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A Rabbit Clinical Trial of Xylazine-Ketamine vs. Fentanyl-Ketamine for General Anesthesia

Falah Mahmood Hameed [a*], Fateh Kadhim [b], Hayder Mohammed Mohsen Al-Tomah [a] and Raeed Altaee [c]

[a] *Surgery and Obstetric Department, University of Kerbala, Iraq.*
[b] *Department of Microbiology and Parasitology, University of Kerbala, Iraq.*
[c] *Department of Physiology, Biochemistry and Pharmacology, Veterinary Medicine Faculty, University of Kerbala, Iraq.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The Aim of Study: The current investigation was designed to compare the anesthetic and physiological effects of ketamine with different pre-anesthetics protocol.
Methods: A total of twelve healthy male rabbits were chosen for the clinical anesthetic trial. Animals were presented to the faculty of veterinary medicine at Kerbala University for skin wound procedures and separated into two equal groups 6 rabbits each (group A and group B). Rabbits in group A were administered an intramuscular injection of xylazine (10mg/kg BW) followed by ketamine (50 mg/kg I.M) after 10 minutes. while those in group B were injected with fentanyl (0.04 mg/kg BW, I.M) first plus ketamine (50 mg/kg I.M) after 10 minutes. The physiological and

**Corresponding author: Email: falah.m@uokerbala.edu.iq;*

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anesthetic parameters to assess the complications that associated with anesthetic, were recorded and analyzed.
Results: The level of induction and recovery varied significantly (P<0.05) among the groups. Compared to group B, group A had a considerably (P<0.05) shorter induction time. Furthermore, group A's mean time for losing pedal reflex revealed a substantial (P<0.05) decrease. Between-group differences in the responses to the pain test and muscular relaxation were statistically significant (P<0.05). Group A experienced a substantially longer (P<0.05) induction period, surgical anesthetic duration, and recovery period than group B. No rabbits died as a result of the anesthetic or the recuperation.
Conclusion: Compared to Fentanyl-ketamine (FK) combination anesthesia, administration of Xylazine with ketamine (XK) apparently does not influence the physiological parameters. Additionally, this method provides a very successful anesthetic procedure for a flawless induction, suitable muscle relaxation, extended anesthesia, and a painless recovery.

Keywords: Ketamine; fentanyl; xylazine; rabbits; general anesthesia.

1. INTRODUCTION

Common companion animals used in research and experimental surgery include rabbits [1, 2]. Rabbits are frequently used for creating a range of human sickness models for prolonged studies because of their biological similarities to humans [3]. For rabbit anesthesia, a wide variety of injectable anesthetic substances are available [4].

Several sedatives and tranquilizers are given to animals having minor or major surgery in order to ease discomfort and relax their muscles. In addition to helping to overcome animal tolerance during examination, these drugs are crucial to veterinary practice because they maintain the depth of anesthesia, reduce the number of anesthetic agents needed, and increase margins of safety [5,6].

Due to its superior analgesic and muscle-relaxing properties over other anesthetics, xylazine is frequently used as a pre-anesthetic in veterinary treatments to produce balanced anesthesia in a variety of species [6]. It produces calming and analgesic effects by blocking the release of catecholamines and dopamine. Additionally, xylazine prevents nerve transmission in the central nervous system, which relaxes striated muscles. Xylazine and ketamine are commonly used together in anesthetic applications [7].

Ketamine has been shown to elevate the heart rate, average arterial pressure, and cardiovascular processes when taken by itself. To lessen these unwanted and constrictive effects, ketamine is utilized in combination with other drug groups as benzodiazepine and alpha-2 agonists [7, 8].

We used fentanyl, a type of opioid agonist, in addition to ketamine to increase the anesthetic effects of ketamine in rabbits for precisely the same causes as previously. Often used in anesthesia, fentanyl has 80 times the analgesic efficacy of morphine [9]. It is also frequently used in veterinary medicine, where it is used to produce satisfactory anesthesia in rabbits after being combined with midazolam and medetomidine [10] and surgical anesthesia in dogs [11].

1.1 The Current Study was Aimed to

1. 1-Assess the anesthetic efficacy of fentanyl and ketamine combination and look into its impact on physiological parameters (temperature in degrees Celsius, heart rate, blood pressure, pulse rate in minutes, and the rate of respiration in breaths per minute) prior to, during, and following anesthesia. and contrasting these outcomes with the rabbit XK trail results.
2. 2- Assess the anesthetic stages; induction, duration of anesthesia and recovery. Which was done by determining of certain reflexes that were recorded in all rabbits during the experiment.

2. MATERIALS AND METHODS

2.1 Experimental Design and Dosage

The present study was conducted on 12 male rabbits. In order to examine the impact of injecting both anaesthetic groups, the study used rabbits that were brought to the faculty of veterinary medicine. Animals were randomly saperated into two equal experimental groups of 6 male rabbits each. Drug administration: Anesthesia was achieved by administration of

xylazine (10mg/kg BW, I.M), then after 10 minutes followed with ketamine (50 mg/kg I.M) for group A. While, group B was given fentanyl (0.04 mg/kg BW, I.M) and, then 10 minutes later ketamine was administered at 50 mg/kg I.M.

2.2 Assessing Physiological Parameters

The physiological parameters; temperature in c^0, heart rate in beats minute, pulse in minute, blood pressure, SPo_2 and respiratory rate in breath minute) were recorded at 0, 5, 10, 20, 30, 40, 50,70 minutes after administering the anesthetics dose for both groups until the time of the recovery. All physiological parameters were taken by patient monitor [12].

2.3 Assessment of Anesthetic Parameters

Induction time: The total number of minutes that passed between the ketamine injection and the loss of the pedal reflex was utilized to determine the induction time. The length of anesthesia is defined as the interval (measured in minutes) between the injection of xylazine and ketamine and the rabbit's first spontaneous head and leg lift [13]. Recovery time: The difference in minutes from the rabbit's first spontaneous head and leg rise to standing independently [14].

2.4 Statistical Analysis

Graph Pad Prism edition 9.0 for Microsoft (Graph Pad Software, San Diego, USA) was used to analyze the results, which are shown as the mean ± standard error of the mean (SEM). Prior to performing a comparative statistical analysis, normality testing was done using the D'Agostino and Pearson tests of normality. Tukey's multiple comparisons test in an analysis of variance (ANOVA) was used to analyze differences between more than two groups, whereas Student's t-tests were used for statistical analysis between two groups. $P < 0.05$ was the threshold for statistical significance.

3. RESULTS AND DISCUSSION

Surgical and diagnostic procedures are basically need to use anesthesia in pet animals. Compared to dogs and cats, anesthesia is associated with more complex perioperative risks in rodents and rabbit [15]. Recent anesthetic procedures advocate medication combinations. This is known as balanced anesthesia that involves the use of numerous medicines in modest doses, with each substance serving a unique role. The major goal is to exploit the favorable properties of chosen medications while minimizing their tendency to depress homeostatic systems [16]. Ketamine is well-known for being a flexible substance with a unique profile that enables its safe use in many different contexts across the globe, including zoos and pet stores. [17, 18]. When taken alone, it leads to increase the mean arterial pressure and heart rate, improves the functions of cardiovascular system. Furthermore, it can also produce muscular hypertonicity, myoclonus and seizures [19, 20]. In comparison to fentanyl-ketamine anesthesia, the current study demonstrated that xylazine-ketamine anesthesia produced a longer duration of anesthesia and a more seamless recovery. The outcomes of the xylazine-ketamine anesthesia were consistent with the previously published research on sheep [21] and chicks [22, 23], as well as rabbits [24, 25, 26].

Fig (1) shows that rabbits in both groups (A) and (B) had the lowest heart rate following injection of anesthetic combinations. The 2-agonist are known to cause significant bradycardia [27]. As a result, the animals given xylazine showed signs of bradycardia. [28] It is also known that opioids produce bradycardia via stimulating the vagal center [29].

When comparing group A to self-control (zero time), the heart rate varied considerably at all periods from (5-70) minutes. While in group B, the times (30 and 50) minutes were drastically altered, while the times (5, 10, and 70) minutes remained unchanged when compared to the self-control (zero time), as shown in Fig (1). As a result, animals given fentanyl developed bradycardia, which is consistent with the finding stated by [30] that fentanyl potentiates the decline in heart rate when combined with other anesthetic drugs. The results showed a significantly greater heart rate in the rabbits anesthetized with group B in comparing to group A. It was significantly ($P<0.05$) decreased through the anaesthetic phase at 10, 30 and 70 minutes (Fig 1), which may be attributed to fentanyl's shorter bradycardiac effect. Although ketamine's stimulatory circulatory effects in rabbits are less pronounced than in other animals [31].

Before induction, all rabbits were tachypneic, with respiration rates varied between 120 breaths per minute until dropping down to the baseline value under anesthesia in both (A&B) groups. Between 5 and 50 minutes after medication

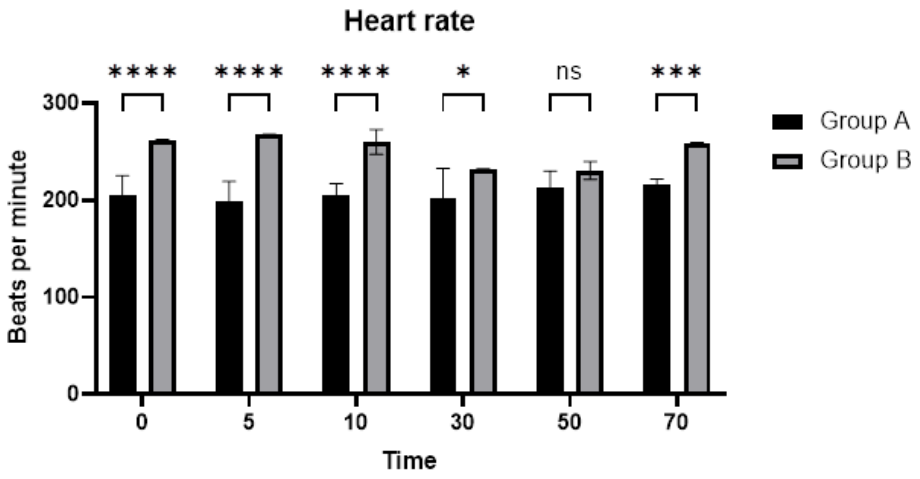

Fig. 1. Effects of anesthetic drug combinations on heart rate

*A combination of anesthetic drugs in group B was significantly increased heart rate compared to group A. ***: values significantly different between anesthetic drug groups. Results are shown as mean +/-SEM, n= 12*

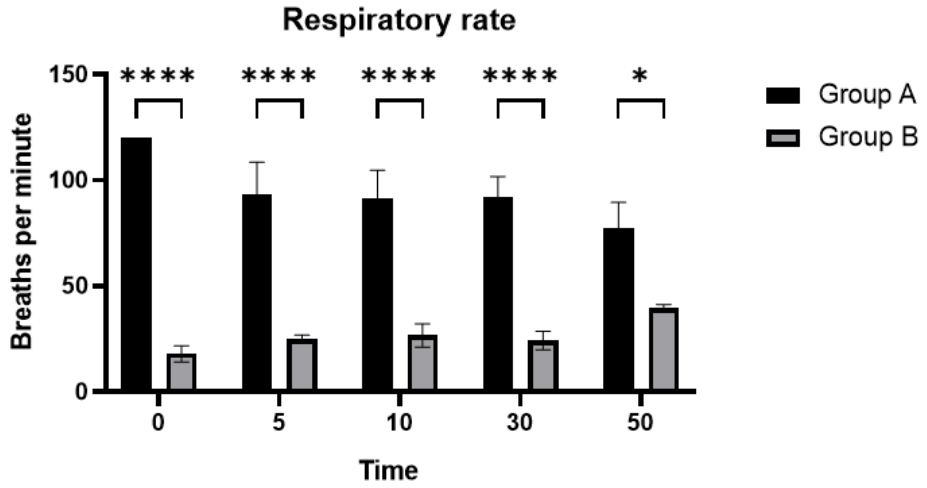

Fig. 2. Effects of anesthetic drug combinations on respiratory rate

*A combination of anesthetic drugs in group A was significantly different than group B in their effect on respiratory rate. ***: values significantly different between anesthetic drug groups. Results are shown as mean +/-SEM, n= 12*

administration, the B group's respiratory rate was substantially lower (P<0.05) than the A group's (Fig 2). These findings agreed with prior research [32,33].

The effects on respiration noticeably were seen in group B, where the respiratory rate dropped significantly; nonetheless, the lowest respiratory rate under anesthesia was 30 in animal 1 at [5], 15 in animal at [20], and 18 in animal 3 at [20].

The opioid component [34] is most likely responsible for the brief duration of apnea seen in some animals in the A group. It is important to stress that the depression of the respiratory is not limited to the administration of B or A, but also happens with other anesthetic regimens in rabbits; consequently, it is recommended that oxygen be administered throughout anesthesia [35].

According to the temperature data, the animals in both groups A and B had a reduction in body temperature over time, which is normal during anesthesia. The changes in temperature within the normal physiological range, on the other hand, imply that the anesthetic combinations of xylazine-ketamine and fentanyl-ketamine utilized

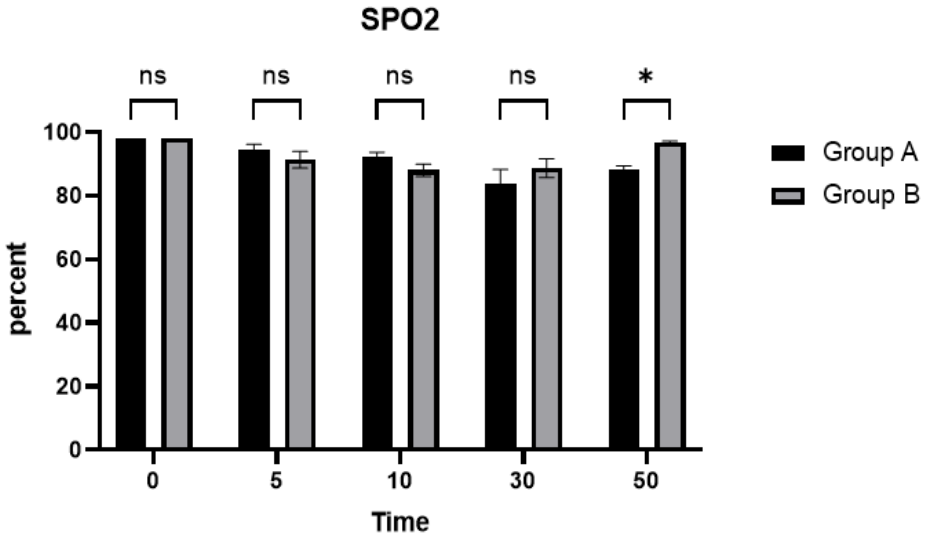

Fig. 3. Effects of anesthetic drug combinations on SPO_2

*A combination of anesthetic drugs in group B was significantly different (P=0.04) than group A in their effect on SPO_2. *: values significantly different between anesthetic drug groups. Results are shown as mean +/-SEM, n= 12*

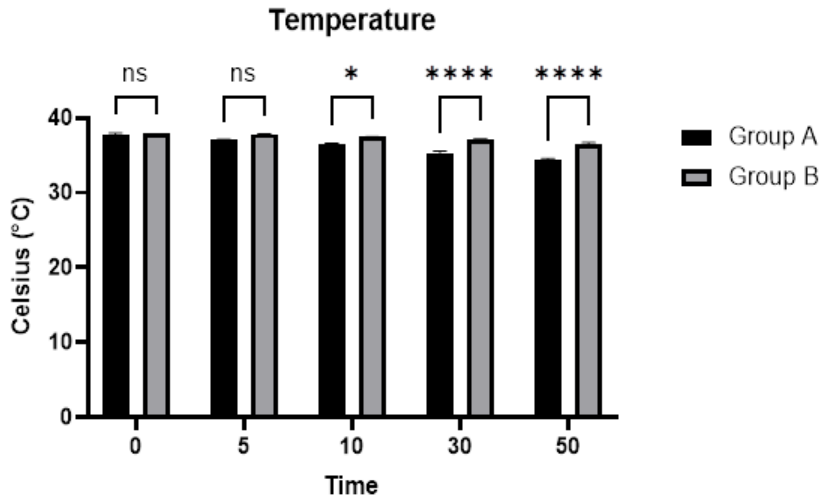

Fig. 4. Effects of anesthetic drug combinations on body temperature

*A combination of anesthetic drugs in group B was significantly increased (P) compared to group A in their effect on body temperature. ***: values significantly different between anesthetic drug groups. Results are shown as mean +/-SEM, n= 12*

in this investigation did not adversely alter the rabbits' thermoregulatory processes, our study agreed with prior research.

It is vital to remember that anesthesia can impact animal body temperature, and maintaining correct temperature management during anesthesia is critical to avoid hypothermia or hyperthermia, both of which can have negative consequences on the animals' physiological reactions and recovery.

The data presented shows no substantial departures from the normal physiological temperature range, suggesting that the anesthetic combinations utilized in this investigation may have produced appropriate anesthesia without producing severe temperature disturbances.

It's also worth mentioning that other factors such as ambient temperature, humidity, and individual variability among animals can also influence

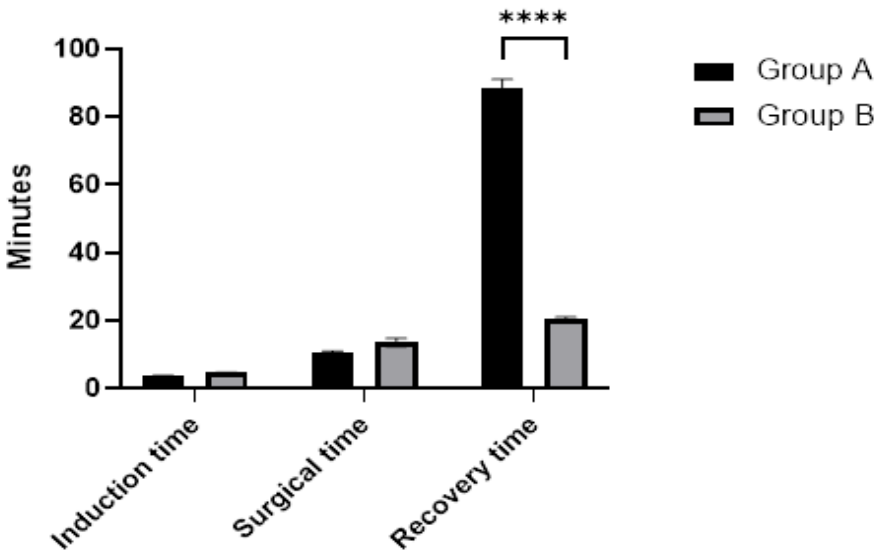

Fig. 5. Effects of anesthetic drug combinations on induction time, surgical time, and recovery time

*A combination of anesthetic drugs in group A was significantly increased (P) compared to group B in their effect on induction time, surgical time, and recovery time. ***: values significantly different between anesthetic drug groups. Results are shown as mean +/-SEM, n= 12*

body temperature during anesthesia. Therefore, it's important to carefully monitor and manage the animals' body temperature during anesthesia to ensure their well-being and successful recovery. Further studies with larger sample sizes and more detailed temperature monitoring may provide additional insights into the effects of the anesthetic combinations on body temperature in rabbits.

The induction time, surgical time, and recovery time are important factors to consider when evaluating the effectiveness of anesthetic combinations in animals. In this study, two different groups (A and B) were compared based on these parameters.

Induction time refers to the time taken for the animals to become fully anesthetized after the administration of the anesthetic drugs. In group A, the induction time ranged from 3 to 4 minutes, with the first animal taking 3 minutes, and the second and third animals taking 4 minutes each. On the other hand, in group B, the induction time ranged from 4 to 5 minutes, with the first two animals taking 5 minutes each, and the third animal taking 4 minutes. These findings suggest that the xylazine-ketamine combination used in group A had a faster onset of anesthesia compared to the fentanyl-ketamine combination used in group B.

Surgical time refers to the duration of the surgical procedure. In group A, the range of the surgical time was from 10 to 12 minutes, and the shortest time observed in the second and third animals (10 minutes each). In group B, the surgical time was from 10 to 16 minutes and the lower time observed in the first animal (10 minutes) and the longest time in the third animal (16 minutes). There were no significant differences in surgical time between the two groups. However, it's worth noting that the actual duration of the surgical procedure may vary depending on the complexity and type of surgery being performed.

Recovery time refers to the time taken for the animals to fully recover from anesthesia and regain normal physiological functions. In group A, the recovery time varying from 80 to 95 minutes, with the shortest time observed in the second animal (80 minutes) and the longest time in the first animal (95 minutes).

In group B, the recovery time ranged from 20 to 22 minutes, with all three animals showing similar recovery times. These findings suggest that the recovery time was shorter in group B compared to group A.

It's important to consider the differences in induction time, surgical time, and recovery time between the two groups in the context of the

specific anesthetic combinations used. The faster induction time observed in group A may be advantageous in cases where rapid immobilization and anesthesia are desired, such as in emergency or short-duration procedures. On the other hand, the shorter recovery time observed in group B may be beneficial in minimizing the duration of post-anesthetic recovery and reducing the risk of complications associated with prolonged recovery periods.

Overall, the data suggests that there were fluctuations in blood pressure in both group A and group B animals over time. Some animals in both groups showed elevated blood pressure values, which could indicate physiological responses to anesthesia or other factors. Monitoring blood pressure during anesthesia is important to ensure the safety and well-being of animals, and any significant fluctuations or elevations should be closely monitored and managed accordingly by the veterinary team. Further analysis and interpretation of the data may require statistical analysis and consideration of other relevant factors, such as animal age, health status, and anesthesia protocols used [36].

4. CONCLUSION

The result of this study suggests that despite of slight biochemical and physiological changes, but the two protocols can be used for general anesthesia induction in rabbits. xylazine-ketamine anesthesia was more likely to induce longest duration, smoothest induction and recovery, As a result, it is appropriate and recommended for use in many longer-term surgical treatments in rabbits. Because fentanyl-ketamine anesthesia had the shortest duration and caused the most convulsions during recovery, therefore it is not recommended to use for the induction of general anesthesia in rabbits.

ETHICAL APPROVAL

The present study was done in accordance to the reference number UOK.VET.SU.2023.08.3 of the Animal Usage Protocol Committee declaration of University of Kerbala. College of Vet. Med.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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