Egyptian Journal of Veterinary Sciences

A Comparative Analysis of Dexmedetomidine, Medetomidine, and Xylazine in Combination with Ketamine in Rats

Pavel O. Qader, Dekan A. Radah*, Shahamand S. Mustafa , Niaz K.H. Amin, Kalle J. Hussen, Peshwaz M. Hawla and Lania N. Abdullah

Surgery and Theriogeniology Department, College of Veterinary Medicine, University of Sulaimani, Bkhtyari, Sulaymaniyah, Iraq.

Abstract

THIS study compared the anesthetic efficacy and safety of three α_2 -adrenergic agonists, xylazine, medetomidine, and dexmedetomidine, each combined with ketamine. The objective was to identify an optimal anesthetic protocol that ensures animal welfare and reliability in laboratory research. Forty male rats were separated into four groups: a control group (CO) given saline, and three treatment groups receiving ketamine 50 mg/kg combined with either 0.1 mg/kg dexmedetomidine (DK), 0.5 mg/kg medetomidine (MK), or 5 mg/kg xylazine (XK) via intraperitoneal injection. The study evaluated anesthesia profiles and physiological parameters during the procedure, while biochemical, renal, and hepatic biomarkers were evaluated after 14 consecutive days. The XK group showed a significantly longer induction time compared to the MK and DK. Correspondingly, maintenance of anesthesia was prolonged in the XK and MK groups compared to the DK group. Physiological assessments revealed significant cardiorespiratory depression in the XK group, marked by pronounced reductions in heart rate, respiratory rate, SpO2, and body temperature. In contrast, the MK and DK groups maintained more stable physiological parameters. Biochemical analysis showed minimal hepatic and renal disturbances in the DK group, with the lowest levels of liver enzymes (ALT, AST, and GGT). The XK group exhibited significantly elevated bile acids, creatine kinase, and electrolyte imbalances. Renal profiles highlighted superior clearance in the DK group. In conclusion, the DK protocol provided rapid induction, stable cardiorespiratory function, and minimal metabolic and organ disturbances. This exceptional safety profile and physiological stability make it an ideal anesthetic regimen for both laboratory and veterinary applications.

Keywords: Xylazine, Medetomidine, Dexmedetomidine, Hepatic Function, Renal biomarker.

Introduction

Anesthesia and analgesia are major components of many interventional studies on laboratory animals. However, many studies have shown improper reporting or use of anesthetics or analgesics in research proposals and published articles. An ideal anesthetic regimen should balance analgesia, muscle relaxation, minimal physiological disturbance, and adequate sedation [1]. Dissociative agents such as ketamine are commonly used due to their quick onset, reasonable safety profile, capacity to maintain respiratory and cardiovascular functions, and multiple administration routes. However, despite its excellent analgesic activity, its tendency to induce muscle rigidity means sedatives must be administered together to produce a balanced anesthetic state as well as muscular relaxation [2].

The α_2 -adrenergic agonist agents (xylazine, medetomidine, and dexmedetomidine) are often used with ketamine, a common anesthetic, for the induction of anesthesia. The central and peripheral nervous systems' presynaptic norepinephrine release can be inhibited, producing hypnotic or sedative effects [3]. The most often used α_2 -adrenergic agent in veterinary practice is xylazine, despite the high frequency of side effects, such as bradycardia and hypotension [4,5]. At lower doses, medetomidine, a more selective drug, is well known for its potent sedative effects. Even more receptor selectivity and fewer adverse effects

*Corresponding authors: Dekan A. Radah, E-mail: dekan.aziz@univsul.edu.iq, Tel.:+ 9647736990798
(Received 24 July 2025, accepted 01 September 2025)
DOI: 10.21608/ejvs.2025.407261.2992

are offered by its pharmacologically active enantiomer, dexmedetomidine [6,7].

As research protocols are improved to prioritize animal welfare, researchers are investigating anesthetic regimens that ensure reliability in depth of anesthesia, reduce variability caused by stress, and rapid recovery times [8]. The selection of a balanced anesthesia is influenced by several factors, such as the nature of the procedure, the physiological condition of the animal, cost, availability, and the minimization of side effects; however, ketamine and α_2 -adrenergic are commonly used together in rodents [9]. In contrast to xylazine and ketamine (XK), some research has shown that ketamine-dexmedetomidine (DK) produces better cardiovascular stability and more seamless recovery phases [10]. Other research suggests that medetomidine- and ketamine- (MK) combinations provide a good balance between safety and effectiveness [11,12]. Several studies have investigated some physiological vital parameters comparing DK to XK protocols and found that DK maintained better oxygen saturation and body temperature homeostasis during prolonged operations [13].

Additionally, there is increasing evidence that anesthetic combinations may have varying effects on biochemical and physiological markers. The hepatic and renal tissues were affected by oxidative stress when specific combinations were administered repeatedly. Due to changes in pharmacodynamic action and modification in α_2-adrenergic dosages in diabetic animal models [12,14].

In the present investigation, three α_2 -adrenergic agonists, xylazine, medetomidine, and dexmedetomidine, in combination with ketamine, will be extensively compared in male rats. It assesses their effects on physiological parameters: heart rate (HR), respiratory rate (RR), body temperature (BT), and oxygen saturation (SpO2). Additionally, anesthesia time protocols (induction time, anesthetic depth or duration, and recovery quality) as well as effects on renal and hepatic biomarkers will be examined. By carrying out this, the study aims to determine the safest and most effective combination to apply in general anesthesia-dependent laboratory research protocols. The findings will support the 3Rs (replacement, reduction, and refinement) framework for ethical anesthetic agent selection, ensure procedural consistency, and maximize animal welfare.

Material and Methods

Experimental Design

This controlled laboratory study was conducted on 40 adults male Wistar rats, each weighing between 250–330 grams, aged estimated 8 to 12 weeks. The animals were housed under standard laboratory conditions (12-hour light/dark cycle, ambient temperature 22 ± 2 °C, and ad libitum access to food and water) for at least one week before the experiment for acclimatization [15,16]. Ethical approval for all procedures was approved (approval no: VET0282) from Committee of the University of Sulaimani College of Veterinary Medicine (UOS-CVM).

The animals were randomly assigned to four experimental groups (n = 10 per group):

- Control (CO): No anesthetic agent administered received physiological saline (0.9% NaCl).
- Xylazine and ketamine (XK): Treated with an anesthetic combination of 5 mg/kg of Xylazine and 50 mg/kg of ketamine.
- Medetomidine and ketamine (MK): Treated with an anesthetic protocol of 0.5 mg/kg of medetomidine and 50 mg/kg of ketamine.
- Dexmedetomidine and ketamine (DK): Treated with anesthetic protocol 0.1 mg/kg dexmedetomidine and 50 mg/kg ketamine.

Each group was subjected to the same monitoring and evaluation protocols to ensure consistency and reproducibility. Anesthetic protocols were administered intraperitoneally (IP). The duration of the following anesthetic phases was recorded.

Assessment of Physiological parameters

Induction time is the measured interval between anesthetic administration and loss of righting reflex. For maintenance time the Period during which the animal remained unresponsive and immobile was assessed. Finally, Recovery time was evaluated from the first voluntary movement until complete restoration of postural reflexes after administering atipamizol (AT). All physiological parameters were recorded at three-time intervals post-induction: 5, 10, and 15 minutes. The parameters included: Heart rate (bpm), Respiratory rate (breaths/min), Core body temperature (°C), Peripheral oxygen saturation (SpO_2 , %), and Perfusion index (%).

Monitoring was performed using a veterinary physiological monitoring suite and multi-parameter patient monitors designed for small animals [17]. Core temperature was measured rectally, and SpO_2 and perfusion index were assessed using a paw-clip pulse oximeter. (Fig. 1)

Blood Collection and Biochemical Assessment

Animals were injected with XK, MK, and DK, once daily via the intraperitoneal (IP) route for 14 consecutive days. The control group (CO) received

an equivalent volume of physiological saline (0.9% NaCl) following the same schedule. Treatments started on Day 0 and continued through Day 14, constituting a two-week exposure period. Throughout the treatment duration, animals were housed under standard laboratory conditions, with ad libitum access to food and water, and were checked daily for general health and any signs of adverse effects.

At the end of the 14-day treatment period, animals were fasted overnight and anesthetized with the same group's treatment. Blood samples were collected via cardiac puncture (exceptional for the CO group collected via lateral tail vein) and transferred into plain tubes for serum separation [18]. Serum was obtained by centrifugation at 3,000 rpm for 10 minutes at 4 °C and stored at 80 °C until biochemical analysis.

Liver function tests were assessed by measuring serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and albumin using an automated biochemical analyzer (Cobas) according to the manufacturer's protocols. Renal function was evaluated by analyzing serum urea, creatinine kinase (CK), and blood urea nitrogen (BUN) levels. All assays were performed using standard colorimetric methods or commercially available diagnostic kits validated for rat serum [19] .

Statistical Analysis

All data statistically analyzed using IBM SPSS Statistics (version 29). Descriptive statistics are reported as mean ± standard deviation (SD). One-way analysis of variance was employed to compare induction, maintenance, and recovery times among groups and the interaction between treatment group and time point for physiological parameters (HR, RR, BT, SpO_2 , and PI) and biomedical markers. A p-value of <0.05 was considered indicative of statistical significance. Graphical representations were generated using GraphPad Prism (version 10.5.0) for data visualization.

Results

The time for induction, maintenance, and recovery phases were compared among the three treatment groups. Results are presented as mean ± standard deviation, and a One-Way ANOVA was used to assess statistical significance among groups (Table 1).

The DK group showed the rapid induction time, in comparison with the MK group, while the XK group had the longest induction time, the difference was statistically significant ($p < 0.001$).

The DK group also had the shortest maintenance time, suggesting a shorter anesthetic duration in comparison to the MK group. XK had the longest maintenance time after administration of atipamezole. The differences were statistically significant ($p < 0.05$).

Although DK showed the shortest mean recovery time, the differences across groups were not statistically significant ($p > 0.05$). The variability in recovery responses may be due to individual differences or inconsistent depth of anesthesia before recovery.

Physiological parameters were recorded in four groups (CO, XK, MK, DK) at different time intervals (0, 5, 10, and 15 minutes). The measured parameters included heart rate (HR), respiratory rate (RR), body temperature, arterial oxygen saturation (SpO_2), and perfusion index (PT). Results are expressed as a line graph and error bars. (Fig. 2).

The CO group at baseline (0 min) showed the highest heart rate (315.8 ± 17.4 bpm). A substantial decrease in HR was seen in the XK group at 10 min (186.6 ± 45.4 bpm), followed by partial recovery at 15 min (272.1 ± 41.5 bpm). Both MK and DK groups showed moderate decreases over time, with MK more stable (223 bpm) and DK (235.8 bpm) by 15 minutes

RR was initially highest in the CO group (85.5 ± 5.6). In the XK group, RR dropped significantly at 5 min (42.0 ± 25.7), then increased at 10 and 15 min, showing possible anesthetic recovery or compensation. The MK and DK groups kept elevated RR, particularly MK at 15 min (67.0 ± 15.3), showing higher respiratory stimulation or stress response.

BT declined slightly in all groups over time. BT profoundly decreased in the XK group from (35.45 ± 1.03 at 5 min to 32.2 ± 1.02 at 15 min), However, MK and DK groups kept stable temperatures, suggesting better thermoregulation or less suppression or hypothermia.

SpO_2 was highest in the normal untreated animals abbreviated as the CO group (95.5 ± 1.87) and significantly dropped in the XK group, reaching a minimum at 10 min (75.9 ± 7.86), while in the DK group and MK groups moderate and consistent with minimal reductions, indicating more stable cardiorespiratory function in comparison.

PI (peripheral blood flow) decreased in the XK group initially (0.35 ± 0.14), then slightly increased over time (At 15 min) the MK and DK groups showed increasing trends toward 15 min (0.57 and 0.68, respectively), suggesting a gradual

improvement in peripheral circulation. The Ne group had moderate perfusion at baseline (0.53 ± 0.14).

Globulin (GLO), albumin (ALB), and total protein (TP) did not significantly change. However, under alpha-2 agonist-based anesthesia, ALB levels were higher in the MK and DK groups ($p = 0.01$), indicating either increased protein synthesis or decreased albumin turnover. For the untreated rats in the CO group, all values (TP: 64.14 ± 5.11 g/L; ALB: 35.10 ± 3.2 g/L) stayed within the normal physiological range, suggesting no hepatic dysfunction (Table 2).

ALT and AST, key markers of hepatocellular injury, showed significant variations. ALT was lowest in DK (28.00 ± 6.78U/L) and highest in MK (44.30 U/L) ($p < 0.001$). AST peaked in MK (184.60 U/L), with the lowest in DK (131.40 U/L) ($p = 0.01$). GGT, another hepatic enzyme, showed a significant reduction in DK ($p < 0.001$), reflecting minimal biliary or hepatic stress. Despite these statistical differences, all enzyme values remained within normal ranges.

TBA (Total Bile Acids) were elevated in all groups, with XK reaching 39.00 µmol/L, much above the CO range (5 ± 3 µmol/L). Although non-significant ($p = 0.09$), this increase might suggest mild cholestatic stress, particularly in xylazine-treated animals.

Creatine Kinase (CK) and Amylase (AMY) were significantly different across groups. CK was highest in XK (596.80 U/L), and the difference was significant (P value <0.05). In addition, AMY was significantly lower in XK, while MK and DK showed normal values ($p < 0.001$), potentially reflecting lower stress levels or sympathetic suppression in the future.

Cholesterol (CHOL) levels were significantly higher in XK and MK ($p < 0.001$), all exceeding the rat norm of 1.8 ± 0.4 mmol/L, meanwhile in DX close to the CO group. In MK, glucose (GLU) peaked at 12.64 mmol/L, which was significantly higher than in XK and DK ($p < 0.001$). Significant differences between the groups were found in creatinine and blood urea nitrogen (BUN) ($p < 0.001$). The DK group had the lowest BUN (1.79 mmol/L), which may show increased renal clearance or hemodilution. BUN/CRE ratio reduced significantly in DK ($p = 0.04$), indicating better renal filtration efficiency compared to XK and MK. tCO_2 (total CO_2) levels were significantly lower than the reference (23 ± 3 mmol/L), especially in XK ($p < 0.001$), pointing toward mild metabolic acidosis in all groups.

Calcium (Ca) was slightly elevated in all groups. Phosphate ($PO4^3$) showed a significant elevation in MK ($p < 0.001$), due to renal phosphate retention or stress-related shifts. Mg (magnesium) was significantly elevated in XK ($p < 0.001$), while MK and DK were within the normal range. $Ca/PO4^3$ ratio, an indicator of vascular calcification was markedly high in the medetomidine-based protocol (99.70 mg/dL).

Discussion

The analytical comparison means ± SD of anesthetic efficacy between three treatment groups XK, MK, and DK based on induction, maintenance, and recovery times presented in Table 2. The statistical differences (as presented by F- and p-values) have important consequences for anesthetic procedure selection in laboratory settings.

The induction time was assessed from anesthetic administration until loss of consciousness, demonstrating statistically significant variations throughout groups ($p = 0.00046$). The DK group demonstrated the shortest induction time, showing a quick onset, suited for time-sensitive treatments [20]. Observed the same results, that combinations containing dexmedetomidine and ketamine enhanced more rapid induction in Inbred Laboratory Mouse Strain (BALB/c mice) when compared to other protocols [20].

Significant differences were also seen in maintenance time between groups ($p = 0.0246$), The DK group had the shortest maintenance time, indicating that it induced anesthesia more rapidly. This is consistent with dexmedetomidine's pharmacokinetic profile, which has a comparatively short duration when mixed with longer-acting agents [21].

Recovery time was not different between groups ($F = 2.68$, $p = 0.101$), however, the DK group recovered the fastest quantitatively. This agrees with the findings that dexmedetomidine-containing mixtures enable rapid recovery due to their reversible effect via atipamezole [22]. These results reveal that the DK procedure is efficient for rapid onset and recovery in the presence of AT (atipamizol), which is ideal for short-term treatments. However, XK and MK procedures may be more appropriate for prolonged operations due to their extended maintenance durations, as reported by investigations are important for experimental animals and welfare [23,24].

HR reduced dramatically in the XK group at 5 and 10 min indicating a profound bradycardia, due to xylazine binding with a_2-adrenergic agonist

receptors, which causes parasympathetic control[25]. The MK and DK groups had more stable HR values, with DK maintaining the highest hemodynamic stability at 15-minute time interval. This is consistent with recent findings that observed cardiovascular depression during sevoflurane anesthesia [26]. Furthermore, dexmedetomidine has a better sedative activity than xylazine, with less cardiovascular suppression when administered with ketamine [27].

XK showed a significant decrease in RR at 5 minutes (42 bpm), which improved slightly over time but remained lower than baseline. In contrast, the MK and DK procedures maintained respiratory rates closer to normal physiology. The greater RR in MK at 5 minutes reflects less respiratory [28].

The XK group had a decline in BT as low as 32.0°C in 10 minutes, inducing hypothermia, a typical result in small rodents under anesthesia due to their high surface area-to-volume ratio and vasodilation [29]. MK and DK maintained preserved body temperatures in comparison with XK, indicating improved thermoregulatory function. Anesthesia-induced hypothermia correlates with recovery durations and increases the rate of mortality during anesthesia in small mammals, especially with xylazine-based regimens [21].

SpO_2 dropped dramatically in XK, reaching an essential point of 75.9% at 10 minutes, which is below acceptable standards and indicates poor ventilation-perfusion balance. Both MK and DK groups sustained acceptable oxygen levels indicating better respiratory function. This is consistent with the results of a previous study, which evaluated inhalational and injectable anesthetics and found that dexmedetomidine combinations enhanced respiratory efficiency [30].

The PI, a measure of peripheral blood flow and vasomotor tone, remained lower in XK and steadily increased in the DK group by 15 minutes. This improvement under DK reflects vasodilation recovery and improved tissue perfusion, which are critical for avoiding organ ischemia during extended anesthesia. The DK combination is adequate in microvascular perfusion, recommending it for imaging and surgical procedures due to its balanced anesthetic depth with minimum perfusion compromise [31].

The hepatic assessment tests revealed that the DK group had reduced levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT), which are all conventional indicators of hepatocellular function and biliary function. These findings are consistent with previous research showing that dexmedetomidine may reduce oxidative stress and inflammation in hepatocytes [32,33]. Although all groups had normal ALT and AST levels, the DK group had much lower levels, indicating reduced hepatic stress, due to dexmedetomidine's increased α_2-adrenoceptor selectivity [34].

Albumin (ALB) levels were higher in the MK and DK groups compared to the XK. Increases within normal limits may indicate increased hepatic synthetic activity or an anti-catabolic profile with better α_2-adrenoceptor agonist selectivity to receptor binding sites (26). Total protein (TP) and globulin (GLO) concentrations were not different between groups, indicating the absence of abnormalities in protein catabolism or immune globulin production [35].

Renal biomarkers showed significant variability, particularly the blood urea nitrogen (BUN) and BUN/Creatinine ratios. The DK group showed lower BUN levels while maintaining stable CRE concentrations. That revealed increased renal excretion or decreased protein catabolism, due to dexmedetomidine's hemodynamic stabilizing effects, which numerous studies investigated to preserve renal function from kidney ischemia [33,36,37]. The DX group had a lower BUN/CRE ratio than the XK and MK groups, which supports the renoprotective concept. In contrast, greater BUN, and CK levels in the XK group are indicative of enhanced muscular breakdown and inadequate renal excretion or perfusion. These findings are consistent with earlier observations that xylazine induced minor renal vasoconstriction and decreased filtration efficiency [37].

Creatine Kinase (CK), an extremely sensitive indicator of muscle breakdown or metabolic stress, was higher in the XK group, in contrast, the CK levels in MK and DK were closer to physiological values and /or the CO group. This is relevant in situations that involve neuromuscular circumstances, such as imaging or electrophysiological research, where muscle damage is indicative of validation of this data analysis [38].

Amylase (AMY) levels were also considerably lower in XK, implying stress-induced inhibition of exocrine pancreatic function or increased sympathetic tone. Ketamine and α_2-agonists may affect hepatic lipid binding or break down as shown by elevated CHO (cholesterol) levels in all groups, particularly in XK and MK. Although the exact mechanism is unknown, there may be a correlation with stress-induced endocrine alterations that may be potential contributors [39]. Glucose (GLU) increased potentially in all groups of treatments; this is

indicative of a_2-agonists induced hyperglycemia, due to decreased insulin and increased hepatic glucose output [40].

Carbon dioxide (tCO_2) levels were significantly lower in all groups than their normal values, with the XK group experiencing the greatest drop. This may involve two causes, firstly is metabolic acidosis, and secondly is respiratory depression, which is a well-documented xylazine side effect [41]. DK-treated animals' tCO_2 levels were closer to the normal threshold, showing improved respiratory balance.

Electrolyte abnormalities have been seen in MK treatment groups, including calcium (Ca^{++}), phosphate ($PO4^3$), and magnesium (Mg) values. MK animals had hyperphosphatemia and the highest calcium-phosphate, which is concerning given the link between high $Ca/PO4^3$ values and soft tissue calcification risks [42]. Additionally, Mg levels in XK were greatest, which could be attributed to muscle injury or decreased renal excretion [43].

Limitations and Future Directions

This study is limited by its small sample size (10 per group), use of only male rats, reliance on non-invasive monitoring for physiological parameters, and short evaluation period, which may restrict clinical relevance. Future studies should include larger, more diverse populations, apply invasive monitoring, assess long-term outcomes, and compare protocols across species to support reliability and animal welfare.

Conclusion

Dexmedetomidine–ketamine (DK) is a highly effective and stable anesthetic protocol suitable for both experimental and clinical use. Its rapid induction, shorter maintenance phase, and superior cardiovascular and respiratory stability make it suitable for both laboratory and veterinary medicine. The DK protocol has minimal hepatic and renal disturbances, reduced muscle enzyme leakage, and keeps a consistent glucose profile, acid-base balance, and electrolyte levels within physiological ranges. XK, on the other hand, has notable physiological alterations, such as elevated creatine kinase, increased blood urea nitrogen, and reduced total CO_2 levels. These changes may reflect less favorable cardiovascular and sedative properties, particularly in sensitive or prolonged procedures. Medetomidine–ketamine (MK) has an improved safety profile over XK but may also cause adverse metabolic responses, such as significant elevations in glucose and phosphorus levels. Despite these alterations, the DK protocol offers a high margin of safety with minimal organ toxicity, making it a valuable possibility in both laboratory and veterinary medicine.

Acknowledgments

The authors wish to express their sincere appreciation to the University of Sulaimani, College of Veterinary Medicine, Department of Surgery and Theriogenology, for providing the essential facilities and academic support necessary for this study. We also acknowledge the Sulaimani Teaching Hospital as the primary location for conducting the practical components of the research. We extend our gratitude to all colleagues and technical staff whose aid in data collection and analysis was crucial to the successful completion of this work.

Conflict of Interest

The authors declare that there are no conflicts of interest on the publication of this paper.

Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics of approval

This study was approved by the Ethics Committee of the College of Veterinary Medicine, University of Sulaimani (approval no: VET0282). The study was conducted under the relevant ethical guidelines and standards.

TABLE 1. is the duration of anesthesia seen following the administration of various anesthetic protocols, allowing for comparison of induction, maintenance, and recovery times associated with each treatment regimen

Parameter	Group XK (min)	Group MK (min)	Group DK (min)	F-value	p-value*
Induction Time	7.49 ± 2.60 [a]	3.76 ± 0.83 [b]	2.58 ± 0.40 [b]	13.41	0.00046
Maintenance Time	8.25 ± 1.71 [a]	7.42 ± 1.06 [a]	3.28 ± 0.47 [b]	4.79	0.0246
Recovery Time (after AT administration)	7.80 ± 3.68 [a]	4.38 ± 3.45 [a]	2.95 ± 1.15 [a]	2.68	0.101

Values are presented as mean ± standard deviation. Different superscript letters within the same row indicate statistically significant differences between groups ($P < 0.05$). CO = control; XK = xylazine + ketamine combination group; MK = medetomidine + combination group; DK = dexmedetomidine + ketamine combination AT = atipamezole.

TABLE 2. Comparative analysis of Hepatic, Renal and General Biochemical Biomarkers in Wistar Rats Following Administration of Different Anesthetic Protocols.

Parameter (Unit)	CO	XK	MK	DK	P-value*
TP (g/L)	64.14 ± 5.11^{a}	68.10 ± 8.61^{a}	71.00 ± 4.85^{a}	68.44 ± 4.45^{a}	0.40
ALB (g/L)	35.10 ± 3.2^{ab}	33.38 ± 1.18^{a}	38.08 ± 1.98^{b}	38.62 ± 2.40^{b}	0.01
ALT (U/L)	40.20 ± 15.7^{ab}	37.00 ± 4.12^{ab}	44.30 ± 18.15^{a}	28.00 ± 6.78^{b}	0.00
AST (U/L)	120.00 ± 40^{a}	152.00 ± 6.32^{b}	184.60 ± 22.36^{c}	131.40 ± 18.66^{ab}	0.01
ALP (U/L)	115.80 ± 55.74^{a}	151.7 ±89.49^{a}	138.20 ± 20.54^{a}	113.40 ± 15.09^{a}	0.00
TBA (µmol/L)	21.44 ± 8.53^{a}	39.00 ± 22.37^{a}	25.20 ± 6.03^{a}	24.94 ± 6.95^{a}	0.12
TBIL (µmol/L)	5.41 ± 0.21^{a}	5.43 ± 2.34^{a}	7.13 ± 2.64^{a}	6.06 ± 2.24^{a}	0.25
GLO (g/L)	28.33 ± 3.22^{a}	34.72 ± 7.46^{a}	32.92 ± 4.38^{a}	29.82 ± 2.29^{a}	0.15
GGT (U/L)	2.00 ± 1.13^{a}	1.05 ± 0.50^{b}	1.29 ± 0.07^{b}	0.70 ± 0.64^{b}	0.00
CK (U/L)	300.19 ± 100.05^{a}	596.80 ± 83.46^{c}	429.10 ± 103.08^{b}	342.20 ± 102.09^{ab}	0.00
AMY (U/L)	400.10±100.22^{ab}	290.20 ± 7.05^{a}	428.80 ± 23.84^{b}	441.20 ± 99.46^{b}	0.00
TG (mmol/L)	1.12 ± 0.33^{a}	1.00 ± 0.23^{a}	0.91 ± 0.16^{a}	0.85 ± 0.21^{a}	0.35
CHOL (mmol/L)	1.80 ± 0.4^{a}	2.28 ± 0.15^{b}	2.27 ± 0.17^{b}	1.94 ± 0.16^{a}	0.00
GLU (mmol/L)	7.00 ± 1.50^{a}	7.19 ± 2.16^{a}	12.64 ± 2.80^{c}	8.38 ± 1.48^{b}	0.00
BUN (mmol/L)	4.02 ± 1.00^{b}	5.28 ± 0.28^{a}	3.22 ± 0.43^{c}	1.79 ± 0.30^{d}	0.00
BUN/CRE	15.02 ± 5.10^{ab}	20.90 ± 3.68^{a}	19.90 ± 7.81^{a}	12.70 ± 5.02^{b}	0.04
tCO_2 (mmol/L)	23.21 ± 3.14^{a}	15.50 ± 0.79^{d}	17.30 ± 1.08^{c}	20.00 ± 1.58^{b}	0.00
Ca^{++} (mmol/L)	2.53 ± 0.22^{b}	2.72 ± 0.09^{a}	2.77 ± 0.15^{a}	2.61 ± 0.03^{ab}	0.04
$PO4^{3}$(mmol/L)	2.04 ± 0.30^{b}	1.95 ± 0.22^{b}	2.87 ± 0.54^{a}	1.72 ± 0.20^{b}	0.00
Ca /$PO4^{3}$ (mg/dL)	50.15 ± 10.11^{c}	65.70 ± 5.31^{b}	99.70 ± 23.75^{a}	56.20 ± 6.98^{bc}	0.00
Mg (mmol/L)	1.01 ± 0.18^{b}	1.31 ± 0.27^{a}	1.14 ± 0.22^{ab}	0.84 ± 0.09^{c}	0.00

Values are presented as mean ± standard deviation. Different superscript letters within the same row show statistically significant differences between groups ($P < 0.05$). TP = Total Protein; ALB = Albumin; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; ALP = Alkaline Phosphatase; TBA = Total Bile Acids; TBIL = Total Bilirubin; GLO = Globulin; GGT = Gamma-Glutamyl Transferase; CK = Creatine Kinase; AMY = Amylase; TG = Triglycerides; CHOL = Cholesterol; GLU = Glucose; BUN = Blood Urea Nitrogen; BUN/CRE = Blood Urea Nitrogen to Creatinine Ratio; tCO_2 = Total Carbon Dioxide (Bicarbonate); Ca^{++} = Calcium; P = Phosphorus (Inorganic Phosphate); Ca/PO43 = Calcium-Phosphorus Product; Mg = Magnesium; CO = control group; XK = xylazine + ketamine combination group; MK = medetomidine + ketamine combination group; DK = dexmedetomidine + ketamine combination group.

Fig. 1. Physiological monitoring of key vital parameters (heart rate, respiratory rate, oxygen saturation, body temperature, and perfusion index) using the PhysioSuite system in Wistar rats following administration of different anesthetic protocols.

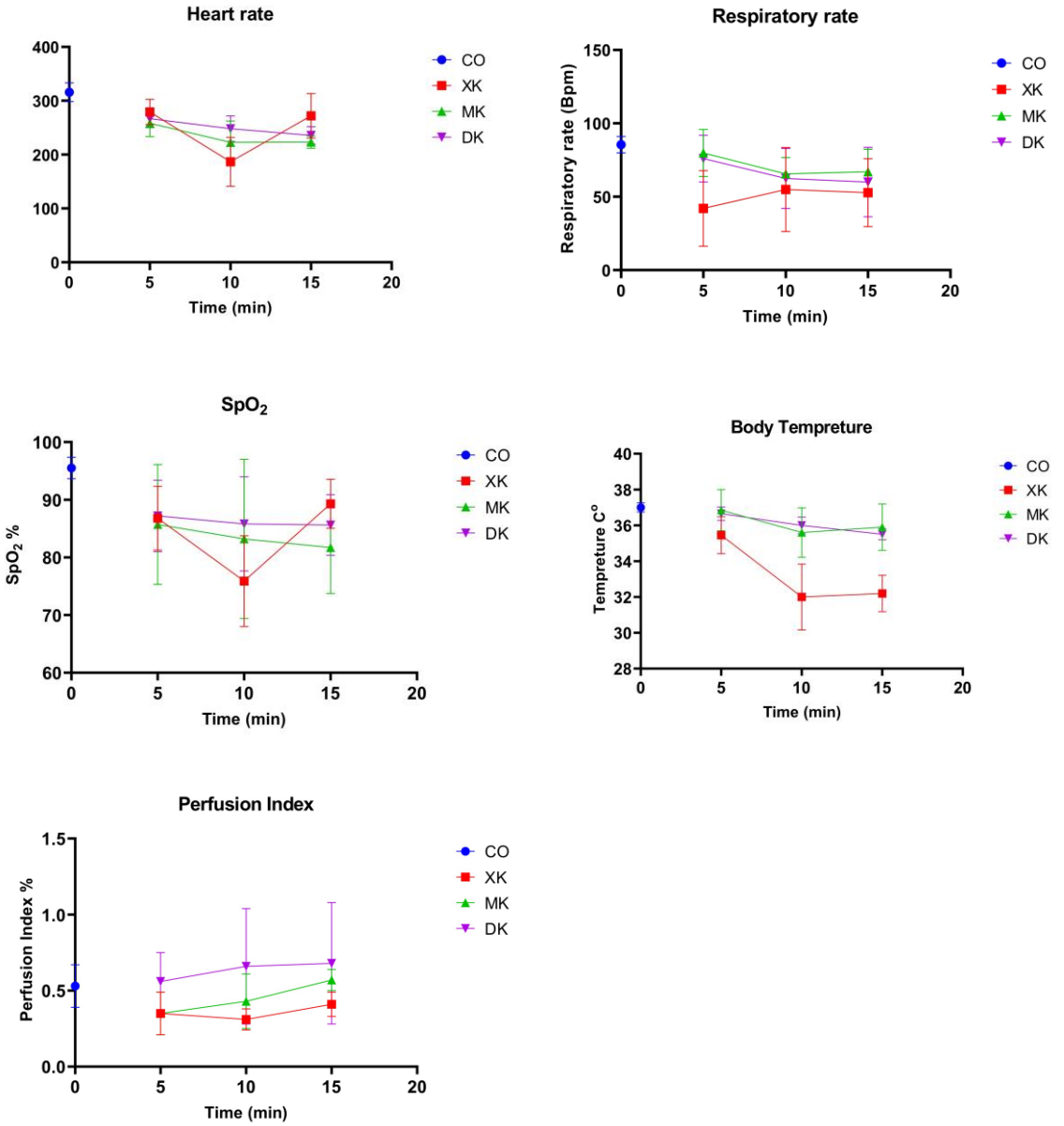

Fig. 2. Line graphs presented a comparative analysis of different anesthesia protocols at different time points, illustrating temporal change in key physiological parameters. CO = Control group (no anesthetic administered); XK = Xylazine + Ketamine combination group; MK = Medetomidine + Ketamine combination group; DK = Dexmedetomidine + Ketamine combination group.

References

1. Ahmadi-Noorbakhsh, S., Farajli Abbasi, M., Ghasemi, M., Bayat, G., Davoodian, N., Sharif-Paghaleh, E., Poormoosavi, S.M., Rafizadeh, M., Maleki, M., Shirzad-Aski, H., Kargar Jahromi, H., Dadkhah, M., Khalvati, B., Safari, T., Behmanesh, M.A., Khoshnam, S.E., Houshmand, G. and Talaei, S.A. Anesthesia and analgesia for common research models of adult mice. *Lab. Anim. Res.*, **38**(1), 40 (2022). DOI:10.1186/s42826-022-00150-3.

2. Matsubara, N.K. and da Silva-Santos, J.E. The Dual Cardiovascular Effect of Centrally Administered Clonidine: A Comparative Study between Pentobarbital-and Ketamine/Xylazine-Anesthetized Rats. *Future Pharmacology*, **4(1)**, 17–29 (2024). DOI:10.3390/futurepharmacol4010003.

3. Baker, J.G., Balaji, P., Bond, R.A., Bylund, D.B., Eikenburg, D.C., Graham, R.M., Hieble, J.P., Hills, R., Michel, M.C., Minneman, K.P., Parra, S., Perez, D. and Summers, R. Adrenoceptors in GtoPdb v.2023.1. *IUPHAR/BPS Guide to Pharmacology CITE*. **2023**(1),1 (2023). DOI:10.2218/gtopdb/f4/2023.1.

4. Jiron, J.M., Mendieta Calle, J.L., Castillo, E.J., Abraham, A.M., Messer, J.G., Malphurs, W.L., Malinowski, C., Grove, K., Reznikov, L.R., Zubcevic, J. and Aguirre, J.I. Comparison of Isoflurane, Ketamine–Dexmedetomidine, and Ketamine–Xylazine for General Anesthesia during Oral Procedures in Rice Rats (*Oryzomys palustris*). *Journal of the American Association for Laboratory Animal Science*, **58**(1), 40–49 (2019). DOI:10.30802/AALAS-JAALAS-18-000032.

5. Alemán-Laporte, J., Bandini, L.A., Garcia-Gomes, M.S.A., Zanatto, D.A., Fantoni, D.T., Amador, Pereira, M.A., Navas-Suárez, P.E., Kirsten, T.B., Jimenez, R.R., Alvarado, G. and Mori, C.C. Combination of ketamine and xylazine with opioids and acepromazine in rats: Physiological changes and their analgesic effect analysed by ultrasonic vocalization. *Lab. Anim.*, **54**(2), 50211 (2020). DOI:10.1177/0023677219850211.

6. Burnside, W.M., Flecknell, P.A., Cameron, A.I. and Thomas, A.A. A comparison of medetomidine and its active enantiomer dexmedetomidine when administered with ketamine in mice. *BMC Vet. Res.*, **9**(1), 48 (2013). DOI:10.1186/1746-6148-9-48.

7. Teng, M.Z., Merenick, D., Jessel, A., Ganshorn, H. and Pang, D.S.J. Consistency in Reporting of Loss of Righting Reflex for Assessment of General Anesthesia in Rats and Mice: A Systematic Review. *Comp. Med.*, **74**(1), 12–18 (2024). DOI:10.30802/AALAS-CM-23-000063.

8. Carbone, L. and Austin, J. Pain and Laboratory Animals: Publication Practices for Better Data Reproducibility and Better Animal Welfare. *PLoS One*. **11**(5), e0155001 (2016). DOI:10.1371/journal.pone.0155001.

9. Hidalgo, M.M.T., de Almeida, A.B.M., dos Santos Silva, L.A., Greghi, J.R., Silva, V.W., Sambatti, N.R., Trautwein, L.G.C. and Martins, M.I.M. Comparison of two pharmacological semen collection times with α2- adrenergic agonist in domestic cats. *Reproduction in Domestic Animals*. **58**(9), 1207–1213 (2023). DOI:10.1111/rda.14420.

10. Connell, A.R., Hookham, M.B., Fu, D., Brazil, D.P., Lyons, T.J. and Yu, J.Y. Comparisons of α2-Adrenergic Agents, Medetomidine and Xylazine, with Pentobarbital for Anesthesia: Important Pitfalls in Diabetic and Nondiabetic Rats. *Journal of Ocular Pharmacology and Therapeutics*, **38**(2), 156–166 (2022). DOI:10.1089/jop.2021.0084.

11. Agrawal, M., Asthana, V. and Sharma, J. Efficacy of intravenous midazolam versus clonidine as premedicants on bispectral index guided propofol induction of anesthesia in laparoscopic cholecystectomy: A randomized control trial. *Anesth Essays Res.*, **8**(3), 302 (2014). DOI:10.4103/0259-1162.143117.

12. Sancak, T. The effects of repeated doses of xylazine-ketamine and medetomidine-ketamine anesthesia on DNA damage in the liver and kidney. *Acta Cir. Bras.*, **38** (2023). DOI:10.1590/acb385723.

13. Chinnadurai, S. Effective Anesthetic Monitoring. In, Wiley,pp.91–101(2025). DOI:10.1002/9781119539278.ch3.

14. Raza, D.A., Abbas, B.T., Dyary, H.O. and Rashid, R.A. Physiological and hematological reference values of wild caucasian squirrels (Sciurus anomalus pallescens) in northern Iraq. *Iraqi Journal of Veterinary Sciences*. **37**(3), 637–642 (2023). DOI:10.33899/ijvs.2022.135861.2538.

15. Wang, A., Foppen, E., Rumanova, V.S., Kool, T., Kalsbeek, A. and Stenvers, D.J. Circadian phase inversion causes insulin resistance in a rat model of night work and jet lag. *Sci. Rep.*, **15**(1), 9687 (2025). DOI:10.1038/s41598-025-91485-z.

16. Massari, L., Benazzo, F., Falez, F., Perugia, D., Pietrogrande, L., Setti, S., Osti, R., Vaienti, E., Ruosi, C. and Cadossi, R. Biophysical stimulation of bone and cartilage: state of the art and future perspectives. *Int. Orthop.*, **43**(3), 539–551 (2019). DOI:10.1007/s00264-018-4274-3.

17. Hollwarth, A. and Vickery, S. Small mammal anaesthesia nursing. *The Veterinary Nurse*, **11**(3), 138–146 (2020). DOI:10.12968/vetn.2020.11.3.138.

18. Lee G. and Goosens K.A. Sampling Blood from the Lateral Tail Vein of the Rat. *Journal of Visualized Experiments*, **99,** 52766 (2015). DOI:10.3791/52766.

19. Babou, S., Chakit, M., El Gui, R., Mesfioui, A. and Sqalli-Houssaini, Y. Acute and Subacute Toxicity Assessment of Ethanolic Extract of Rosmarinus officinalis in Female Wistar Rats. *Egyptian Journal of Veterinary Sciences*, **56**(13), 389–402 (2025). DOI:10.21608/ejvs.2025.369735.2715.

20. Buitrago, S., Martin, T.E., Tetens-Woodring, J., Belicha-Villanueva, A. and Wilding, G.E. Safety and efficacy of various combinations of injectable anesthetics in BALB/c mice. *J. Am. Assoc. Lab. Anim. Sci.*, **47**(1), 11–17 (2008).

21. Gargiulo, S., Greco, A., Gramanzini, M., Esposito, S., Affuso, A., Brunetti, A. and Vesce, G. Mice Anesthesia, Analgesia, and Care, Part I: Anesthetic Considerations in Preclinical Research. *ILAR J.* **53** (1), E55–E69 (2012). DOI:10.1093/ilar.53.1.55.

22. Albrecht, M., Henke, J., Tacke, S., Markert, M. and Guth, B. Influence of repeated anaesthesia on physiological parameters in male Wistar rats: a telemetric study about isoflurane, ketamine-xylazine and a combination of medetomidine, midazolam and fentanyl. *BMC Vet. Res.*, **10**(1), 310 (2014). DOI:10.1186/s12917-014-0310-8.

23. Janssen, B.J.A., De Celle, T., Debets, J.J.M., Brouns, A.E., Callahan, M.F. and Smith, T.L. Effects of anesthetics on systemic hemodynamics in mice. *American Journal of Physiology-Heart and Circulatory Physiology*, **287**(4), H1618–H1624 (2004). DOI:10.1152/ajpheart.01192.2003.

24. Erickson, R.L., Terzi, M.C., Jaber, S.M., Hankenson, F.C., McKinstry-Wu, A., Kelz, M.B. and Marx, J.O. Intraperitoneal Continuous-Rate Infusion for the Maintenance of Anesthesia in Laboratory Mice (Mus musculus). *J. Am. Assoc. Lab. Anim. Sci.*, **55**(5), 548–57 (2016).

25. Sitnikova, E., Rutskova, E. and Smirnov, K. Alpha2-Adrenergic Receptors as a Pharmacological Target for Spike-Wave Epilepsy. *Int. J. Mol. Sci*., **24**(2), 1477 (2023). DOI:10.3390/ijms24021477.

26. Çam, B.M., Topçu, H., Tiryaki, E.S. and Arslan, G. Effect of caffeine on respiratory rate, recovery time, and brain wave activity during emergence from sevoflurane anaesthesia in rats. *Revista Española de Anestesiología y Reanimación (English Edition)*. **72**(6), 501730 (2025). DOI:10.1016/j.redare.2025.501730.

27. Navarro, K.L., Huss, M., Smith, J.C., Sharp, P., Marx, J.O. and Pacharinsak, C. Mouse Anesthesia: The Art and Science. *ILAR J*. **62**(1–2), 238–273 (2021). DOI:10.1093/ilar/ilab016.

28. Oh, S.S. and Narver, H.L. Mouse and Rat Anesthesia and Analgesia. *Curr. Protoc*., **4**(2),955 (2024). DOI:10.1002/cpz1.995.

29. Bennett, K. and Lewis, K. Sedation and Anesthesia in Rodents. *Veterinary Clinics of North America: Exotic Animal Practice*, **25**(1), 211–255 (2022). DOI:10.1016/j.cvex.2021.08.013.

30. Jiang, X., Tang, X., Liu, S. and Liu, L. Effects of dexmedetomidine on evoked potentials in spinal surgery under combined intravenous inhalation anesthesia: a randomized controlled trial. *BMC Anesthesiol*., **23**(1), 36 (2023). DOI:10.1186/s12871-023-01990-9.

31. Tremoleda, J.L., Kerton, A. and Gsell, W. Anaesthesia and physiological monitoring during in vivo imaging of laboratory rodents: considerations on experimental outcomes and animal welfare. *EJNMMI Res*., **2**(1), 44 (2012). DOI:10.1186/2191-219X-2-44.

32. Engin, M., Toy, S. and Turgut, M. A Comparison of Preoperative and Postoperative Anxiety Levels Affecting Preoperative and Postoperative Processes of Orthopedics Patients. *Ann. Med. Res*., **29**(6), 1 (2022). DOI:10.5455/annalsmedres.2021.10.595.

33. Vollrath, J.T., Schindler, C.R., Herrmann, E., Verboket, R.D., Henrich, D., Marzi, I. and Störmann, P. Evaluation of Cyfra 21-1, Angiopoetin-2, Pentraxin-3, Srage, IL-6, and IL-10 in polytraumatized patients with concomitant thoracic trauma - Helpful markers to predict pneumonia? *Shock*, **60**(3), 392–399 (2023). DOI:10.1097/SHK.0000000000002186.

34. Babou, S., Chakit, M., El Gui, R., Mesfioui, A. and Sqalli-Houssaini, Y. Acute and Subacute Toxicity Assessment of Ethanolic Extract of Rosmarinus officinalis in Female Wistar Rats. *Egyptian Journal of Veterinary Sciences*, **56**(13), 389–402 (2025). DOI:10.21608/ejvs.2025.369735.2715.

35. Zhang, H., Xie, S., Li, Y., Li, J., Deng, P., Zeng, H., Cao, H., Liu, M., Li J., Feng, W., Ye, P., Ge, Y., Zeng, J. and Zeng, Y. The potential performance of serum albumin to globulin ratio, albumin and globulin in the diagnosis of periprosthetic joint infection and prediction of reinfection following reimplantation. *BMC Musculoskelet Disord*., **23**(1), 730 (2022). DOI:10.1186/s12891-022-05533-0.

36. Araújo, M.A., Deschk, M., Wagatsuma, J.T., Floriano, B.P., Siqueira, C.E., Oliva, V.NLS. and Santos, P.SP. Cardiopulmonary effects of reverse Trendelenburg position at 5° and 10° in sevoflurane-anesthetized steers. *Vet Anaesth Analg*., **44**(4), 854–864 (2017). DOI:10.1016/j.vaa.2017.03.006.

37. Clegg, S.R. and Millson, S.H. From Saliva to Faeces and Everything in Between: A Guide to Biochemical Analysis Using Animal Samples for Biomarker Detection. *Comp Cogn Behav Rev*., **16**, 1–19 (2021). DOI:10.3819/CCBR.2021.160002.

38. Li, S., Wang, A., Zhang, Y., Tian, X., Meng, X., Wang, Y., Li, H. and Wang, Y. Creatine Kinase Is Associated With Recurrent Stroke and Functional Outcomes of Ischemic Stroke or Transient Ischemic Attack. *J. Am. Heart Assoc*., **11**(6) (2022). DOI:10.1161/JAHA.121.022279.

39. Ferreira, T.H. and Cameron, S. Physiology, Pathophysiology, and Anesthetic Management of Patients with Neurologic Disease. In, Wiley, pp.822–846 (2024). DOI:10.1002/9781119830306.ch39.

40. El-Nasser, M.A., Al-Hozab, A. and Alshaheen, T. Effects of Diazepam and Xylazine on Changes of Blood Oxygen and Glucose Levels in Mice. *Adv. Anim. Vet. Sci*., **6**(3) (2018). DOI:10.17582/journal.aavs/2018/6.3.121.127.

41. Demery, C., Moore, S.C., Levitt, E.S., Anand, J.P. and Traynor, J.R. Xylazine exacerbates fentanyl-induced respiratory depression and bradycardia. *J. Pharmacol. Exp. Ther*., **392**(7), 103616 (2025). DOI:10.1016/j.jpet.2025.103616.

42. Yang, S., Zeng, Z., Yuan, Q., Chen, Q., Wang, Z., Xie, H. and Liu, J. Vascular calcification: from the perspective of crosstalk. *Molecular Biomedicine*, **4**(1), 35 (2023). DOI:10.1186/s43556-023-00146-y.

43. Yadav, S., Yadav, J., Kumar, S. and Singh, P. Metabolism of Macro-elements (Calcium, Magnesium, Sodium, Potassium, Chloride and Phosphorus) and Associated Disorders. In, Springer Nature Singapore, Singapore, pp.177–203 (2024). DOI:10.1007/978-981-97-4723-8_8.

تحليل مقارن بين زيلازين والميديتوميدين وللديكسميديتوميدين مع الكيتامين في الفئران

بافيل عمر قادر، ديكان على رظا*، شاهاماند سروان مصطفي، نياز كاوه أمين، كالي جحفر حسين، بيشواز م. حولا، لانيا نوري عبدوالله

قسم الجراحة وعلم الوراثة، كلية الطب البيطري، جامعة السليمانية، بختياري، السليمانية، العراق.

الملخص

قارنت هذه الدراسة فعالية التخدير وسلامته لثلاثة منبهات مستقبلات a_2-adrnergic وهي الزيلازين والميديتوميدين والديكسميديتوميدين، كل منها مقترن بالكيتامين. كان الهدف هو تحديد بروتوكول التخدير الأمثل الذي يضمن رفاهية الحيوانات وموثوقية الأبحاث المختبرية. تم تقسيم أربعين جرذاً ذكراً إلى أربع مجموعات: مجموعة مراقبة (CO) أعطيت محلول ملحي، وثلاث مجموعات علاجية أعطيت ٥٠ مجم/كجم من الكيتامين مقترنة إما بـ ٠.١ مجم/كجم من ديكسميديتوميدين (DK) أو ٠.٥ مجم/كجم من ميديتوميدين (MK) أو ٥ مجم/كجم من زيلازين (XK) عن طريق الحقن داخل الصفاق. قيمت الدراسة ملامح التخدير والمعلمات الفسيولوجية أثناء الإجراء، بينما تم تقييم المؤشرات الحيوية الكيميائية الحيوية والكلوية والكبدية بعد ١٤ يومًا متتاليًا. أظهرت مجموعة XK وقت تحريض أطول بشكل ملحوظ مقارنة بمجموعتي MK و DK. وبالمقابل، تم إطالة فترة الحفاظ على التخدير في مجموعتي XK وMK مقارنة بمجموعة DK. كشفت التقييمات الفسيولوجية عن انخفاض كبير في وظائف القلب والجهاز التنفسي في مجموعة XK، تمثل في انخفاض ملحوظ في معدل ضربات القلب ومعدل التنفس وSpO2 ودرجة حرارة الجسم. في المقابل، حافظت مجموعتي MK وDK على معلمات فسيولوجية أكثر استقرارًا. أظهر التحليل الكيميائي الحيوي اضطرابات كبدية وكلوية طفيفة في مجموعة DK، مع انخفاض مستويات إنزيمات الكبد (ALT وAST وGGT). أظهرت مجموعة XK ارتفاعًا ملحوظًا في الأحماض الصفراوية والكرياتين كيناز واختلالات في التوازن الكهربائي. أبرزت الملامح الكلوية تحسنًا في التصفية في مجموعة DK. في الختام، وفر بروتوكول DK تخفيزًا سريعًا ووظيفة قلبية تنفسية مستقرة واضطرابات استقلابية وعضوية طفيفة. هذا الملف الأمني المتفوق والاستقرار الفسيولوجي يجعله نظامًا مثاليًا للتخدير في كل من التطبيقات المختبرية والبيطرية.

الكلمات الدالة: زيلازين، ميدتوميدين، ديكسميدتوميدين، كيتامين، وظيفة الكبد، وظيفة الكلى.