**A Comparison Study of Nefopam / ketamine, Tramadol / ketamine and xylazine / ketamine anaesthesia in Rabbit**

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**SUMMARY**

This study were preformed to evaluate and compare between three anesthetic regime, using injectable anesthesia (Nefopam / ketamine), (Tramadol / Ketamine) and (xylazine / ketamine) in anesthetic protocols in rabbits. Eighteen adult local breed rabbits from both sexes weighing (1.1-1.8) Kg. were divided equally into three groups they were housed indoor to accommodate the place of experiments. The following physiological parameters (heart rate, respiratory rate and rectal body temperature) were recorded before the intramuscular injection of the drugs for each group (zero time) as a self group. Group (A) were injected tramadol hydrochloride 10% 15 mg/kg B.W as premedication, after 10min. Ketamine hydrochloride 10% at a dose of 10 mg/kg, 50 mg/kg B.W., group (B) were injected Xylazine 2%10mg/kg B.W. as premedication, after 10min. the animals were injected as same in group (A). and group (C) were injected Nefopam 2% mg/kg B.W. as premedication, after 10min. the animals were injected as same in group (A) and (B). Stages of anesthesia (induction time, surgical time and recovery time) and physiologic parameters (heart rate, respiratory rate and Rectal body temperature) were evaluated. The most significant changes were reported in group (B) which useful regimen clinically for anesthetize rabbits due to long surgical time.

**INTRODUCTION**

Rabbits are often considered as difficult in relation to anesthesia. This probably relates to the fact that the dosage needed to induce anesthesia and those producing toxic effect are close (1). Tramadol (Zylol)®, (Searole)®, (Tramal)® is centrally acting analgesic drug which has been in clinical use in Germany for 17 years old and has launched in the united kingdom(2). Its used primarily as analgesic, but it has demonstrated usefulness in treating opioid withdrawal in human beings (3). Tramadol crosses the blood brain barrier and placental barrier and has been found to produce humorous positive responses in vertebrates including analgesia for moderate and sever pain, antitussive, antidepressant, anti-inflammatory and immunostimulatory effects, an ability to lower glucose in diabetes and local anesthetic effect (4).

Ketamine is one of the dissociative agents that can be used as a sole agent for induction anesthesia or in combination with other agents for induction and maintenance (5). Its metabolized by the liver and excreted in urine (6). It is an unsatisfactory sole agent for surgical procedures due to the poor muscle relaxation, therefore, it is used in combination with other agents such as Xylazine or Medetomedine to provide surgical anesthesia (7). Xylazine is a typical α2–adrenoceptors agonist, thiazine derivative drug, widely used as sedative and analgesic drug to treat various types of pain in all species of animals. It has sedative, analgesic, anesthetic and muscle relaxant properties in animals when used alone or in combination with other agents like Ketamine (8,9). It gives a safe anesthetic effect in horses, cattle, sheep, goat, cat and dogs when co administrated with Ketamine to induce short period of surgical anesthesia (10,11). Parenteral anesthetic combination such as Ketamine / Xylazine have become the agent of choice for anesthesia in the rabbits because Ketamine and Xylazine combination are effective, easily administered and inexpensive (12,13).

The aim of the present study was to evaluate and compare between three anesthetic regime, using injectable anesthesia (Nefopam / ketamine), (Tramadol / Ketamine) and (xylazine / ketamine) in rabbits .

**MATERIALS AND METHODS**

Eighteen adult local breed rabbits from both sexes weighing (1.1-1.8)Kg. were divided equally into three groups they were housed indoor to accommodate the place of experiments. The following physiological parameters (heart rate, respiratory rate and rectal body temperature) were recorded before the intramuscular injection of the drugs for each group (zero time) as a self group.

Group (A) were injected intramuscularly by: Tramadol hydrochloride 10% (Ibn Hayyan Pharm-Homs-Syria) 15 mg/kg B.W as premedication, after 10min. Ketamine hydrochloride 10% (alfasan, Holland) at a dose of 10 mg/kg, 50 mg/kg B.W.

Group (B) were injected intramuscularly by: Xylazine 2% (alfasan, Holland ) 10mg/kg B.W. as premedication, after 10min. the animals were injected as same in group (A).

Group (C) were injected intramuscularly by: Nefopam 2% (Biocodex, France) mg/kg B.W. as premedication, after 10min. the animals were injected as same in group (A) and (B). The induction time recorded from the time of injection of Ketamine to the complete loses of consciousness. The same physiological parameters was taken as mention in control after intramuscular injection of the drugs at periods of (10, 20, 30, 40, 50 and 60) min.

The surgical anesthesia recorded from the time of complete lose of sensation until the rabbit response to external stimuli, recovery time were also recorded from the time of response to the external stimuli until returned to its normal condition (complete consciousness). Pinching by artery forceps was used to determine the analgesic effect of the anesthetic combination and make sure for the entrance to the surgical stage, in addition to that pricking by needle test were also used.

**Statistical analysis**

Statistical analysis of data was performed using SAS (Statistical Analysis System - version 9.1). One-way, Two ANOVA and Least significant differences (LSD) post hoc test were performed to assess significant differences among means. P < 0.05 was considered statistically significant (14).

**RESULTS AND DISCUSSION**

The induction time, surgical anesthesia and recovery time were summarized in table (1) as the following:

**Table (1):** Mean values (±Standard Error) of subjective scores qualifying anesthesia (induction time, surgical anesthesia and recovery time)**/**minute

|  |  |  |  |
| --- | --- | --- | --- |
| **Time**  **Group** | **Induction time** | **Surgical time** | **Recovery time** |
| **Group A**  **n=6** | 7.16  ±  0.60**a** | 28.50  ±  1.47**b** | 30.50  ±  1.38**b** |
|  |  |  |  |
| **Group B**  **n=6** | 7.16  ±  0.30**a** | 47.33  ±  1.76**a** | 74.16  ±  1.53**a** |
|  |  |  |  |
| **Group C**  **n=6** | 8.00  ±  0.258**a** | 28.83  ±  0.83**b** | 16.83  ±  0.90**c** |
| **LSD** | 1.257 | 4.259 | 3.932 |
| P≤ 0.05 | | | |

**Means with a different letter in the same column significantly different (P≤0.05)**

The analgesic effect of anesthetic drugs combination in all groups were determine by scratched by artery forceps in order to confirm for the entrance to the surgical stage. In general, all animals not response to these tests.

The result revealed that no significant differences (P≥ 0.05) were observed of induction time value among groups. Surgical time was increase significantly (P≤ 0.05) in group (B) when compared with other groups. Meanwhile, recovery time recorded a decrease value significantly (P≤ 0.05) in group (C) and (A) respectively when compared with the group (B) (table 1). The current study showed that the surgical period of the group (B) was enough for the most surgical interference; However, groups (A and C) surgical interference of skin and muscles only. The results of the depth of anesthesia and the determination of analgesic effect of the anesthetic combination agree with other workers (1**5**).

Results of physiological parameters of heart rate, respiratory rate and rectal body temperature were summarized in tables (2,3 and 4) respectively as the following:

**Table (2):** Heart rate before, during and after general anesthesia administration in rabbits (beats/minute "bm")

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Time**  **Group** | **0** | **10** | | **20** | **30** | **40** | **50** | **60** |
| **Group A**  **n=6** | 216.66  ±  13.08  A a | 215.33  ±  11.60  A a | | 176.66  ±  4.21  B b | 170.00  ±  6.95  BC ab | 145.00  ±  6.70  D a | 140.00  ±  3.41  D b | 150.83  ±  4.90  CD a |
|  | |  |  |  |  |  |
| **Group B**  **n=6** | 201.16  ±  6.37  A a | 191.50  ±  5.71  AB b | | 168.66  ±  6.25  BC a | 150.16  ±  3.91  C b | 149.83  ±  10.86  C a | 156.66  ±  6.54  C ab | 164.16  ±  4.16  C a |
|  | |  |  |  |  |  |
| **Group C**  **n=6** | 219.33  ±  6.54  A a | 212.66  ±  18.09  A ab | | 182.83  ±  7.50  B a | 175.66  ±  6.09  BC a | 158.33  ±  5.42  C a | 167.66  ±  14.73  BC a | 172.33  ±  7.46  BC a |
| **LSD** | 23.894 | | P≤ 0.05 | | | | | |

Means with a different small letter in the same column significantly different (P≤0.05)

Means with a different capital letter in the same row significantly different (P≤0.05)

0= Self control.

The results were showed that group (A) had a significant decrease (P≤ 0.05) of heart rate at time 20 to 60 minutes when compared with the zero time (self control). Meanwhile, group (B) was recorded highly significant decrease (P≤ 0.05) of heart rate at 20 to 60 minutes when compared with the zero time. The results in group (C) were showed significant decrease (P≤ 0.05) in heart rate at time 20 and 60 minutes when compared with the zero time (self control). The results of heart rate at zero time (Self control) were agree with (16) who reported that the normal values of heart rate which ranged between 130-325 beats/minutes. A significant decrease in heart rate could be noticed with variable degrees this could be due to bradycardiac effect of xylazine (17) and these results were also agreed with (18).

**Table (3):** Respiratory rate before, during and after general anesthesia administration in rabbits (breath/minute "bpm")

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Time**  **Group** | **0** | | **10** | **20** | **30** | **40** | | **50** | **60** | |
| **Group A**  **n=6** | 143.33  ±  5.57  A a | | 48.66  ±  4.36  B a | 44.00  ±  4.47  B a | 37.50  ±  3.22  C a | 37.33  ±  2.71  C a | | 38.16  ±  3.54  C b | 44.66  ±  4.34  B a | |
|  |  | |  |  |  | |  |  | |  |
| **Group B**  **n=6** | 110.33  ±  5.98  A b | | 60.16  ±  3.01  B a | 51.00  ±  2.75  BC a | 48.00  ±  2.87  C a | 42.16  ±  3.28  C a | | 43.50  ±  1.54  C b | 46.16  ±  1.88  C a | |
|  |  | |  |  |  | |  |  | |  |
| **Group C**  **n=6** | 143.33  ±  8.62  A a | | 51.83  ±  4.96  B a | 43.83  ±  2.63  BC a | 40.33  ±  3.31  C a | 44.50  ±  5.16  BC a | | 52.16  ±  7.52  B a | 57.50  ±  8.34  B a | |
| **LSD** | 13.22 | P≤ 0.05 | | | | | | | | |

Means with a different small letter in the same column significantly different (P≤0.05)

Means with a different capital letter in the same row significantly different (P≤0.05)

0= Self control.

Respiratory rate was recorded a significant decrease (P≤ 0.05) at time and 10 to 60 minutes when compared with zero time (self control) in all groups. The results revealed that a highly significant decrease (P≤ 0.05) in respiratory rate were showed at 40 minutes in group (A) and (B) when compared with other period time. The results of respiratory rate values of zero time (self control) was not completely in accordance with the results of other works (19, 20). This could be due to many reasons concerning the animals themselves such as: breed, age, sex, individual variations and could be due to ambient conditions occurred during experiment. Generally, all animals suffered from respiratory rate depression after 10 minutes from injection of the anesthetic mixture, and this depression was significant, but it became no significant within periods started after 10 minutes until60 minutes, and this depression persisted until recovery or shortly after recovery, these result in line with (1) who wrote that, the rate of respiration depends on the used anesthetic. The general tendency is a decrease of the number of breaths per minute, to about 30 to 60/min. When the rate is under 30 breath/minutes, or less than 50% of the normal rate, there should be concern. Presented results, also agree with (21) which reported that general anesthesia may worsen hypoxia or exacerbate cardiac arrhythmias. Decreased respiratory effort due to the effects of the anesthetic agents which can lead to passive collapse of diseased airways. The decline of respiratory rate in rabbits had been showed previously by other workers (22).

**Table (4):** Rectal body temperature before, during and after general anesthesia administration in rabbits (ºC)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Time**  **Group** | **0** | **10** | **20** | **30** | | **40** | | **50** | **60** | |
| **Group A**  **n=6** | 38.53  ±  0.25  A a | 38.16  ±  0.13  A a | 37.75  ±  0.10  AB a | 37.21  ±  0.18  BC ab | | 36.93  ±  0.16  CD ab | | 36.10  ±  0.36  D b | 36.81  ±  0.30  CD b | |
|  |  |  |  |  | | |  |  | |  |
| **Group B**  **n=6** | 38.66  ±  0.20  A a | 37.93  ±  0.45  AB a | 37.55  ±  0.31  BC a | 36.70  ±  0.22  D b | | 36.41  ±  0.54  D b | | 36.90  ±  0.40  CD b | 37.05  ±  0.51  CD ab | |
|  |  |  |  |  |  | | |  | |  |
| **Group C**  **n=6** | 38.38  ±  0.26  A a | 38.13  ±  0.18  AB a | 37.81  ±  0.15  AB a | 37.86  ±  0.13  AB a | | 37.51  ±  0.11  B a | | 37.71  ±  0.10  AB a | 37.76  ±  0.16  AB a | |
| **LSD** | 0.7993 | P≤ 0.05 | | | | | | | | |

Means with a different small letter in the same column significantly different (P≤0.05)

Means with a different capital letter in the same row significantly different (P≤0.05)

0= Self control.

The results were showed in group (A) had a significant decrease (P≤ 0.05) in rectal body temperature at 30 to 60 minutes when compared with the with other time periods. Meanwhile, results of group (B) were recorded a significant decrease (P≤ 0.05) in rectal body temperature at 20 until 60 minutes when compared with other time periods. The result of group (C) showed a significant decrease (P≤ 0.05) in the rectal temperature at 40 minute compared with other time periods.

There was no effect of tramadol on body temperature, while decrease the body temperature at 20 minutes this result supported by (15,23) who found that tramadol has limited effect on thermal threshold. The xylazine cause decrease of rectal temperature (24) as in our study, the α 2 agonist depresses the thermoregulatory mechanisms in the body and either hypothermia or hyperthermia occurs depending on the temperature of environment (25), these results occurred because of the loss of normal thermoregulatory mechanism due to the release of monoamines in the anterior hypothalamus since the nor adrenaline lowers and S –hydroxyl tryptamine (5HT) hypothalamus (26).

In conclusion, (xylazine, ketamine) combination were enough for the most surgical interference due to long surgical time. (tramadol, ketamine) and (nefopam, ketamine) combinations were used in surgical interference of skin and muscles only.

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