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Article

A Comparative Evaluation of the Anesthetic Efficacy and Hepatic Safety of Tiletamine-Zolazepam and Ketamine-Diazepam in New Zealand White Rabbits

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Abstract: This study aimed to compare the anesthetic efficacy, physiological stability, and hepatic effects of tiletamine-zolazepam (TZ) versus ketamine-diazepam (KD) in rabbits. Forty healthy male New Zealand White rabbits (2–3 kg) were randomly assigned into five groups: a saline control, three tiletamine-zolazepam (TZ) dose groups (32, 7.5, and 3.5 mg/kg IV), and a ketamine-diazepam (KD) group (20 + 1 mg/kg IV). Anesthetic depth, duration, and physiological parameters were monitored for 60 minutes. Blood samples were collected before anesthesia and on days 1, 3, 5, and 7 post-injection to assess liver function. The TZ-High group (32 mg/kg) exhibited the longest duration of anesthesia but also showed severe cardiorespiratory depression, characterized by a significant drop in respiratory rate and heart rate. Furthermore, this group displayed marked elevations in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels at 24 and 72 hours, indicating significant hepatotoxicity. In contrast, the KD and TZ-Mid groups provided adequate anesthesia with better physiological stability and minimal biochemical alterations. It is concluded that while high-dose tiletamine-zolazepam provides prolonged anesthesia, it induces severe and unacceptable hepatotoxicity and cardiorespiratory distress in rabbits. The combination of ketamine-diazepam or a mid-range dose of tiletamine-zolazepam offers a safer alternative for procedures in rabbits.

Keywords: Rabbit, Tiletamine-Zolazepam, Ketamine-Diazepam, Toxicity, Anesthesia, Hepatic Safety

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1. Introduction

The domestic rabbit (Oryctolagus cuniculus) is widely kept as a companion animal and is also an important model in biomedical research. It is used in wide range fields such

as ophthalmology, cardiovascular studies, infectious disease, and toxicology [1]. Rabbits are preferred because they are easy to handle, have a manageable body size, and share several physiological features with humans [2]. However, anesthesia in rabbits remains a challenge. Compared to other domestic animals, rabbits have a higher risk of complications and death during or after anesthesia [3,4]. This is due to several factors, including their anatomy, small cardiopulmonary reserve, and strong stress response, which can sometimes cause sudden cardiovascular failure [5,6]. These risks highlight the need for safe and reliable anesthetic protocols for both veterinary practice and laboratory use.

Injectable anesthesia is commonly used in rabbits because it is simple to administer, acts quickly, and can be used even in facilities without inhalation equipment. Two of the most widely used injectable combinations are ketamine with diazepam (KD) and tiletamine with zolazepam (TZ). The KD mixture combines the dissociative effect of ketamine with the muscle relaxation and sedative action of diazepam. It is generally considered to provide stable cardiovascular function [7]. TZ has the advantage of a longer duration of anesthesia, but it is sometimes associated with unstable recovery, respiratory depression, and other physiological disturbances [8,9]. Even though both regimens are widely practiced, there is concern that they may cause subclinical organ injury to vital organs such as the liver and kidneys, especially when given in higher doses [8,10].

Most studies so far have only compared the depth of anesthesia, induction, and recovery between these agents. Information about their long-term safety on liver function in rabbits is still limited. In particular, the effects of different doses of TZ have not been fully compared with KD using laboratory blood markers. This knowledge is important, because organ toxicity not only affects the health and welfare of the animals, but may also interfere with research outcomes where rabbits are used as models [11].

The aim of this study was to compare the anesthetic efficacy, physiological effects, and possible liver toxicity of three intravenous doses of tiletamine-zolazepam with a standard clinical dose of ketamine-diazepam in New Zealand White rabbits. The assessment included anesthesia quality, duration, recovery, and monitoring of heart rate, respiratory rate, and body temperature. In addition, liver function tests were performed. The results are intended to provide practical recommendations for safer anesthetic use in rabbits, with the goal of improving both clinical care and the reliability of experimental research.

2. Materials and Methods

2.1. Animals

In this investigation, 40 clinically healthy male New Zealand White rabbits, each weighing 2-3 kg, underwent five different anesthetic protocols. The rabbits were individually housed in cages for 7 days for acclimatization before the experiments and were provided with standard rabbit chow with locally available forage and water ad libitum. Before initiating the experiment, the animals were fasted for 6 hours, and water was withheld for 2 hours.

2.2. Experimental design

The animals were randomly assigned to 5 groups of 8 rabbits each (Groups 1, 2, 3, 4, and 5). Animals were randomly allocated to experimental groups using a computer-generated random sequence. The sample size of n=8 per group was selected to provide adequate statistical power for analysis of variance (ANOVA). Group 1 served as a saline-injected control to isolate the effects of handling and injection stress from the pharmacological effects of the anesthetic agents. Groups 2, 3, and 4 received tiletamine-zolazepam (TZ) (Zoletil™ 50, Virbac), and Group 5 received ketamine hydrochloride (Aneket, Neon Laboratories) and diazepam hydrochloride (Calmpose, Sun Pharma). The dosing regimens are detailed in Table 1. High-dose TZ group was intentionally selected to probe safety boundaries and to enable detection of dose-related biochemical changes.

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Table 1. Experimental Design and Dosing Regimen.

Parameter	Group 1 (Control)	Group 2 (TZ-High)	Group 3 (TZ-Mid)	Group 4 (TZ-Low)	Group 5 (KD)
Treatment	Saline (0.9% NaCl)	Tiletamine-Zolazepam	Tiletamine-Zolazepam	Tiletamine-Zolazepam	Ketamine + Diazepam
Dose	1 mL/kg	32 mg/kg	7.5 mg/kg	3.5 mg/kg	20 + 1 mg/kg
Route	Intravenous (IV)	Intravenous (IV)	Intravenous (IV)	Intravenous (IV)	Intravenous (IV)
Sample Size (n)	8	8	8	8	8

2.3. Anesthetization and Monitoring

On the day of the experiment, rabbits were weighed and transferred from the housing room to the operating room using a pet carrier. Heart rate, respiratory rate, and temperature were recorded before anesthesia. Hair on the hind limb and ear vein was trimmed, and a topical local anesthetic cream (Lidocaine) was applied to the ear vein to minimize discomfort during blood collection. Anesthesia was administered through the saphenous vein. Anesthetic depth was monitored by assessing the absence of the pedal withdrawal reflex in response to a toe pinch, loss of the ear pinch reflex, and loss of the righting reflex when placed in a lateral recumbent position. Heart rate, respiratory rate, and body temperature were monitored before anesthesia (0 min) and at 10-minute intervals up to 60 minutes after the injection of the anesthetic. Heart rate and peripheral oxygen saturation (SpO_2) were measured continuously using a pulse oximeter. Respiratory rate was recorded by visual counting of thoraco-abdominal excursions and confirmed intermittently by auscultation with a stethoscope. Body temperature was measured with a digital rectal thermometer at predefined timepoints.

2.4. Biochemical Analysis

Blood samples (approx. 2 mL) were collected from the marginal ear vein before anesthesia (baseline) and on the 1st, 3rd, 5th, and 7th day post-injection to monitor various biochemical markers. This well within recommended limits (≤10% total blood volume without fluid replacement) for multiple sampling when distributed over one week. The blood was collected in vacutainers with a gel and clot activator and allowed to coagulate at room temperature. Samples were then centrifuged at 1500 × g for 10 minutes, and the serum was separated and stored at -20 C until biochemical analysis. The serum was analyzed for a comprehensive hepatic panel using commercially available assay kits with a spectrophotometer. Hepatic markers include; Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), Gamma-Glutamyl Transferase (GGT), Total Bilirubin, Total Protein, and Albumin.

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3. Results

3.1. Anesthetic and Physiological Effects

The anesthetic parameters are summarized in Table 2. There was no significant difference in onset time among anesthetic groups (p=0.489). The duration of anesthesia was longest in the TZ-High group (58.50±4.34 min), which was significantly longer than all other groups (p<0.001). The recovery time for the TZ-High group (265.5±25.8 min) was profoundly prolonged and significantly longer than all other groups (p<0.001).

Table 2. Anesthetic parameters in rabbits administered with different anesthetic combinations (Mean ± SD, n=8/group).

Criteria	Group 1 (Control)	Group 2 (TZ-High)	Group 3 (TZ-Mid)	Group 4 (TZ-Low)	Group 5 (KD)	p-value
Onset time (min)	N/A	0.25±0.06	0.21±0.05	0.23±0.04	0.41±0.25	0.489
Duration of loss of pedal withdrawal reflex (min)	0	58.50±4.34^{a}	31.25±8.19^{b}	20.13±3.18^{c}	24.75±8.90^{c}	<0.001
Recovery time (min)	0	265.5±25.8^{a}	139.3±14.1^{b}	54.8±9.7^{c}	125.1±11.5^{b}	<0.001

Means within the same row with different superscript letters (a, b, c) differ significantly (p<0.05). N/A = Not Applicable.

Heart rate (Table 3) and respiratory rate (Table 4) were significantly altered. The TZ-High group developed profound bradycardia (45.50 ± 8.10 bpm) and severe respiratory depression (14.20 ± 2.50 breaths/min) at 30 minutes, both of which were significantly more severe than in any other group (p<0.001).

Table 3. Heart rate (beats per minute) at key time points (Mean ± SD, n=8/group).

Time (min)	Group 1 (Control)	Group 2 (TZ-High)	Group 3 (TZ-Mid)	Group 4 (TZ-Low)	Group 5 (KD)	p-value
Before	245.10 ± 28.30	251.50 ± 31.00	260.30 ± 25.50	248.80 ± 29.10	270.60 ± 20.40	0.512
30	239.50 ± 25.10^{a}	45.50 ± 8.10^{e}	195.40 ± 18.20^{b}	205.10 ± 22.80^{b}	140.30 ± 19.50^{d}	<0.001
60	241.30 ± 22.90^{a}	75.80 ± 10.20^{d}	188.90 ± 15.70^{b}	201.60 ± 24.00^{b}	145.80 ± 16.10^{c}	<0.001

For each time point, means within the same row with different superscript letters (a, b, c, d, e) differ significantly (p<0.05).

Table 4. Respiratory rate (breaths per minute) at key time points (Mean ± SD, n=8/group).

Time (min)	Group 1 (Control)	Group 2 (TZ-High)	Group 3 (TZ-Mid)	Group 4 (TZ-Low)	Group 5 (KD)	p-value
Before	46.20 ± 5.10	47.50 ± 5.90	45.80 ± 4.80	46.60 ± 5.30	48.10 ± 4.40	0.618
30	45.90 ± 4.50^{a}	14.20 ± 2.50^{d}	28.50 ± 3.10^{c}	36.10 ± 4.20^{b}	31.40 ± 3.80^{c}	<0.001
60	46.50 ± 4.20^{a}	19.60 ± 2.80^{d}	30.20 ± 2.90^{c}	35.50 ± 4.00^{b}	32.80 ± 3.10^{bc}	<0.001

For each time point, means within the same row with different superscript letters (a, b, c, d) differ significantly (p<0.05).

3.2. Serum Biochemical Findings

The TZ-High group exhibited severe hepatic toxicity. Hepatic Injury: The TZ-High group showed a sharp, significant increase in serum ALT and AST, indicative of acute hepatocellular injury (Table 5). This was accompanied by significant elevations in GGT and Total Bilirubin and a significant decrease in Total Protein and Albumin by Day 7, indicating cholestasis and impaired hepatic synthetic function (Table 6). All other groups showed only minor, transient changes.

Table 5. Serum Hepatic Biomarkers (Mean ± SD, n=8/group).

Parameter (U/L)	Group	Before	Day 1	Day 3	Day 7
ALT	1 (Control)	68.4 ± 10.1	70.1 ± 9.8^{c}	67.5 ± 11.2^{c}	69.3 ± 8.9^{b}
	2 (TZ-High)	72.1 ± 11.5	195.7 ± 33.4^{a}	248.6 ± 45.1^{a}	145.8 ± 22.6^{a}
	3 (TZ-Mid)	69.8 ± 9.5	115.3 ± 18.2^{b}	85.4 ± 14.3^{b}	71.5 ± 10.4^{b}
	4 (TZ-Low)	70.5 ± 8.8	88.6 ± 12.9^{bc}	74.1 ± 9.9^{c}	68.1 ± 9.2^{b}
	5 (KD)	73.3 ± 12.4	120.8 ± 20.5^{b}	90.2 ± 15.1^{b}	75.4 ± 11.8^{b}
p-value		*0.915*	*<0.001*	*<0.001*	*<0.001*
AST	1 (Control)	95.3 ± 15.2	98.8 ± 14.1^{c}	94.6 ± 13.8^{c}	96.1 ± 12.5^{b}
	2 (TZ-High)	101.7 ± 18.9	295.3 ± 60.2^{a}	188.4 ± 35.7^{a}	110.5 ± 19.3^{a}
	3 (TZ-Mid)	98.2 ± 16.5	145.1 ± 25.8^{b}	115.9 ± 20.1^{b}	99.8 ± 15.4^{b}
	4 (TZ-Low)	96.9 ± 14.8	110.2 ± 19.3^{bc}	101.3 ± 16.6^{bc}	95.5 ± 14.1^{b}
	5 (KD)	103.1 ± 20.1	155.6 ± 28.4^{b}	121.7 ± 22.3^{b}	101.4 ± 17.8^{b}
p-value		*0.887*	*<0.001*	*<0.001*	*0.048*
ALP	1 (Control)	94.5 ± 13.3	95.1 ± 12.9^{b}	93.8 ± 14.0^{c}	94.2 ± 13.5^{c}
	2 (TZ-High)	98.2 ± 15.1	121.6 ± 20.3^{a}	155.4 ± 28.9^{a}	180.3 ± 35.2^{a}
	3 (TZ-Mid)	95.8 ± 14.0	112.7 ± 18.5^{ab}	101.5 ± 16.2^{bc}	96.1 ± 14.8^{c}
	4 (TZ-Low)	93.9 ± 12.8	98.3 ± 13.1^{b}	95.2 ± 13.5^{c}	94.5 ± 13.1^{c}
	5 (KD)	99.6 ± 16.2	115.4 ± 19.8^{a}	105.8 ± 17.1^{b}	100.3 ± 16.5^{bc}
p-value		*0.921*	*<0.01*	*<0.001*	*<0.001*

For each parameter, means within the same column with different superscript letters (a, b, c) differ significantly ($p<0.05$).

Table 6. Comprehensive Serum Hepatic Function Markers (Mean ± SD, n=8/group).

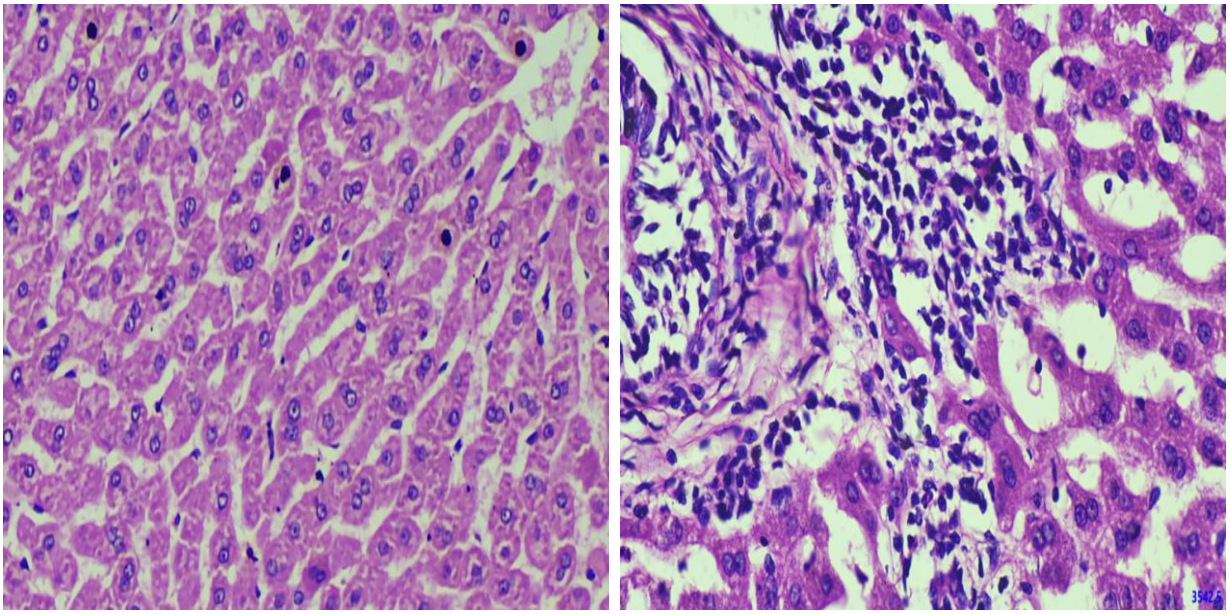
Parameter	Group	Before	Day 3	Day 7
Total Protein (g/dL)	1 (Control)	6.5±0.4	6.4±0.5^{a}	6.6±0.3^{a}
	2 (TZ-High)	6.6±0.5	5.1±0.6^{b}	4.5±0.7^{b}
	3 (TZ-Mid)	6.4±0.3	6.2±0.4^{a}	6.3±0.5^{a}
	4 (TZ-Low)	6.5±0.4	6.4±0.5^{a}	6.5±0.4^{a}
	5 (KD)	6.7±0.6	6.5±0.5^{a}	6.6±0.4^{a}
p-value		*0.781*	*<0.001*	*<0.001*
Albumin (g/dL)	1 (Control)	3.8±0.3	3.7±0.4^{a}	3.8±0.3^{a}
	2 (TZ-High)	3.9±0.4	2.9±0.5^{b}	2.4±0.6^{b}
	3 (TZ-Mid)	3.7±0.3	3.6±0.3^{a}	3.7±0.4^{a}
	4 (TZ-Low)	3.8±0.2	3.8±0.4^{a}	3.9±0.3^{a}
	5 (KD)	3.9±0.5	3.8±0.4^{a}	3.8±0.5^{a}
p-value		*0.812*	*<0.001*	*<0.001*
GGT (U/L)	1 (Control)	4.1±1.1	4.3±1.0^{c}	4.0±0.9^{b}
	2 (TZ-High)	4.5±1.3	15.8±3.1^{a}	9.7±2.5^{a}
	3 (TZ-Mid)	4.2±0.9	5.9±1.5^{b}	4.5±1.1^{b}
	4 (TZ-Low)	4.0±1.0	4.8±1.2^{bc}	4.2±1.0^{b}
	5 (KD)	4.6±1.4	6.2±1.8^{b}	4.8±1.3^{b}
p-value		*0.899*	*<0.001*	*<0.001*
Total Bilirubin (mg/dL)	1 (Control)	0.3±0.1	0.3±0.1^{c}	0.2±0.1^{b}
	2 (TZ-High)	0.4±0.2	1.9±0.4^{a}	1.1±0.3^{a}
	3 (TZ-Mid)	0.3±0.1	0.5±0.2^{b}	0.3±0.1^{b}

	4 (TZ-Low)	0.3±0.1	0.4±0.1^{bc}	0.3±0.1^{b}
	5 (KD)	0.4±0.1	0.6±0.2^{b}	0.4±0.2^{b}
p-value		*0.754*	*<0.001*	*<0.001*

For each parameter, means within the same column with different superscript letters (a, b, c) differ significantly (p<0.05).

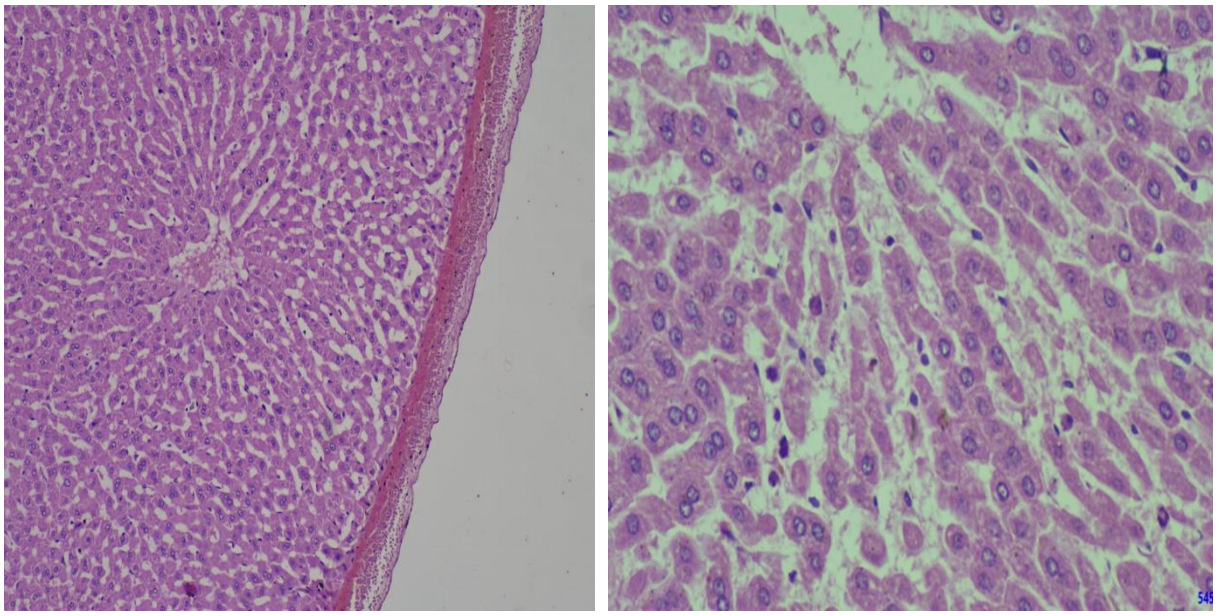
3.4. Histopathological Findings

All groups showed vacuolar degeneration around the centrilobular region, but Group D showed less of it. Hepatocytes in the periportal region exhibited vacuolar degeneration; however, it was less severe than in the centrilobular region. In all groups, the sinusoids around the centrilobular region were dilated. In Group A, there was higher dilation relative to the sinusoids of the periportal area, while in the other groups, there was no dilation around the periportal area. In Group A, there was subcapsular congestion, which was absent in all other groups. In Groups B and C, there was an accumulation of mononuclear inflammatory cells around the portal area, a localized loss of hepatocytes around the central vein, and Kupffer cell proliferation. (Fig. 1-4).



(**a**) (**b**)

Figure 1. (**a**) Photomicrograph of a rabbit liver section showing vacuolar degeneration of hepatocytes around the centrilobular region. (Hematoxylin and Eosin stain, 10X magnification); (**b**) Photomicrograph of a liver section from a rabbit in Group (TZ-7.5 mg/kg), demonstrating a prominent accumulation of mononuclear inflammatory cells around the portal area. (Hematoxylin and Eosin stain, 10X magnification).



(**a**) (**b**)

Figure 2. (**a**) Photomicrograph of a liver section from a rabbit in Group (TZ-32 mg/kg). Note the presence of subcapsular congestion. (Hematoxylin and Eosin stain, 10X magnification); (**b**) Photomicrograph of a liver section from a rabbit illustrating focal loss of hepatocytes and proliferation of Kupffer cells around the central vein. (Hematoxylin and Eosin stain).

4. Discussion

This study directly compared the anesthetic effects and organ-specific toxicities of two injectable protocols: tiletamine-zolazepam (TZ) at three dose levels and a standard dose of ketamine-diazepam (KD). The results showed clear differences between the two regimens, with TZ—especially at higher doses—being associated with major safety concerns and organ damage, whereas KD demonstrated a much safer profile.

The study revealed that TZ produced a distinct dose-dependent toxicity. Rabbits receiving the highest TZ dose (32 mg/kg) experienced prolonged anesthesia, delayed recovery, marked respiratory depression, and significant biochemical evidence of both liver damage. In contrast, KD and lower doses of TZ caused only mild, temporary changes in biochemical parameters and were normalized without lasting organ injury. This confirms the very narrow safety margin of TZ and emphasizes the critical importance of careful dose selection in clinical use. From a practical standpoint, these findings strongly suggest that KD is the more predictable and safer choice for rabbit anesthesia, particularly in routine practice.

High-dose TZ produced the longest anesthesia period, averaging about 58 minutes, compared with 25 minutes for KD. While longer anesthesia may initially seem advantageous, it was accompanied by a number of risks. Rabbits receiving high-dose TZ had a dangerously prolonged recovery, with a mean recovery time of 265.5 ± 25.8 minutes (approximately 4.4 hours), which was significantly longer than all other groups. This group had also shown clinical signs such as ataxia, lethargy, hypothermia, and dehydration. These complications, combined with the severe respiratory depression observed, made this protocol especially dangerous. Since rabbits have limited physiological reserves, such prolonged recovery times increase the likelihood of critical complications unless continuous monitoring and supportive care are available [12,13].

By comparison, the KD protocol resulted in a recovery time (125 ± 11.5 min) that was significantly shorter than the high-dose TZ group. Although this recovery was longer than that of the TZ-Low group, it was clinically smoother and safer, with fewer complications like ataxia and dehydration. Although KD may not provide sufficient analgesia for highly invasive surgeries, its safety advantages make it an appropriate option for short or minimally invasive procedures [14]. Its predictable effects give veterinarians greater control over anesthesia management, lowering the risk of post-anesthetic complications.

Hepatic toxicity was especially pronounced in the high-dose TZ group. Significant elevations in ALT and AST indicated hepatocellular injury, while increased GGT and bilirubin suggested cholestasis. Reductions in total protein and albumin levels further reflected impaired liver synthetic function. These findings together show a multi-dimensional pattern of liver damage with high-dose TZ. Importantly, the toxicity was dose-dependent. Rabbits receiving mid-dose TZ (7.5 mg/kg) displayed only mild and reversible increases in liver enzymes, while those given low-dose TZ (3.5 mg/kg) or KD showed negligible hepatic effects. This

gradient confirms that hepatotoxicity risk rises sharply with higher TZ doses, whereas KD carries a much lower risk [10].

Cardiovascular and respiratory effects further distinguished the protocols. High-dose TZ produced profound and sustained bradycardia, alongside depression of respiratory rate. The combination of unstable HR and severe RR suppression markedly reduces organ perfusion and oxygen delivery, posing a significant risk for rabbits, which have limited cardiopulmonary reserves [17,18]. By comparison, KD caused only mild bradycardia and moderate, stable reductions in RR, without the dangerous instability observed in TZ-High. This greater cardiorespiratory stability explains in part the reduced risk of organ injury and smoother anesthetic profile seen in the KD group, reinforcing its clinical value as a safer and more predictable choice [19].

Overall, the findings suggest that high-dose TZ (32 mg/kg) should be avoided in rabbits because it can cause severe acute liver failure, life-threatening respiratory depression, and very prolonged recovery times. KD, while producing shorter anesthesia, demonstrated a safer and more stable profile, making it the preferred option for short or minimally invasive interventions. Even moderate doses of TZ should be used cautiously, as the observed biochemical changes suggest toxicity thresholds are reached quickly. For clinical practice, these results emphasize the importance of prioritizing safety and predictability over prolonged anesthesia duration in rabbits.

This study was primarily based on biochemical markers without histopathological examination. While the results strongly indicate organ injury, tissue-level evidence would provide more definitive conclusions about lesion severity and distribution in different organs such as kidney, lungs, heart and brain. Additionally, only healthy adult rabbits were studied; the adverse effects of TZ may be even more severe in geriatric or subclinically ill animals [20,21]. Future research should include histopathology in wider organ systems, primarily, liver, kidney, lungs, heart and brain, longer-term biochemical monitoring, and investigations in at-risk populations to refine safety margins. Parallel evaluation of analgesic efficacy would also be useful, helping clinicians select the most suitable anesthetic protocol for both routine and invasive surgical procedures.

Beyond the immediate clinical implications, these findings also carry significance for refining anesthetic protocols in laboratory animal medicine and translational research. Rabbits are commonly used in biomedical studies, therefore ensuring reproducible and humane anesthetic strategies is critical both ethically and scientifically [22]. The clear evidence that tiletamine-zolazepam shows a dose-dependent pattern of systemic toxicity underscores the need for stringent anesthetic monitoring and individualized adjustments in experimental designs. Furthermore, the contrast between TZ and KD highlights a broader principle that extending anesthesia duration with high drug doses often comes at the expense of safety, especially in species with limited cardiopulmonary reserves. In this regard, KD emerges not only as the safer clinical option but also as the regimen that better aligns with the principles of refinement in animal research. Incorporating adjunct strategies such as multimodal analgesia, supplemental oxygenation, and active thermal support could further optimize outcomes, particularly when anesthesia must be prolonged [23]. Future investigations might also explore whether modified KD regimens or alternative benzodiazepine combinations provide equal efficacy with even greater safety margins. Ultimately, the findings of this study should encourage veterinarians and researchers to reconsider drug selection strategies with a priority on organ protection, recovery quality, and minimizing animal welfare risks.

5. Conclusions

The results of this comprehensive investigation demonstrate that while tiletamine-zolazepam at a dose of 32 mg/kg provides a prolonged duration of surgical anesthesia in rabbits, it is unequivocally associated with severe, acute hepatotoxicity. This liver damage is characterized by marked elevations in hepatocellular and cholestatic enzymes and is compounded by a progressive failure of hepatic synthetic function. Furthermore, this dose induces profound and clinically unacceptable cardiorespiratory depression. In stark contrast, the combination of ketamine-diazepam and lower doses of tiletamine-zolazepam offered shorter, effective periods of anesthesia but with a significantly wider margin of safety and minimal impact on hepatic function. Given the substantial risks, the high-dose tiletamine-zolazepam protocol cannot be recommended for use in New Zealand White rabbits. Ketamine-diazepam or lower doses of tiletamine-zolazepam represent far safer and more reliable anesthetic choices for this species.

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