# Effect of Repeated Dose of Ketamine Hydrochloride on Renal Function Tests

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**Abstract**
The aim of the present study was to determine the effect of repeated dose of ketamine Hcl as a general anesthesia on renal function in rabbits, which evaluating by using biochemical tests. 45 adult local breed male rabbits were employed in this study. The results revealed a significant increase in the level of urea and creatinine during the experimental periods at (P≤0.05).
Keywords: General anesthesia, repeated dose of ketamine Hcl, renal functions test in Rabbits, Biochemical tests, urea level, creatinine level.

## Introduction

The internationally animal experimentation ethic requires minimized animal pain (1-3) in which they refer that using any anesthetics agents in different animals for different medical or surgical situations must represented anesthetic drug of choice in which can described the best and first agent in treating or dealing a particular conditions or animal spp..Sometimes alternative agent can be used to get the same effect but this agent doesn't act in the same manner of the drug of choice (4-6) .A repeated doses could be suitable solution to maintain some therapeutic treatments during painful wound care or regular dental care or even during surgical operation (7) .Both xylazine –ketamine combination are widly used (8),but this combination dose not give a suitble anesthetic period to cover the surgical interferance that need more than 30 -45 minutes for intramuscular injection and 15 minutes for intravenous injection (4),for prolong duration of this combination by using repeated dose technique to overcome this shortage. (9).
The aims of this study is to determine the effect of repeated dose of ketamine hydrochloride on renal function during surgical operation and after one week p. o in rabbits .

## Materials and Methods

A 45 adult local breed male rabbits were used ,mean weight was (1.7 ± 0.7) kg,they were housed in special metal cages (30×70×60) cm in an air-conditioned room in the animal house of veterinary medicine college, Baghdad university, under ethical approval no. P.G. 1839 at 22/9/2022.The animals were kept under observation one week prior to the study for adaptation with free access for food and water.
The experimental animals divided randomly to two main experiments as following:
Experiment I: (n=30) rabbits were divided to two groups A and B .
**Group A:** This group was given a repeated dose of ketamine only and they were include 3 subgroups:

Subgroup AD2

Include 5 rabbits received a mixture of 17.5 mg/ kg xylazine and 25 mg/kg of ketamine intramuscularly (3); then after 15 minutes received a second dose of 25mg/kg Ketamine intramuscularly.

Subgroup AD3

Include 5 rabbits received a mixture of 17.5 mg/ kg xylazine and 25 mg/kg of ketamine intramuscularly then after 15 minutes received a second dose of 25mg/kg Ketamine intramuscularly ; then a third dose of ketamine was injected after 15 minutes later.

Subgroup AD5

Include 5 rabbits received a mixture of 17.5 mg/ kg xylazine and 25 mg/kg of ketamine intramuscularly then after 15 minutes received a second dose of 25mg/kg Ketamine intramuscularly; then a third dose of ketamine was injected after 15 minutes and 15 minutes later a fourth dose was injected and finally a fifth dose of ketamine was injected after 15 minutes.
**Group B:** This group was given a repeated dose of ketamine and a laprotomy incision was done under this protocol; this group was divided to 3 subgroups

Subgroup OD2

Include 5 rabbits received a mixture of 17.5 mg/ kg xylazine and 25 mg/kg of ketamine intramuscularly then after 15 minutes received a second dose of 25mg/kg Ketamine intramuscularly.

Subgroup OD3

Include 5 rabbits received a mixture of 17.5 mg/ kg xylazine and 25 mg/kg of
15 minutes later.

Subgroup OD5

Include 5 rabbits received a mixture of 17.5 mg/ kg xylazine and 25 mg/kg of ketamine intramuscularly then after 15 minutes received a second dose of 25mg/kg Ketamine intramuscularly; then a third dose of ketamine was injected after 15 minutes and 15 minutes later a fourth dose was injected and finally a fifth dose of ketamine was injected after 15 minutes.
**Laparotomy technique:** The animals were lay on dorsal recumbency in which a ventral midline incision

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beginning at the xiphoid and extended to cranial to the prepupce (10). The operation field was aseptically prepared in a routine manner at the ventral abdominal wall. a longitudinal midline incision in the skin, subcutaneous tissue, linea alba and peritoneum was performed., the subcutaneous tissue, abdominal muscles and peritoneum were closed via simple intrrupted pattern.(11).

**Experiment II**( n= 15) The same steps and procedure which mentioned in experimental I - Group A was done and After one week, these 15 rabbits were given the same repeated dose as following:

### Subgroup WD2

Include 5 rabbits received a mixture of 17.5 mg/ kg xylazine and 25 mg/kg of ketamine intramuscularly then after 15 minutes received a second dose of 25mg/kg Ketamine intramuscularly.

### Subgroup WD3

Include 5 rabbits received a mixture of 17.5 mg/ kg xylazine and 25 mg/kg of ketamine intramuscularly then after 15 minutes received a second dose of 25mg/kg Ketamine intramuscularly ; then a third dose of ketamine was injected after 15 minutes later.

### Subgroup WD5

5 rabbits received a mixture of 17.5 mg/ kg xylazine and 25 mg/kg of ketamine intramuscularly then after 15 minutes received a second dose of 25mg/kg Ketamine intramuscularly; then a third dose of ketamine was injected after 15 minutes and 15 minutes later a fourth dose was injected and finally a fifth dose of ketamine was injected after 15 minutes.

### Statistical Analysis

The Statistical Analysis System- SAS (2012) program was used to detect the effect of difference factors in study of parameters-test and Least significant difference-LSD test (Analysis of Variation-ANOVA) was used to significant compare between mean.

## Results

The results revealed significantly increase of urea level at 5hrs in all doses (2D,3D, and5D) compared to control at 0 time, the urea level decline at (24 and 72 hrs.) and reach below the base line in 2D group. In 3D group the urea level increase significantly at 5hrs., 24hrs., and 72Hrs in which it records 114.15 ±1.3. In 5D group increase in urea level at 5Hrs ,24Hrs, and 72Hrs respectively compared to control at 0 time. while in the 5dose group the urea level increase at 5Hrs,24Hrs, and 72Hrs respectively compared to control at 0 time. from the data of urea level significantly increase in 3D and 5D group at 5Hrs,72Hrs, and 72Hrs compare to 2D at the same time (**Table 1**).

**Table 1 Effects of repeated dose of ketamine on urea level (ng/dl)**

| Time/ hrs.Groups | Control (0 time) | 5Hrs. | 24Hrs. | 72Hrs. | LSD |
|---|---|---|---|---|---|
| 2D | 38.43 ±2.5Ab | 63.08 ±2.5Ba | 31.26 ±1.5Bc | 32.25 ±1.4Cbc | 6.90 * |
| 3D | 38.43 ±2.5Ad | 95.70 ±3.6Ab | 74.00 ±3.4Ac | 114.15 ±1.3Aa | 8.92 * |
| 5D | 38.43 ±2.5Ac | 57.50 ±2.3Bb | 73.54 ±3.2Aa | 69.80 ±2.6Ba | 8.05 * |
| LSD | 1.85 NS | 6.41 * | 7.05 * | 8.51 * | --- |

Means with different big letters in the same column and small letters in the same row are significantly different. (P≤0.05).

The results In 2D group showed no important significant change of creatinine level at the 5hrs ,24hrs ,and 72hrs compare to control 0 time ,while In 3D group, a significant statistical sign in creatinine level was recorded in 5hrs and then increased further in 24hrs then decreased at 72hrs. In the 5D group, no statistically significant change. After 5hrs. while the results indicated in 24hrs increase in creatinine level is the highest in the table to decrease significantly more in 5D. In the 72hrs Significant increase in 5.835 ±0.42 compared to other doses 1.39 ±0.07 and 1.26 ±0.24. The observed increase compared with baseline but no significant among dose with times, but 62.04 ±2.7 and 5.835 ±0.42 were significant **Table (2)**.

**Table 2 Effects of repeated dose of ketamine on creatinine level (ng/dl) without operation**

| Time/ hrs.Groups | Control (0 time) | 5Hrs. | 24Hrs. | 72Hrs. | LSD |
|---|---|---|---|---|---|
| 2D | 0.663 ±0.08Aa | 1.386 ±0.13Aa | 1.17 ±0.08Ba | 1.39 ±0.07Ba | 0.893 NS |
| 3D | 0.663 ±0.08Ab | 1.68 ±0.15Ab | 62.04 ±2.7Aa | 5.835 ±0.42Ab | 6.73 * |
| 5D | 0.663 ±0.08Aa | 1.29 ±0.09Aa | 1.37 ±0.07Ba | 1.26 ±0.24Ba | 1.85 NS |
| LSD | 0.179 NS | 0.772 NS | 6.91 * | 3.02 * | --- |

Means with different big letters in the same column and small letters in the same row are significantly different. (P≤0.05).

Level of urea and Creatinine under surgical interference showed a significant increase in 3D group in comparison with other groups after 5hrs., from complete recovery **(table 3).**

**Table 3:** Effects of repeated dose of ketamine on renal function tests under operation

| Groups parameters | Control | 2D | 3D | 5D | LSD |
|---|---|---|---|---|---|
| Urea | 38.43 ±2.6 d | 85.4 ±2.9 b | 109 ±5.3 a | 76.9 ±2.9 c | 7.44 * |
| Creatinine | 0.663 ±0.08 c | 1.139 ±0.04 bc | 1.88 ±0.0 a | 1.7796 ±0.07 ab | 0.709 * |

Means with different big letters in the same column and small letters in the same row are significantly different. (P≤0.05).

After one week, the results showed a significant increase in both urea and creatinine level in 3D

group (table 4).

**Table 4:** Effects of repeated dose of ketamine on renal function tests after one week.

| Groups Parameters | Control | 2D | 3D | 5D | LSD |
|---|---|---|---|---|---|
| urea | 38.43 ±1.8 c | 71.7 ±2.9 b | 89.5 ±3.6 a | 76.7 ±3.2 b | 9.62 * |
| Creatinine | 0.663 ±0.02 b | 1.74 ±0.04 a | 1.615 ±0.07 a | 1.440 ±0.07 a | 0.617 * |

Means with different big letters in the same column and small letters in the same row are significantly different. (P≤0.05).

## Discussion

Normal renal function regulated by a balance between opposing neurohormonal systems which control vasomotor tone, diuresis, and natriuresis. Surgical stress tips the balance in favor of renal vasoconstriction and salt and water retention, which may last for days after operation. ( 12). Therefore anaesthesia and surgical stress can affect renal function and body fluid regulation indirectly as well as directly, The indirect effects, through influences on haemodynamics, sympathetic activity and humoral regulation,which are more pronounced than the direct ones. (13) in fact, renal effects of anaesthetics in man and animals depend on the species, the anaesthetic and the method used to study the effect (14). In general Our results agree with (8), in which they found that the level of urea and creatinine were increased in xylazine-ketamine in which ketamine was injected 10 minutes after intramuscular injection of xylazine. The changes in renal function test conduct with(15) who mentioned that renal effects of anaesthesia doappear to be dose-related and are favourablyinfluenced by adequate repletion ofextracellular fluid. According to (16)who mentioned that Ketamine can reduce renal cortical blood flow and urine output and, hence, decreases glomerular filtration rate and increases plasma BUN and creatinine levels.

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