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Influence of a Second Dose of Ketamine-Xylazine Mixture on Hematological and Biochemical Profiles in Canine Anesthesia

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Abstract Combination of ketamine and xylazine used as anesthetic agents in veterinary practice in developing countries and even in rural areas in developed countries. This protocol provides anesthesia for approximately 30 minutes, often necessitating a second dose for extended procedures. Study aimed to investigate the effects of administering a second dose of ketamine and xylazine on biochemical and hematological parameters in dogs. An experimental, randomized, crossover study. Twelve mongrel dogs of both sexes were used in this study, their body weights ranged from (16-25kg) kg with an average of (18.83kg) and the ages were between 6 and 18 months. Each dog was administered by two doses of ketamine and xylazine. Blood samples were collected before the first dose (S1), 30 minutes after the first dose (S2), 30 minutes after the second dose (S3), and 24 hours after the first dose (S4). The results show significant changes in several biochemical (lactate dehydrogenase P-value 0.000 and glucose P-value 0.001) and hematological (white blood cell P-value 0.067 and platelets P-value 0.058) parameters. While most other hematological and biochemical parameters show no significant differences before, during and after anesthesia. The administration of a second dose of ketamine and xylazine should be judiciously determined through a rigorous risk-benefit analysis. It is advisable to utilize a second dose only when necessary to complete a procedure, as significant biochemical and hematological changes were observed in our study. Other ways it should be avoided.

Keywords: Biochemical, hematological, injectable anesthesia, Ketamine, xylazine

Introduction Ketamine hydrochloride is a dissociative anesthetic agent, but also provides analgesia through its inhibitory action on N-methyl D-aspartate (NMDA) receptors which enhance pain transmission to the CNS (1-4). Anesthesia with ketamine alone can lead to catalepsy (muscle rigidity and seizure) and undesirable recoveries. Therefore, it is usually administered with other agent such as a benzodiazepines and α2-Agonists (2, 4, 5) to produce a more balanced anesthesia, in which different components of anesthesia such as unconsciousness, analgesia and muscle relaxation, by combining of drugs to decrease side-effects while providing good quality anesthesia (6, 7). One of most used drugs with ketamine is Xylazine which is α2-Agonist that produce analgesia, muscle relaxation, and sedation (8-10).

In developing countries, due to shortages and limited access in facilities like inhalational anesthesia and anesthetic machines, ketamine is widely used to produce anesthetic state to perform various surgical procedures. However, due to ketamine's short duration of action (11, 12) in which Anesthesia lasts for 20-30 minutes (2) and according to Grimm et al. (4) lasts for 28–36 minutes, sometimes it require to give a second dose before the effect of first dose is over, especially when the animal is vicious and need to be anesthetize for preparation (clipping and disinfection) which take much time of total duration of ketamine. This practice of administering multiple doses of ketamine, especially in combination with xylazine, raises concerns about potential cumulative effects and associated risks. Therefore, this research

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aims to comprehensively investigate the effects of two consecutive doses of ketamine and xylazine on patients, with a particular focus on assessing potential risks and adverse outcomes.

Materials and methods

Ethical approve

This study was approved for the animal care at the College of Veterinary Medicine, University of Dohuk, Under the No. VM2022/1003UD dated 17/11/2024

For this research 12 apparently healthy, mongrel dogs of both sexes were used. Their body weights ranged from (16-25kg) kg with an average of (18.83kg) and the ages were between 6 and 18 months. All of these dogs received medications to eliminate ecto and endoparasites and kept under same conditions and feed (dry food) for 2 weeks as adaptation period and during the experiment period.

The dogs were grouped for administration of xylazine and ketamine. Site of injection of anesthesia and blood sampling (cephalic vein) had been prepared routinely (clipping and disinfection). Butterfly catheter was applied into cephalic vein. The doses were calculated according to the animal's weight.

Atropine sulphate was given at a dose of 0.04 mg/kg B.Wt, then after 5 minutes, a mixture of ketamine (15mg/kg B.Wt) and xylazine (1mg/kg B.Wt) was administered intravenously as first dose. Then after 30 minutes (of first dose) same amount of ketamine and xylazine administered as second dose (Hall and Clarke, 1991).

Respiratory rate, heart rate, rectal temperature, blood pressure including systole, diastole and mean arterial pressure, and hemoglobin oxygen saturation (SPO_2) were taken by an electronic multi-parameter monitor (CE New Vet Veterinary Vital Signs ICU Patient Monitor/ China)

Blood samples were taken from each animal from the cephalic vein as follows, first sample (S1) before anesthesia, second sample (S2) after 30 minutes of administration of anesthesia, third sample (S3) after 30 minutes of giving second dose of ketamine and xylazine, and the fourth sample (S4) after 24 hrs. (next day) from the first dose of anesthesia. All dogs were kept alive after experiment none of them died during or after experiment.

Figure 1: Timeline of sampling and administration of KX. The Blue arrow represents the hours, the orange arrows represent sampling and red arrows represent administration of KX.

Samples were kept in plane vacutainer tubes for biochemical analysis and heparinized tubes for hematological tests. The hematological samples, shortly after collection, were analyzed by veterinary auto hematology analyzer (Geno TEK, CA) to measure white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), and platelet count (PLT). Serum samples were obtained by centrifuging blood samples at 3000 RPM for 10 minutes and stored in Eppendorf tubes in a deep freeze until analysis. Biochemical parameters, including glucose, alkaline phosphatase, creatinine, creatine kinase (CK), aspartate transaminase (AST), total protein (TP), albumin (ALB), globulin (GLB), triglycerides (TG), urea, uric acid, potassium (K), sodium (Na), calcium (Ca), chloride (Cl), triglycerides, cholesterol, lactate dehydrogenase (LDH), total bilirubin (TBIL), and direct bilirubin (DBIL), were obtained using Cobas 600 analyzer for tissue enzymes and (ST-200 plus sense cores) to measure electrolytes.

The data were statistically analyzed with the Minitab software version 18.1 (Minitab, Inc., United States). ANOVA (fisher pairwise comparison) were used to compare between (S1, S2, S3, and S4) of both biochemical and hematological parameters. Values obtained were expressed as mean ± standard errors. Differences were considered to be significant when $P \leq 0.05$

Results

In the present study physiological parameters (Respiratory rate, heart rate, rectal temperature, blood pressure including systole, diastole and mean arterial pressure, and SPO_2) were published in as another article. The hematological and biochemical parameters were recorded in all the 12 dogs at different intervals as mentioned above, and showed in the table 1, 2 and 3 below.

There were no significant differences found between baseline and through anesthesia values of some hematological parameters (RBC, HGB and HCT). However, WBC significantly increase in S3 compared to S2 and PLT significantly decreased in S2 which compared to other groups (S1, S3 and S4) (Table 3). Also, there were no significant differences found between before, during, and after anesthesia on most biochemical values (Urea, Creatinine, Uric acid, TG,

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CHO, ALT, TSB, Bilirubin, Protein, ALB, GLB, CK, AST, ALP, Na, K, CL and Ca). Then again, LDH value statistically increases according to (P ≤ 0.05) in S3 and S4 and highly significant increase reported in S2 which compared to baseline value. There was significantly increase of glucose showed in S2 and highly significant increase (P≤0.05) reported in S3 than before anesthesia (Table 1 and Table 2).

Table 1: Effects of two doses of Ketamine and Xylazine on serum biochemical parameters.

	Urea	Creatinine	LDH	Uric acid	Glucose	TG	CHO	ALT
S 1 (0 Hr.)	29.80±2.18 A	0.312±0.024 A	58.2±10.2 C	0.206±0.036 A	88.2±4.22 C	58.20±1.16 A	251.6±11.5 A	18.20±2.22 A
S2 (½ Hr.)	27.60±1.69 A	0.346±0.016 A	195.4±9.6 A	0.284±0.028 A	110.8±3.28 B	67.60±5.00 A	274.0±12.8 A	8.60±2.16 A
S3 (1 Hr.)	25.60±2.42 A	0.358±0.009 A	146.6±14.1 B	0.350±0.101 A	130.6±10.9 A	61.80±1.93 A	277.8±10.1 A	19.20±1.66 A
S4 (24Hr.)	26.20±2.97 A	0.360±0.033 A	165.6±9.5 A B	0.182±0.034 A	92.4±3.83 B C	62.40±4.43 A	285.2±16.1 A	24.60±5.94 A
	ANOVA summery (P – values)							
	0.610	0.431	0.000	0.196	0.001	0.339	0.315	0.535

Means in each column sharing different letters are significantly different at P- value < 0.05. ± denotes standard errors.

Table 1: Effect of two doses of Ketamine and xylazine on serum biochemical parameters

Timeline (Hr)	TSB	D. Biliru	S. Protein	S Albumin	S. Globulin	CK	AST	ALP
S1(0)	0.018±0.0020 A	0.018±0.011 A	5.034±0.555 A	3.120±0.204 A	1.914±0.357 A	175.80±4.07 A	14.60±1.12 A	130.40±5.66 A
S2(½)	0.056±0.0225 A	0.038±0.021 A	5.486±0.467 A	3.204±0.140 A	2.282±0.337 A	174.8±20.1 A	18.75±2.14 A	139.2±10.3 A
S3(1)	0.038±0.0066 A	0.030±0.006 A	5.286±0.261 A	3.294±0.050 A	1.972±0.241 A	222.8±30.3 A	17.20±1.96 A	153.6±12.3 A
S4(24)	0.046±0.0108 A	0.028±0.005 A	5.028±0.219 A	3.050±0.128 A	1.978±0.183 A	222.2±25.5 A	18.20±2.82 A	135.2±13.5 A
	ANOVA summery (P – values)							
	0.240	0.726	0.823	0.652	0.802	0.254	0.532	0.486

Means in each column sharing different letters are significantly different at P- value < 0.05. ± denotes standard errors.

Table 3: Effect of two doses of Ketamine and xylazine on hematological parameters

Timeline (hr)	WBC	RBC	HGB	HCT	PLT
S 1 (0)	51.68±4.27 AB	4.104±0.286 A	133.0±10.2 A	25.68±2.02 A	550±110 A
S2 (½)	43.88±4.90 B	4.295±0.294 A	138.0±7.88 A	27.52±1.77 A	223.0±38.1 B
S3 (1)	59.12±1.43 A	4.546±0.248 A	150.0±6.38 A	28.60±1.61 A	581±103 A
S4 (24)	55.03±3.59 AB	4.188±0.135 A	135.0±9.23 A	25.725±0.528 A	564.8±76.7 A
	ANOVA summery (P – values)				
	0.067	0.617	0.489	0.527	0.058

Means in each column sharing different letters are significantly different at P- value < 0.05. ± denotes standard errors.

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Discussion

Little number of literatures were found about using of Ketamine and Xylazine in dogs, that why, some of our results were compared with their use in other species or using one of them with another anesthetic agents.

The surgical procedures require proper anesthesia and analgesia to accomplish an operation, recovery, and welfare of animal. Therefore, a combination of drugs used to obtain a smooth anesthesia, gain advantages and reduce disadvantages of used drugs. In general, the ketamine-xylazine considered to be save when its used as anesthetic protocol (13), like other drugs they are not without adverse effects and their usage should be based on a risk–benefit analysis (4, 14).

In the current study we found that there are significant changes in some biochemical (LDH and glucose) and hematological (WBC and PLT) parameters in dogs after ketamine – xylazine administration. Beside that there are increases or decrease in some parameters but that changes are not significant statistically.

The reason of increased glucose levels after administration of ketamine is due to its effect of sympathetic stimulation to the pancreas causing reduction of insulin secretion which may induce hyperglycemia (8, 11, 15).

Our results show significant increase LDH, contrary to the results of Samimi et al. (16), who worked on 10 camels, and partially agreed with, Arabmomeni et al. (17), that showed significant increase in LDH in young experimental group comparing to the control group, and no significant differences between other groups in 40 male rats.

The urea slightly decreased in after administration of KX comparing to the S1, but that was not significant. These agreed with Shaaban et al. (18), whose results showed significant decrease of BUN (urea) in propofol-ketamine groups in dogs.

HCT in this study slightly increased in S2 and S3 comparing to baseline (S1) but that was not significant statistically. Biswas and his colleagues (19), stated that PCV (HCT) in ewes increased but not significantly after 1 Hr. of administration of ketamine-xylazine and significantly increased after 24 Hrs. on the other hand, Chauhan and Pandey (20), mentioned that PCV did not show significant changes in dogs after ketamine-fentanyl administration. Erhardt and his colleagues (21), reported no effect of ketamine/xylazine (100/5 mg/kg) on hematocrit when injected IM into mice, implying lack of hemoconcentration due to osmotic diuresis secondary to hyperglycemia.

In current study the WBC were significantly increased. Contradictory to our results, Kamal et al. (22), reported in their study a gradual decrease in TLC in Group X-K throughout the experiment on the dogs. In their study on rats (23), they stated that there are no changes in WBC count after repeated doses of ketamine alone administered intraperitoneally every other day for 12 day.

In our study we observed a significant decrease in platelet count within the S2 phase, followed by a return to normal values throughout the experimental period. This initial decline in platelet numbers can be attributed to platelet destruction, as reported by previous research (24). The subsequent recovery of platelet counts to normal levels is likely due to the release of epinephrine, a hormone known to stimulate splenic ejection of platelets (25). Ketamine administration, a known trigger for epinephrine release (15), may have played a crucial role in this process.

Conclusion

In conclusion, our study investigated the effects of ketamine-xylazine anesthesia on hematological and biochemical parameters in dogs. We observed significant changes in some parameters, such as increased WBC and LDH levels, as well as decreased PLT counts and elevated glucose levels. These findings are consistent with previous research and can be attributed to the pharmacological effects of these agents.

Our study reaffirms that ketamine-xylazine anesthesia, when administered alongside Atropine sulfate, is an effective anesthetic protocol for achieving excellent muscle relaxation and smooth recovery in dogs. Importantly, we noted that the administration of a second dose (S3) did not result in significant differences in most parameters, underscoring the need for a risk-benefit analysis when considering a second dose. It should only be administered when essential to complete a procedure, and otherwise, it should be avoided.

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Conflict of interest

The authors declare that there is no conflict of interest.

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