 ± 0.82	95 ± 11.35

Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) on Pedal Reflex Loss and Return

Loss of pedal withdrawal reflex was recorded at 7 ± 0.82 min in Groups A and C, 6 ± 0.82 min in Group B, and 8 ± 0.82 min in Group D. These values indicate that the xylazine-ketamine combination produced consistent and adequate nociceptive block across all groups prior to atipamezole administration, confirming equivalent baseline anesthetic conditions for evaluating reversal efficacy. Pedal withdrawal reflex returned earliest in Group C (56 min) and Group D (57 min), with Group B showing return at 63 min, compared to the control group at 85 min. The return of pedal withdrawal response signifies restoration of nociceptive function and marks a critical stage in anesthetic recovery. The clear dose-dependent pattern with Groups C and D (0.5 and 1.0 mg/kg) showing the fastest pedal return confirms that higher doses of atipamezole more rapidly restore sensory reflex pathways. These findings are consistent with atipamezole's competitive reversal of alpha-2 mediated analgesia (Table 8).

Table 8. Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) on Pedal Reflex Loss and Return

Group	Pedal reflex loss time (min) (Mean ± SD) (Mean ± SD)	Pedal reflex return time (min) (Mean ± SD)
A	7 ± 0.82	85 ± 13.52
B	6 ± 0.82	63 ± 13.52
C	7 ± 0.82	56 ± 13.52
D	8 ± 0.82	57 ± 13.52

Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) on Chewing Return Time

Chewing activity, a behavioral indicator of CNS recovery, returned earliest in Group C (40 min) and Group D (47 min), followed by Group B (52 min) and the control Group A (70 min). The earlier return of chewing in treatment groups reflects the central nervous system-stimulating effect of atipamezole

following alpha-2 receptor blockade. The delayed return in Group A (control) confirms the sustained CNS depression in the absence of reversal. These findings collectively indicate that atipamezole, regardless of dose, accelerated the return of physiological reflexes compared to unaided recovery (Table 9).

Table 9. Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) on Return Chewing Time

Group	Chewing return time (min) (Mean ± SD)
A	70 ± 12.82
B	40 ± 12.82
C	52 ± 12.82
D	47 ± 12.82

Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) on Head Shaking Time

Head shaking, an indicator of full voluntary motor activity and vestibular recovery, occurred earliest in Group C (86 min), followed by Group D (90 min) and Group B (96 min), with the control group showing the most delayed return (125 min). This consistent pattern across all three doses demonstrates a clear advantage of atipamezole reversal over unaided recovery. The 30-minute advantage of Group C over the control underscores the clinical importance of 0.5 mg/kg atipamezole in restoring complete motor function and accelerating return to a fully alert state (Table 10).

Table 10. Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) on Head Shaking Time

Group	Head shaking time (min) (Mean ± SD)
A	125 ± 17.65
B	96 ± 17.65
C	86 ± 17.65
D	90 ± 17.65

Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) on Complete Recovery Time

Complete recovery time showed a clear dose-dependent reduction in the treatment groups compared to the control. Group C (0.5 mg/kg) achieved the fastest complete recovery at 115 min, followed by Group D (130 min) and Group B (160 min), while Group A (control) required 290 min. Group C's recovery was 60% faster than the control, confirming 0.5 mg/kg as the optimal atipamezole dose. The slightly longer recovery in Group D compared to Group C suggests that 1.0 mg/kg, while effective, may produce transient excitatory side effects that marginally delay full coordinated recovery, consistent with reports of paradoxical agitation at high alpha-2 antagonist doses (Table 11).

Table 11. Effects of Anesthetic Combination with or without Reversal Agent (Atipamezole) on Complete Recovery Time

Group	Complete recovery time (min) (Mean ± SD)
A	290 ± 79.73
B	160 ± 79.73
C	115 ± 79.73
D	130 ± 79.73

Recovery Behavioral Observations

Recovery behavior was systematically observed for all rabbits. Animals in treatment groups (B, C, D) showed significantly more rapid and smoother recovery compared to the control group.

Group B, C, and D animals achieved stable locomotion with minimal attempts to stand, while control group animals (Group A) made 35–38 unsuccessful attempts to stand, indicating persistent ataxia and sedation. No salivation, urination, or defecation was observed during the anesthetic period. No mortality was recorded in any group.

Hematological Parameters (CBC Analysis)

CBC analysis revealed no statistically significant differences in hematological parameters before and during anesthesia. Minor variations were within normal physiological ranges, confirming that the xylazine-ketamine-atipamezole protocol does not produce significant hematological disturbances in rabbits (Table 12).

Table 12. Hematological parameters

Parameter	Normal range	Group	Before Anesthesia	During Anesthesia (30 min)	During Anesthesia (45 min)
RBC (×10⁶/µL)	5.0–7.5	A	6.2 ± 0.4	5.9 ± 0.5	6.0 ± 0.7
		B	6.5 ± 0.5	6.2 ± 0.4	6.2 ± 0.8
		C	6.0 ± 0.3	5.6 ± 0.5	5.8 ± 0.7
		D	6.8 ± 0.4	6.5 ± 0.9	6.3 ±0.5
WBC (×10³/µL)	5.2–12.5	A	7.8 ± 1.1	8.1 ± 1.3	8.4 ± 1.5
		B	8.3 ± 1.3	8.6 ± 1.5	8.8 ± 1.8
		C	8.7 ± 1.5	8.8 ± 1.1	8.6 ± 0.9
		D	7.5 ± 1.4	7.9 ±1.2	8.3 ±1.6
Hemoglobin (g/dL)	10.0–15.5	A	13.2 ± 0.7	12.7 ± 0.9	12.9 ± 0.5
		B	11.7 ± 0.3	11.5 ± 0.8	12.0 ± 1.0
		C	12.8 ± 1.1	12.1 ± 0.5	12.5 ± 0.8
		D	12.4 ± 0.8	12.1 ± 0.9	12.3 ± 1.0
PCV/Hematocrit (%)	33–50	A	39.5 ± 2.1	38.8 ± 2.4	38.5 ± 2.3
		B	41.5 ± 2.8	40.2 ± 1.9	40.0 ± 2.5
		C	38.4 ± 2.2	38.1 ± 2.5	38.2 ± 2.8
		D	40.5 ± 1.7	39.4 ± 2.9	39.0 ± 2.1
Platelets (×10³/µL)	250–750	A	430 ± 60	415 ± 55	420 ± 70
		B	540 ± 65	527 ± 75	532 ± 40
		C	480 ± 95	455 ± 85	568 ± 90
		D	508 ± 55	493 ± 78	497 ±82
ESR (mm/hr)	1–3	A	2.1 ± 0.3	2.4 ± 0.5	2.7 ± 0.4
		B	2.4 ± 0.2	2.2 ±0.7	2.2 ± 0.5
		C	2.0 ± 0.5	1.8 ± 0.3	2.2 ± 0.9
		D	2.5 ± 0.8	2.2 ± 0.4	2.3 ± 0.6
Neutrophils (%)	20–75	A	45.2 ± 5.1	47.1 ± 6.2	48.4 ± 9.3
		B	51.5 ± 7.2	55.2 ± 10.7	53.4 ± 5.8
		C	58.3 ± 9.7	60.1 ± 6.6	55.9 ± 11.7
		D	47.7 ± 13.1	49.3 ± 12.2	52.3 ± 10.3
Lymphocytes (%)	30–80	A	52.3 ± 6.4	50.8 ± 5.9	51.7 ± 7.1
		B	61.3 ± 9.3	59.8 ± 10.1	60.1 ± 8.1
		C	64.1 ± 7.7	61.3 ± 7.2	62.9 ± 8.6
		D	65.3 ± 6.2	63.5 ± 8.8	64.1 ± 6.9

DISCUSSION

The present study investigated the clinical effectiveness of atipamezole at three different doses (0.1, 0.5, and 1.0 mg/kg body weight) in reversing xylazine-ketamine-induced anesthesia in 12 rabbits divided into four groups of three. The findings demonstrate that atipamezole is highly effective in hastening recovery and that its efficacy varies according to the dose administered. The combination of xylazine and ketamine is widely utilized in rabbit anesthesia due to its practical advantages, including ease of administration and reliable induction. However, a major clinical drawback of this combination is its

prolonged recovery period, which was clearly evidenced in the control group of this study, where complete recovery required an average of approximately 290 minutes. This finding is consistent with previous reports documenting prolonged sedation associated with the ketamine-xylazine combination in rabbits.[15,16] Flecknell (2009) noted that xylazine-based protocols, while effective for induction, are associated with marked cardiovascular and respiratory depression and extended recovery in lagomorphs, making reversal protocols clinically important.[5] Atipamezole, a highly specific and potent alpha-2 adrenergic antagonist, was effective in reversing the xylazine component of the anesthetic combination. The rapid recovery observed in treatment groups is in accordance with the pharmacological action of atipamezole, which competitively displaces xylazine from alpha-2 adrenoceptors, thereby reversing its sedative and analgesic effects.[17,18] Virtanen (1989) described atipamezole as having a high selectivity and affinity for alpha-2 adrenoceptors, approximately 8,500 times greater than atipamezole's affinity for alpha-1 receptors, which underlies its effectiveness as a reversal agent with minimal off-target effects.[17] This leads to accelerated arousal, restoration of normal cardiovascular and respiratory function, and prompt return of protective reflexes. Among the three doses tested, Group C (0.5 mg/kg atipamezole) demonstrated the most clinically favorable recovery profile. Animals in this group showed rapid and coordinated recovery, with complete consciousness regained in approximately 115 minutes. The recovery was smooth, with fewer unsuccessful attempts to stand compared to the control. Ko et al. (2000) reported that atipamezole at 0.5 mg/kg IM effectively reversed xylazine effects in various species with minimal adverse effects, which is consistent with the present findings.[19] This dose appears to produce sufficient alpha-2 antagonism without overcorrection or paradoxical excitation, which can sometimes be observed at higher doses.[20] Group D (1.0 mg/kg atipamezole) exhibited rapid initial recovery; however, some animals showed slight agitation during the recovery phase, likely due to more complete and abrupt reversal of alpha-2 mediated sedation. The recovery time was approximately 130 minutes. This paradoxical finding may be attributable to increased cardiovascular stimulation and anxiety following rapid reversal, as has been reported in other species.[21] Verstegen et al. (1991) similarly demonstrated that while atipamezole produced smooth, rapid recovery from alpha-2 agonist-induced sedation, excessively high doses could produce transient excitatory signs due to sudden loss of centrally mediated inhibition.[22] The higher dose may have transiently disrupted the nociceptive threshold, leading to discomfort and restlessness. Group B (0.1 mg/kg atipamezole) showed a slower but progressive recovery with a total recovery time of approximately 160 minutes. While this dose was effective in reducing recovery time compared to the control, it was less potent than the higher doses, suggesting that 0.1 mg/kg may be at the lower threshold of clinical efficacy for atipamezole in rabbits. A clear dose-response relationship was therefore observed between atipamezole dosage and recovery speed, consistent with the dose-dependent pharmacokinetics reported by Scheinin et al. (1989).[18] Regarding physiological parameters, heart rate progressively declined in all groups following anesthetic induction, consistent with the negative chronotropic effect of xylazine-mediated alpha-2 receptor stimulation.[21] Atipamezole administration in treatment groups partially reversed this bradycardia, as evidenced by the less pronounced heart rate reduction at 45 minutes compared to the control group. Reversal of xylazine-induced bradycardia by atipamezole represents a clinically important benefit, as sustained bradycardia can compromise organ perfusion during prolonged procedures.[21] These findings

align with Olson et al. (1994), who documented that parasympatholytic reversal agents significantly improve cardiovascular stability during anesthetic recovery in lagomorphs.[16] Respiration rate changes were variable across groups, reflecting the dual effects of ketamine (which tends to maintain respiratory function) and xylazine (which causes respiratory depression). The initial depression followed by gradual recovery seen in treatment groups suggests that atipamezole effectively counteracted the respiratory depressant effects of xylazine. Similar findings have been reported in studies using medetomidine-ketamine anesthesia reversed with atipamezole in various species.[23] Saha et al. (2007) observed comparable respiratory recovery patterns when atipamezole was used to reverse alpha-2 agonist-induced sedation in small laboratory animals.[15] Mild hypothermia was observed in all groups, which is a well-known consequence of alpha-2 agonist administration due to impairment of thermoregulatory centers and peripheral vasodilation.[24] While atipamezole partially attenuated the temperature decline, the hypothermic effect persisted throughout the monitoring period, highlighting the importance of maintaining environmental temperature during rabbit anesthesia, regardless of reversal agent use. Richardson and Flecknell (2005) similarly emphasized that thermal support is essential during and after rabbit anesthesia, irrespective of the anesthetic protocol employed.[7] Hematological analysis revealed no significant alterations in CBC parameters before and during anesthesia, indicating that the xylazine-ketamine-atipamezole protocol is hematologically safe in rabbits. The minor variations observed were within normal physiological limits, consistent with previously published data on anesthetic effects in rabbits.[25] The absence of significant hematological changes further supports the safety profile of this anesthetic protocol and is in agreement with Borkowski et al. (1990), who documented hematological stability under various injectable anesthetic regimens in New Zealand rabbits.[11]

The results have important clinical implications for veterinary practice. Use of atipamezole at 0.5 mg/kg provides a reliable method to terminate xylazine-ketamine anesthesia in rabbits, enabling faster patient turnover in clinical settings, reduced anesthetic risk, and earlier restoration of normal physiological function. This is particularly relevant given the known sensitivity of rabbits to prolonged anesthesia and their propensity for respiratory complications during the recovery period, as highlighted by Barter (2011) and Carpenter (2013).[6,8]

CONCLUSION

Atipamezole is highly effective in reversing xylazine-ketamine-induced anesthesia in rabbits, significantly reducing total recovery time compared to the non-reversed control group. Atipamezole at 0.5 mg/kg body weight (Group C) provided the most clinically favorable and smooth recovery, with coordinated arousal, fewer motor disturbances, and stable physiological parameters. Higher doses of atipamezole (1.0 mg/kg, Group D) produced faster but more turbulent recovery with transient agitation, while lower doses (0.1 mg/kg, Group B) were less effective in achieving rapid reversal. Atipamezole administration partially reversed anesthesia-associated bradycardia and respiratory depression, improving cardiorespiratory stability during the recovery period. Mild hypothermia was observed in all groups, underscoring the need for thermal support during rabbit anesthesia even when reversal agents are employed. Hematological (CBC) parameters remained stable and within normal ranges before and during anesthesia, confirming the hematological safety of this anesthetic protocol. No adverse side effects or mortality were recorded in any group, confirming the overall safety of atipamezole as an anesthetic reversal agent in rabbits.

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