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Renal Biochemical Response to Ketamine-Xylazine, Propofol and Tiletamine-Zolazepam in Local Rabbits (*Oryctolagus cuniculus*)

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Abstract

The aim of this trial was to focus on the impact of three commonly used anesthetic protocols on renal biochemical markers: plasma concentrations of urea and creatinine in wild domestic Algerian rabbits (*Oryctolagus cuniculus*), the protocols which were evaluated, ketamine-xylazine; propofol; and tiletamine-zolazepam. Thirty-tow healthy adult rabbits of both sexes were selected by chance (randomly) divided into four groups with eight rabbits in each group. Group one (control), was injected with IV injection of saline solution. Group two, was treated with IV xylazine (5 mg/kg) and ketamine (35 mg/kg). Group three, was treated with IV propofol (8 mg/kg) and Group four was treated with IV tiletamine-zolazepam (10 mg/kg). Blood samples were taken at baseline following a 15 day quarantine and acclimation period. A follow-up blood sample was collected 120 minutes after anesthetic administration. Plasma creatinine and urea levels were used as indicators of renal function. Statistical analysis revealed that plasma urea ($P < 0.001$) and creatinine ($P = 0.0004$) levels were significantly decreased under ketamine-xylazine anesthesia compared to baseline values. In contrast, in the propofol group, both plasma urea and creatinine concentrations showed a significant increase ($P < 0.05$), whereas in the tiletamine-zolazepam group, only creatinine levels were significantly elevated. These findings suggest that the impact of the anesthetic agent on renal function depends on the type of anesthetic use mainly, the decrease in renal function markers, such as urea and creatinine with the use of the ketamine-xylazine combination shows the possible renoprotective effect of the combination. Whereas, changes were small, these findings focus on that consideration which should be given to select an anesthetic protocol, particularly when dealing with compromised renal animals, in order to ensure accurate biochemical interpretation, and to minimize the risk of nephrotoxicity.

Keywords: Anesthesia; creatinine; renal function; urea; rabbit, nephrotoxicity.

Introduction

The rabbit (*Oryctolagus cuniculus*) is a pet and livestock animal used for biomedical or surgical research [1]. They are considered as complex animals to undertake anesthetic process due to the narrow margin between the dosage required for effective anesthesia and respiratory arrest following their strong reflex responses, the difficulty of tracheal intubation due to the small size of their glottis, and their respiratory reactivity, which can lead to respiratory arrest in case of poor anesthesia management [2]. The prized domestic role of rabbits, and their presence in research laboratories often make them susceptible to being anesthetized, both for diagnostic and surgical procedures. However, anesthesia in rabbits poses a higher risk compared to dogs and cats, due to their heightened sensitivity and stress-prone nature [3], it necessitates strict anesthetic procedures to minimize stress and

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suffering during these stages. Considering the welfare of laboratory animals which is a crucial issue, it is recommended to adopt safe and appropriate techniques to ensure their protection during these procedures.

Rabbit anesthesia is treated with a variety of injectable anesthetic drugs [4]. In rabbits, anesthesia is frequently associated with ketamine and xylazine [5, 6]. When separated ketamine, a dissociative anesthetic, produces cataleptic sedation, hypertonicity with superficial analgesia and limited muscle relaxation [7]. Ketamine is commonly given in combination with xylazine or diazepam to optimize muscle relaxation and analgesia while prolonging the effect [8]. Xylazine, an alpha-2 receptor sedative agonist, enhances these effects by causing muscle relaxation and analgesia. However, this combination may also result in side effects like respiratory depression, bradycardia, hypertension, hyperglycemia, and diuresis [9], in spite of all these risks, it is still frequently used due to its ability to produce accurate surgical anesthesia.

Tiletamine, a dissociative anesthetic, is frequently combined with zolazepam, a benzodiazepine with calming properties, to ensure effective anesthetic management in various animals, mainly rabbits. This combination promotes muscle relaxation and extends its effectiveness compared to ketamine [10]. Nevertheless, it only provides moderate analgesia and can cause negative effects such as respiratory depression, lack of breathing and, in the event of excessive doses, cause nephrotoxicity [11, 12]. Despite the absence of a specific antidote such as ketamine [13], this mixture is considered safe when dosed and monitored appropriately.

Propofol, a lipophilic anesthetic, is commonly used for induction and maintenance of anesthesia in animals as well as humans. Known for its rapid onset, limited efficacy, and quality of recovery, it is suitable for induction and infusion. It guarantees durable anesthesia over long periods while allowing for rapid recovery [14].

To assess the overall health of the animal and prevent potential anesthesia complications, it is essential to conduct a renal and hepatic biochemical analysis before any anesthetic intervention. The renal indicators blood urea nitrogen (BUN) and creatinine reflect the glomerular flow rate and play a crucial role in monitoring renal function, thereby facilitating the detection of lesions or dysfunctions [15].

This research aims to focus on renal biochemical analysis, with the goal of evaluating the kidney's response to different molecules (Ketamine-xylazine, Propofol, and tiletamine-zolazepam) in the local rabbit. For this, we evaluated the levels of urea and creatinine in the latter. These criteria facilitate the comparison and monitoring of the potential effects of anesthetics on renal function, while allowing for a better understanding of the biochemical changes related to anesthesia.

Material and Methods

Animals

In this study, 32 clinically healthy local breed rabbits of both sexes were sampled from a commercial supplier. The average body weight of the animals, measured using a precision balance (Digital balance, WS-20, China.), ranged between 2.30 and 2.90 kg.

They were housed in stainless steel cages in the animal facility of the Institute of Veterinary Sciences at Batna 1 University, adhering to environmental standards and conditions as follows: temperature, 20 to 22°C, relative humidity, 50% to 55%, 10 to 15 Air changes per hour (h) and a light cycle of 12 h/12 h (day/night) [16, 17].

The cages receive one or two weekly cleanings and disinfections. The rabbits received a pellet diet (150 g/d) and had access to fresh water available at all times. Before starting the experiments. The rabbits were quarantined for 15 days before their use to allow adaptation to environmental conditions.

The ethical approval for this study was granted by the Ethics Committee of the Institute of Veterinary and Agricultural Sciences (ISVSA), University of Batna 1, under decision number 026/DV/ISVSA/UB1/2023. It is worth noting that all the experiments were performed during the light phase of the cycle (between 09 h 00 and 12 h 00), since the lighting is a critical factor affecting the physiological parameters, behavior and rabbits [18].

Protocol of anesthesia

The rabbits in this study were randomly divided into four treatment groups, with each group consisting of 8 individuals (n=Hight).

The control animals (C) were given 1 ml of normal saline solution intravenously, while the experimental animals were divided into three groups, the first group (KX) received the combination of Ketamine (Ketamile®, Troy Laboratories) at 35 mg/kg and xylazine (Xylazine pro 2%®, vetopharm) at 5 mg/kg, the second group (P) received Propofol (Provive® 1 %, El Kendi) at 8 mg/kg, and the last group (TZ) received the combination of Tiletamine/Zolazepam (Zoletil 50®, Virbac) at 10 mg/kg Lateral auricular vein was injected with. The doses and route of administration were decided on the basis of the pilot studies and information found in the literature of previous studies on anesthetics involving laboratory rabbits [19].

Blood sample and analysis

The sampling areas were shaved and disinfected with chlorhexidine soap and alcohol, blood samples were taken just before the injection (0 min), then at

120 min after the injection of anesthetics or saline solution at the marginal ear vein and the external saphenous vein using an epicranial.

Two ml blood samples were collected in dry tubes, without anticoagulant, and allowed to clot. The samples were then centrifuged 1200 G and 4°C for 20 min, after which serum was separated to biochemically analyses urea and creatinine. The analyses was performed in a private medical laboratory using the RX © DAYTONA clinical chemistry analyzer from the Randox RX series.

Statistical analysis

To provide a more descriptive and analytical assessment of the response variables (plasma urea and creatinine levels), a two-tailed paired Student's t-test was applied to compare the mean values before and after anesthesia within each experimental group. Additionally, a two-tailed unpaired Student's t-test was used to compare the mean post-anesthetic plasma concentrations in each experimental group with those of the control group at selected time points. Prior to these analyses, the Shapiro-Wilk test was performed to assess the normality of the data distribution. All statistical analyses were conducted using MedCalc® software version 22.030, with the level of significance set at $\alpha = 0.05$. Data are presented as mean ± standard deviation (SD), and results were considered statistically significant when $P < 0.05$.

Results

Plasma urea and creatinine levels:

The variations in renal biochemical parameters before and after 120 minutes of anesthetic induction show significant differences according to the protocols used (Table 1). In the KX group (ketamine-xylazine), a very highly significant reduction in urea and creatinine was observed ($P = 0.0004$), indicating a marked impact on renal function. The P group (propofol) showed significant variations for both parameters ($P < 0,01$), while the TZ group (thiopental-zolazepam) revealed no difference for urea but a highly significant difference for creatinine ($P = 0.0023$).

Compared to the control group (C) (table 2), plasma urea concentrations decreased very highly significantly in the Ketamine-Xylazine (KX) group ($P \leq 0.001$). In contrast, no significant difference was observed in the Propofol (P) and Tiletamine-Zolazepam (TZ) groups compared to the control. Regarding creatinine, the KX protocol induced a very highly significant decrease in plasma concentrations ($P \leq 0.001$), whereas the Propofol (P) and Tiletamine-Zolazepam (TZ) protocols caused a very highly significant increase compared to the control group ($P \leq 0.001$). These results are shown in Fig. 1 and 2.

Discussion

This study explores the effects of three common anesthetic protocols on renal biochemical parameters in rabbits (ketamine-xylazine, propofol, tiletamine-zolazepam). The results reveal short-term alterations in plasma urea and creatinine concentrations, indicating variations in renal function according to the anesthetic protocols. These observations highlight the importance of choosing appropriate protocols to minimize the impacts on the health of laboratory animals.

In our study, we noticed a highly significant decrease in plasma urea and creatinine levels 120 min after the administration of the ketamine-xylazine (KX) protocol. This result is in agreement with the observations of [20], which showed a significant decrease in creatinine levels in the KX treated groups after 30 minutes, suggest a short-term preservation of renal function. However, our results are contradictory to those of [21], which reported an increase in blood urea and serum creatinine levels 120 min after KX anesthesia in rabbits. which may reflect a time-dependent shift in renal perfusion or function. These discrepancies likely stem from variations in the experimental design, including animal species, strain, age, anesthetic dose, or the timing of sample collection.

Pharmacologically, ketamine is a dissociative anesthetic that primarily acts as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor by binding to the phencyclidine-binding site and blocking glutamate-induced excitatory transmission in the central nervous system [22], its mechanism of action produces anesthesia, analgesia, and anti-inflammatory effects [23]. Additionally, ketamine interacts with opioid, monoaminergic, and muscarinic receptors, contributing to its analgesic and sympathomimetic effects [24]. Its sympathoadrenergic stimulation can increase heart rate, blood pressure, and renal sympathetic nerve activity (RSNA) [25], which may help maintain renal perfusion in the short term. However, it has also been reported to reduce renal cortical blood flow, leading to a transient decrease in glomerular filtration rate (GFR) [26], which may cause short-term elevations in renal biochemical markers, though usually within physiological limits [27].

Xylazine, an alpha-2 adrenergic agonist, produces sedation, analgesia, and muscle relaxation by inhibiting norepinephrine release centrally [28] Peripherally, it causes bradycardia, hypotension, and a reduction in cardiac output, potentially reducing renal blood flow and GFR [29]. However, several studies suggest that xylazine may exert renal-protective effects under specific conditions. [30, 31], demonstrated that xylazine enhances renal excretory responses through both renal nerve–dependent and –independent mechanisms mediated by central alpha-2

adrenergic receptors in rats anesthetized with ketamine. Moreover, [29] showed that xylazine induces diuresis and natriuresis independently of changes in GFR or vasopressin activity.

The combined use of ketamine and xylazine appears to provide a pharmacodynamic balance. Ketamine's sympathetic stimulation may counteract xylazine-induced hypotension, preserving effective renal perfusion. This synergistic interaction may explain the observed decrease in renal markers in our study, particularly when the combination is administered at moderate doses in healthy animals, contrasting with the observations of [27].Furthermore, the rapid hepatic metabolism of both drugs, followed by renal elimination of their metabolites (e.g., norketamine for ketamine), suggests the need for caution in patients with hepatic or renal dysfunction, where drug clearance may be delayed [24]

Clinically, our findings suggest that the KX protocol, when administered appropriately, may be safe in terms of short-term renal function in rabbits. However, due to the complex pharmacokinetics and hemodynamic effects of both agents, close monitoring remains essential, especially in patients with pre-existing renal compromise. Further studies, including histopathological evaluation and long-term renal assessments, are recommended to fully establish the safety profile of this anesthetic combination.

For the Propofol group, a significant increase in plasma creatinine levels was noticed, while urea concentrations remained unchanged. These observations are consistent with previous work by [32], which found an increase in creatinine levels. Moreover, divergent studies report different results regarding the observation of no significant change in creatinine or urea levels after propofol anesthesia [33]. These results suggest a possible transient reduction in glomerular filtration, likely induced by systemic vasodilation on the renal arteries and a decrease in blood pressure.

From a pharmacological perspective, propofol acts as a potent GABA- A- receptor agonist, inducing central nervous system depression that facilitates anesthetic induction. However, its effects on renal function in rabbits can be attributed to its significant cardiovascular actions, in rabbits and other animals. Studies have shown that propofol causes immediate and transient narrowing of large arteries, reduced left ventricular performance, and increased peripheral vascular resistance in rabbits [34]. It induces dose-dependent reductions in myocardial contractility, mean arterial pressure, and heart rate, with persistent depression even after dose reduction [35] These effects are attributed to propofol's direct actions on vascular smooth muscle and endothelial cells, leading to peripheral vasodilation and myocardial depression [36] The combined cardiovascular effects of propofol result in systemic hypotension, which can be particularly concerning in patients with pre-existing heart conditions[36].

These hemodynamic changes can lead to reduce renal blood flow and glomerular filtration rate (GFR), potentially causing pre-renal azotemia [37], and thus an accumulation of nitrogenous waste products such as urea and creatinine in the plasma. Furthermore, propofol's high lipid solubility results in tissue accumulation, which may prolong its systemic effects [38]. The drug is primarily metabolized in the liver, and its metabolites are excreted renally, potentially influencing renal biochemical parameters.

This interpretation is supported by additional studies. [39] demonstrated that propofol relaxes rabbit renal arteries via activation of Ca^{+2} activated potassium channels, although they noted that its systemic hypotensive effect generally prevails and may ultimately reduce effective renal blood flow. Similarly, [40] found that propofol anesthesia led to an increase in blood urea nitrogen (BUN) levels in rabbits post-induction. In our study, the slight elevations in serum urea and creatinine observed under propofol anesthesia likely represent a transient pre-renal azotemia.

Clinically, these increases in urea and creatinine during propofol anesthesia in rabbits most likely reflect a reversible pre-renal impairment caused by reduced renal perfusion. In healthy animals, such changes are generally mild and reversible. However, they underscore the importance of maintaining adequate intravascular volume and monitoring renal parameters during propofol anesthesia. Fluid therapy and hemodynamic support should be considered when needed, especially in rabbits with pre-existing renal or cardiac conditions, to avoid exacerbation of azotemia.

In this study, the administration of the TZ protocol at a dose of 10 mg/kg resulted in a significant increase in serum creatinine concentrations, without any notable change in urea levels. These results are consistent with those of [33], who also observed an increase in plasma creatinine with the TZ protocol, suggesting a transient impairment of glomerular filtration or an increase in protein catabolism.

Tiletamine, as a dissociative anesthetic similar to ketamine, primarily acts as a non-competitive antagonist of NMDA receptors, blocking glutamate binding and inhibiting the thalamocortical and limbic systems, thereby inducing anesthesia and analgesia [41, 42] (Popik et al., 2017; Mion, 2021). However, tiletamine alone is known for its nephrotoxic effects in rabbits, causing severe renal tubular necrosis at high doses (32–64 mg/kg), associated with abnormal increases in blood urea nitrogen and serum creatinine

levels, and mild nephrosis at lower doses [11, 12]. Furthermore, hepatic metabolism and renal excretion of tiletamine pose a risk of accumulation in animals with renal insufficiency, which could exacerbate toxic effects [43].

Zolazepam, a benzodiazepine used in combination with tiletamine in the TZ protocol, acts as a positive allosteric modulator of GABA_A receptors. By binding to a specific site located between the α and γ subunits of the receptor, it increases the affinity of GABA for its receptor, leading to more frequent chloride channel openings. This action results in neuronal hyperpolarization, thus reducing neuronal excitability and producing sedative, anxiolytic, muscle-relaxant, and anticonvulsant effects [44]. Unlike tiletamine, zolazepam does not exhibit direct renal toxicity.

In our study, the increase in creatinine without a significant change in urea may reflect a transient renal effect of tiletamine, not aggravated by zolazepam. This suggests a partial modulation of nephrotoxic effects at this dose, but also highlights the importance of monitoring renal biomarkers following TZ anesthesia, especially in animals with compromised renal function.

Clinically, these results underline the importance of thoroughly evaluating renal function before administering the TZ protocol, particularly in animals with pre-existing renal conditions. The increase in creatinine suggests a temporary alteration in renal function that may be exacerbated in cases of renal failure. Therefore, dose adjustment may be necessary to minimize the risk of nephrotoxic side effects. Such precautions are especially critical in veterinary practices involving fragile or at-risk patients.

Conclusion

The results of this study demonstrate that the evaluated anesthetic protocols KX, P and TZ have distinct impacts on renal biochemical parameters. The KX protocol appears to exert a protective effect on renal function, likely due to its ability to maintain better hemodynamic stability. In contrast, P and TZ induced more pronounced biochemical variations, although these remained within acceptable physiological limits.

Although the elevation of creatinine appears to be transient and not associated with acute renal failure, these changes could have more significant consequences in animals with pre-existing renal or cardiovascular comorbidities. Careful monitoring of renal parameters before and after anesthesia remains crucial. These results underscore the importance of rigorous management of anesthetic doses and careful interpretation of biochemical data in anesthetized or recovering animals. To further explore these observations, additional studies are necessary to elucidate the underlying mechanisms and to evaluate the long-term effects of these anesthetic agents on renal function.

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Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical of approval

The ethical approval for this study was granted by the Ethics Committee of the Institute of Veterinary and Agricultural Sciences (ISVSA), University of Batna 1, under decision number 026/DV/ISVSA/UB1/2023

TABLE 1. Analysis of Changes in Renal Parameters Before and After Anesthesia in Each Anesthetic Protocol Group.

Time and treatment group		urea (g/l)	P value	Creatinine (mg/dl)	P value
C	0min	0,44 ± 0,17		0,78 ± 0,94	
	120min	0,38 ± 0,14	p> 0.05	0,72 ± 0,96	p> 0.05
KX	0min	0,43 ± 0,13		0,82 ± 1,70 ***	
	120min	0,08 ± 0,03***	p = 0.0001	0,51 ± 0,84	p = 0.0004
P	0min	0,31 ± 0,08		0,9 ± 1,60	
	120min	0,35 ± 0,09 *	P = 0,0157	0,96± 1,50 *	P = 0,0462
TZ	0min	0,36 ± 0,13		0,82 ± 1,08	
	120min	0,49± 0,06	P = 0,0523	1,30 ± 1,19 **	P = 0,0023

All values are expressed as mean ± the standard error of the mean. A column without superscripts indicates no significant difference among the anesthesia groups

* Significant difference ($0.01 \leq P < 0.05$), ** a highly significant difference ($0.001 \leq P < 0.01$), and *** very highly significant difference ($P \leq 0.001$).

TABLE 2. Effects of Anesthetic Protocols on Plasma Urea and Creatinine Levels in Rabbits 120 Minutes After IV Injection (n=8 per Group): Control (C), Ketamine-Xylazine (KX), Propofol (P), and Tiletamine-Zolazepam (TZ)

Products	C	KX	P	TZ	P value*
urea (g/l)	0,38 ± 0,14	0,08± 0,03 ***	0,35 ± 0,09	0,49 ± 0,06	P= 0,0001
Creatinine (mg/dl)	0,72 ± 0,96	0,51 ± 0,84***	0,96± 1,50 ***	1,30± 1,19 ***	P= 0,0001

All values are expressed as mean ± the standard error of the mean. A column without superscripts indicates no significant difference among the anesthesia groups ($p \geq 0.05$).
*** indicate a very highly significant difference ($P \leq 0.001$).

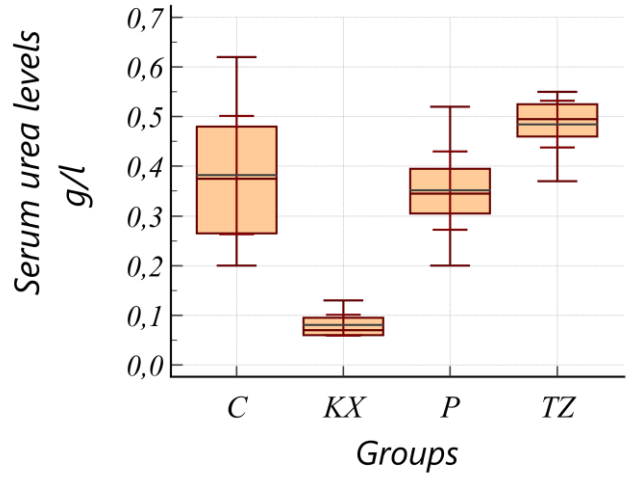

Fig. 1. The figure shows the variations in serum urea levels between the groups compared to the control.
The whisker box of the Control partially overlaps, this overlap with the whisker boxes of groups P and TZ indicates that there is no statistically significant difference.
The boxes of Control and KX do not overlap, which is a statistically significant sign, indicating that there is likely a significant difference between the two data sets.
We note the absence of overlap between KX, P, and TZ, which indicates the presence of a significant difference between the three groups.

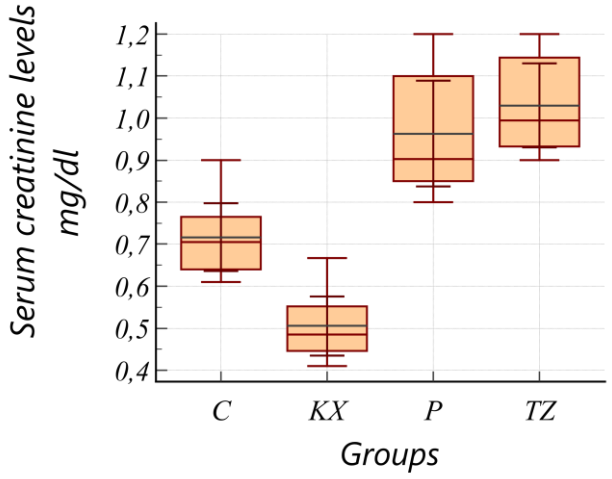

Fig. 2. Box plots illustrate the Comparison of Serum Creatinine Levels between Groups relative to the control
The figure shows the variations in serum creatinine levels between the groups compared to the control.
The whisker box of the Control does not overlap with the other boxes, which is a statistically significant sign, indicating that there is probably a significant difference between the groups.
We note the overlap between the two groups P and TZ, which indicates the absence of a significant difference.
The boxes of KX, P, and TZ do not overlap, which is a statistically significant sign, indicating that there is probably a significant difference between the KX group and the P and TZ groups.

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الاستجابة البيوكيميائية الكلوية لكيتامين-زيلازين، وبروبوفول، وتيليتامين-زولازيبام في الأرانب المحلية(Oryctolagus cuniculus)

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الملخص

هدفت هذه الدراسة إلى تقييم تأثير ثلاثة بروتوكولات تخدير شائعة الاستخدام على المؤشرات البيوكيميائية لوظيفة الكلى، وتحديدًا تركيزات اليوريا والكرياتينين في بلازما الأرانب الجزائرية المحلية(Oryctolagus cuniculus) .البروتوكولات التي تم تقييمها كانت الكيتامين-زيلازين؛ البروبوفول؛ والتيلتامين-زولازيبام . تم تقسيم 23 أرنبًا بالغًا سليمًا من كلا الجنسين عشوائيًا إلى أربع مجموعات، كل مجموعة تحتوي على 8 أرانب. تلقت المجموعة الأولى (المجموعة الضابطة) محلولًا ملحيًا وريدياً، ومجموعة تلقت حقنة وريدية من مزيج الكيتامين-زيلزين (35 و5 ملغ/كغ على التوالي)، ومجموعة تلقت بروبوفول (8 ملغ/كغ)، والمجموعة الأخيرة تلقت تيلتامين-زولازيبام (10 ملغ/كغ). تم أخذ عينات الدم في البداية بعد فترة حجر صحي وتكيف لمدة 15 يومًا ثم تم جمع عينة دم أخرى بعد 120 دقيقة من إعطاء المخدر ، وتم قياس تركيزات اليوريا والكرياتينين في البلازما كمؤشرات لوظيفة الكلى. أظهرت التحليلات الإحصائية أن مزيج الكيتامين-زيلزين أدى إلى انخفاض كبير في مستويات اليوريا ($P < 0.001$) والكرياتينين مقارنة بالقيم الأساسية($P = 0.0004$) ، مما يشير إلى تأثير وقائي محتمل على الكلى. في المقابل، لوحظت زيادة في تركيزات الكرياتينين ($P < 0.05$) دون تغييرات في مستويات اليوريا في مجموعتي البروبوفول والتيلتامين-زولازيبام. تشير هذه النتائج إلى أن اختيار بروتوكول التخدير المناسب له أهمية بالغة، خاصةً في الحيوانات ذات الوظائف الكلوية الضعيفة، لضمان تقليل خطر السمية الكلوية.

الكلمات الدالة: التخدير, الكرياتينين, اليوريا, وظائف الكلى, الأرنب, التسمم الكلوي.