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The adjunct pre-anesthetic effect of a Single Oral Dose of Gabapentin on Ketamine-Anesthesia in Rabbits

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ABSTRACT: General anesthesia in laboratory animals is essential for ensuring humane procedures and reliable experimental results. However, safe and effective anesthesia can be challenging due to species-specific physiological status. This study assessed the outcome of a single oral dose of gabapentin (25 mg/kg) on ketamine-induced general intravenous anesthesia in rabbits. A total of 36 healthy adult New Zealand rabbits were randomly divided into two groups: a control group receiving oral saline and a gabapentin group receiving 25 mg/kg gabapentin, both administered 60 minutes prior to intravenous ketamine anesthesia. Induction time, depth of anesthesia, hemodynamic parameters, recovery quality, and duration of anesthesia were assessed. The gabapentin group exhibited a significantly shorter induction time (2.3 ± 0.4 minutes) compared to the control group (3.8 ± 0.6 minutes; $p < 0.001$). The depth of anesthesia was excellent in the gabapentin group, with all rabbits scoring 0 (absent reflexes), while the control group showed variable reflex responses (mean score = 0.6 ± 0.3; $p < 0.01$). Hemodynamic parameters remained stable in both groups, with no significant differences. Recovery quality was superior in the gabapentin group (score = 3) compared to the control group (score = 1.8 ± 0.5; $p < 0.001$), with no convulsions or twitches observed. The duration of anesthesia did not differ significantly between groups (21.5 ± 1.2 minutes vs. 22.0 ± 1.5 minutes; $p = 0.35$). These findings demonstrate that gabapentin significantly enhances the quality of ketamine anesthesia in rabbits, reducing induction time, improving anesthetic depth, and ensuring smooth recovery. Gabapentin is a safe and effective premedication for optimizing anesthesia protocols in laboratory rabbits.

KEYWORDS: Anesthesia, Gabapentin, Premedication, Rabbits.

1. Introduction

General anesthesia is a critical component of both human and veterinary medicine, enabling the performance of surgical procedures and diagnostic interventions without causing pain or distress to the subject. In laboratory animals, such as rabbits, the use of general anesthesia is essential for ensuring humane treatment during experimental procedures, as well as for maintaining the integrity of scientific data by minimizing stress-induced physiological changes [1]. Rabbits are widely used in biomedical research due to their small size, easy to handle, and their physiological similar to humans in certain aspects, such as cardiovascular and respiratory systems [2, 3, 4]. However, achieving safe and effective anesthesia in rabbits can be challenging due to their unique physiological and pharmacological responses, necessitating the exploration of novel anesthetic adjuvants to improve outcomes. Gabapentin, a gamma-aminobutyric acid (GABA) analog, has gained attention in both veterinary medicine and human for its multimodal pharmacological effects, including anticonvulsant, analgesic, and anxiolytic properties [5]. Although initially developed for the treatment of epilepsy, gabapentin has been increasingly used as an adjunct to manage neuropathic pain and perioperative anxiety in animals [6]. Its mechanism of action involves binding to the $\alpha 2\delta$ subunit of voltage-gated calcium channels, thereby modulating neurotransmitter release and reducing neuronal excitability [7, 8, 9]. In veterinary

practice, gabapentin has been shown to enhance the effects of other anesthetic agents, reduce the required doses of induction drugs, and provide smoother recovery profiles [10, 11, 12, 13]. Despite its growing use, the specific effects of gabapentin on anesthetic protocols in rabbits remain underexplored, warranting further investigation. Ketamine, a dissociative anesthetic, is commonly used in veterinary medicine due to its rapid onset of action, analgesic properties, and minimal effects on cardiovascular function [14, 15, 16, 17]. In rabbits, ketamine is often combined with other agents, such as xylazine or diazepam, to achieve balanced anesthesia [1]. However, ketamine alone can cause inadequate muscle relaxation and poor analgesia, necessitating the use of adjuncts to optimize its effects [2]. The combination of ketamine with gabapentin has shown promise in other species, but its efficacy and safety in rabbits have not been thoroughly studied. The primary objective of this research is to evaluate the effect of a single 25 mg/kg oral dose of gabapentin on ketamine-induced general anesthesia in rabbits. Specifically, the study aims to assess the impact of gabapentin on the depth and duration of anesthesia, hemodynamic stability, and recovery quality. By investigating the potential benefits of gabapentin as an anesthetic adjunct, this study seeks to contribute to the development of safer and more effective anesthetic protocols for laboratory rabbits, ultimately improving animal welfare and the reliability of experimental outcomes.

2. Materials and Methods

2.1. Ethical Approval

This study was conducted in strict accordance with the guidelines for care and use of laboratory animals approved by the Animal Care and Use Committee, Assiut University–faculty of Veterinary Medicine, Assiut, Egypt (registration number: 04-2023-200245)

2.2. Animal Population and Study Design

A total of 36 healthy adult New Zealand White rabbits (Oryctolagus cuniculus), weighing between 2.8 kg and 3.5 kg, were used in this study. The rabbits were housed in individual cages under controlled environmental conditions (temperature: 22–25°C, humidity: 55–60%, and a 12-hour light/dark cycle) with free access to water and a standard laboratory diet. Animals were acclimatized to the housing conditions for a minimum of 7 days prior to the experiment to minimize stress-related variables. The study employed a randomized, blinded, controlled experimental design. Rabbits were randomly allocated into two groups using a computer-generated randomization table. Group 1 (Control Group): Received a placebo (oral saline) 60 minutes prior to ketamine-induced anesthesia. Group 2 (Gabapentin Group): Received a single oral dose of gabapentin (25 mg/kg) 60 minutes prior to ketamine-induced anesthesia. The sample size was determined using a power analysis ($\alpha = 0.05, \beta = 0.20$) based on preliminary data to ensure adequate statistical power.

2.3. Medications and Doses

Gabapentin: A commercially available gabapentin capsule (gaptin ®, delta pharma company, Egypt) was administered orally at a dose of 25 mg/kg on fully stomach. The dose was selected based on previous pharmacokinetic and pharmacodynamic studies in rabbits and other species [10, 5].

Ketamine: Ketamine hydrochloride (50 mg/mL) was administered intravenously at a dose of 35 mg/kg to induce general anesthesia. This dose was chosen based on established protocols for ketamine anesthesia in rabbits [1].

Placebo: An equivalent volume of sterile saline was administered orally to the control group to maintain blinding.

All medications were prepared and administered by a researcher blinded to the group assignments to eliminate bias.

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2.4. Clinical Evaluation and Assessment of Anesthetic Effects

The anesthetic effects were evaluated using a standardized scoring system and physiological monitoring. The following parameters were recorded at baseline (prior to drug administration), during induction, maintenance, and recovery phases of anesthesia, induction Time: Time from ketamine administration to loss of righting reflex (LORR), depth of Anesthesia: Assessed using the pedal withdrawal reflex (PWR) and palpebral reflex. Reflexes were scored as present (1) or absent (0), Hemodynamic Parameters: Heart rate (HR), respiratory rate (RR), and oxygen saturation (SpO2) were monitored non-invasively using a veterinary multiparameter monitor, Recovery Quality: Recovery was assessed using a modified recovery scoring system (0 = poor, 1 = fair, 2 = good, 3 = excellent) based on the time to return of righting reflex, presence of ataxia, and behavioral distress, Duration of Anesthesia: Defined as the time from LORR to the return of spontaneous movement. All observations and measurements were performed by a trained investigator blinded to the treatment groups to ensure objectivity.

2.5. Statistical Analysis

Data was analyzed using statistical software (SPSS version 29.0.2, IBM, USA). Normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables were compared between groups using an independent t-test or Mann-Whitney U test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Repeated measures ANOVA were used to compare changes in hemodynamic parameters over time within and between groups. Data is presented as mean ± SD. A p-value of ≤ 0.05 was considered statistically significant.

3. Results

3.1. Animal Population and Group Distribution

A total of 36 healthy adult New Zealand White rabbits were used in this study. The animals were randomly divided into two groups of 18 rabbits each. Group 1 (Control Group) received a placebo (oral saline) 60 minutes prior to ketamine-induced anesthesia, while Group 2 (Gabapentin Group) received a single oral dose of gabapentin (25 mg/kg) 60 minutes prior to ketamine-induced anesthesia. All rabbits completed the study without adverse events or exclusions.

3.2. Induction Time

The induction time, defined as the time from ketamine administration to loss of righting reflex (LORR), was significantly shorter Figure. 1 in the gabapentin-ketamine group compared to the control group. The mean induction time in the gabapentin-ketamine group was 2.3 ± 0.4 minutes, while in the control group, it was 3.8 ± 0.6 minutes. This difference was statistically significant ($p \leq 0.001$), indicating that gabapentin significantly reduced the time required to achieve anesthesia.

3.3. Depth of Anesthesia

The depth of anesthesia was assessed using the pedal withdrawal reflex (PWR) and palpebral reflex. In the gabapentin-ketamine group, all rabbits exhibited a consistent and excellent depth of anesthesia (Figure. 1), with reflex scores of 0 (absent reflexes) throughout the maintenance phase. In contrast, the control group showed variable reflex responses, with scores ranging from 0 to 1 (present reflexes), yielding a mean reflex score of 0.6 ± 0.3. The difference in reflex scores between the two groups was statistically significant ($p \leq 0.01$), demonstrating that gabapentin enhanced the depth of anesthesia.

3.4. Hemodynamic Parameters

Hemodynamic parameters, including heart rate (HR), respiratory rate (RR), and oxygen saturation (SpO2), were monitored throughout the anesthetic period. The gabapentin-ketamine group exhibited slightly lower values compared to the control group, but these differences were not statistically significant (Figure. 1). Specifically,

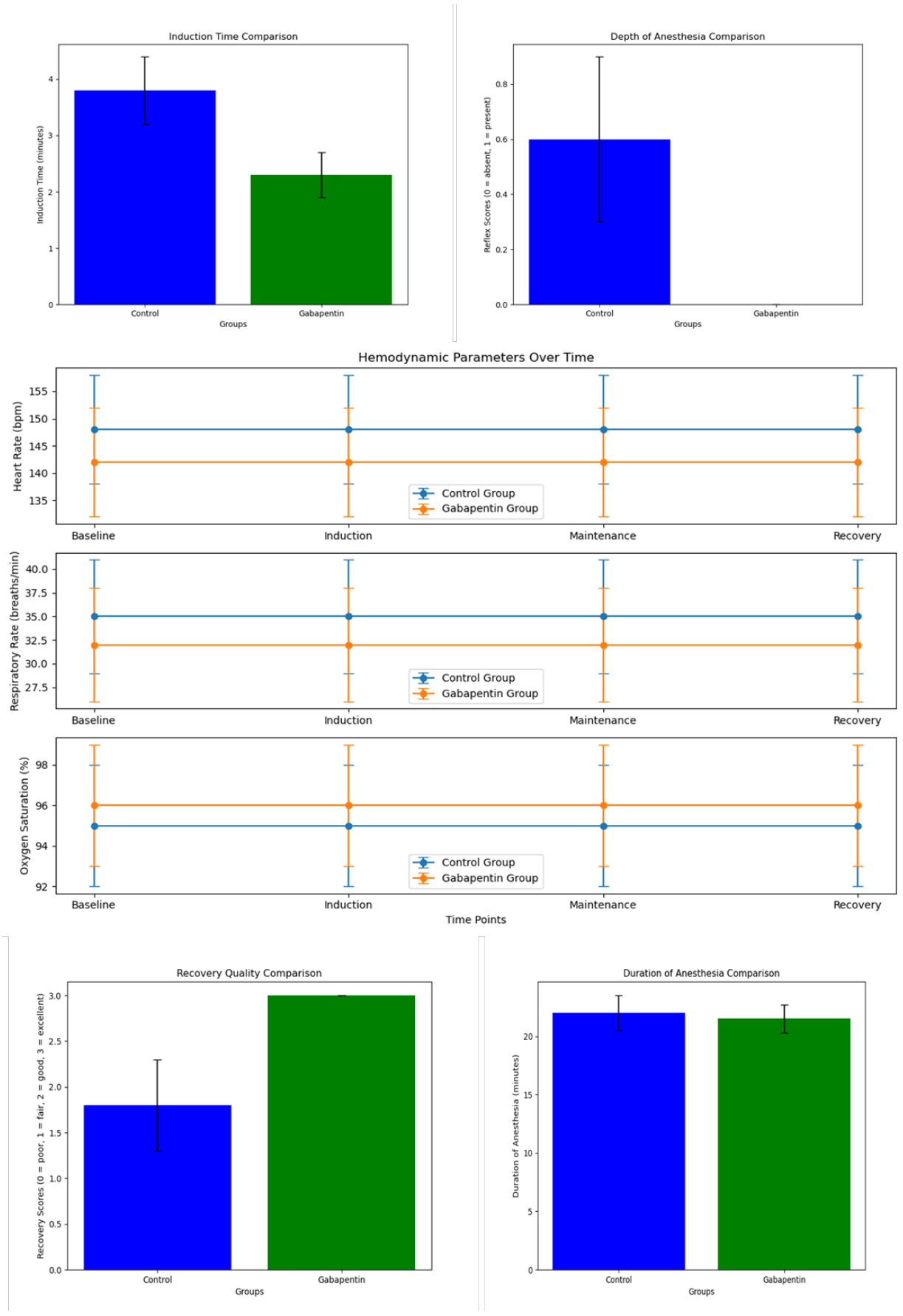

Figure 1: Graphs illustrate the induction time, depth of anesthesia, hemodynamic parameters over time, recovery quality and duration of anesthesia among examined groups.

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the heart rate (HR) was 142 ± 8 bpm in the gabapentin-ketamine group and 148 ± 10 bpm in the control group (p = 0.12). The respiratory rate (RR) was 32 ± 5 breaths/min in the gabapentin-ketamine group and 35 ± 6 breaths/min in the control group (p = 0.18). Oxygen saturation (SpO2) was 96 ± 2% in the gabapentin-ketamine group and 95 ± 3% in the control group (p = 0.45). These results indicate that gabapentin did not adversely affect hemodynamic stability.

3.5. Recovery Quality

The recovery quality was significantly better in the gabapentin-ketamine group compared to the control group. Rabbits in the gabapentin-ketamine group exhibited excellent recovery (score = 3), characterized by a smooth and rapid return of the righting reflex, absence of ataxia, and no signs of distress (Figure. 1). In contrast, the control group showed variable recovery quality, with scores ranging from fair to good (1.8 ± 0.5), and some rabbits exhibited convulsions and muscle twitches. The difference in recovery scores between the two groups was statistically significant ($p \leq 0.001$), highlighting the superior recovery profile associated with gabapentin.

3.6. Duration of Anesthesia

The duration of anesthesia, defined as the time from LORR to the return of spontaneous movement, was not significantly different (Figure. 1) between the two groups. The mean duration of anesthesia in the gabapentin-ketamine group was 21.5 ± 1.2 minutes, while in the control group, it was 22.0 ± 1.5 minutes. This difference was not statistically significant (p = 0.35), indicating that gabapentin did not alter the overall duration of anesthesia.

4. Discussion

The primary objective of this study was to evaluate the effect of a single oral dose of gabapentin on ketamine-induced general anesthesia in rabbits. Our results demonstrate that gabapentin enhances the quality of anesthesia by reducing induction time, improving anesthetic depth, and ensuring a smooth recovery. The study contributes to the growing body of literature supporting the use of gabapentin as an anesthetic adjunct in rabbits as lab animal species. Rabbits are a widely used animal model in biomedical research due to their small size, easy to control, and physiological similarities to humans in certain aspects, such as cardiovascular and respiratory systems [18, 19, 20, 21]. However, rabbits are also known for their unique pharmacological responses and sensitivity to stress, making anesthesia challenging [1]. Our study highlights the utility of rabbits as a model for evaluating anesthetic protocols and underscores the importance of optimizing anesthesia to ensure both animal welfare and reliable experimental outcomes. The use of gabapentin as a premedication in rabbits has not been extensively studied, and our findings contribute valuable data to this field. Gabapentin, a gamma-aminobutyric acid (GABA) analog, has been widely studied for its analgesic, anxiolytic, and anticonvulsant properties in both humans and animals [5]. In veterinary medicine, gabapentin has been used as a premedication to reduce perioperative anxiety, enhance analgesia, and improve recovery quality [6]. Our study corroborates these findings, as rabbits in the gabapentin-ketamine group exhibited a significantly shorter induction time, a consistent and excellent depth of anesthesia, and superior recovery quality compared to the control group. These results are consistent with studies in other species, such as dogs and cats, where gabapentin has been shown to reduce the required doses of induction agents and improve recovery profiles [10, 22]. In human medicine, gabapentin has been extensively studied as a perioperative adjunct to reduce postoperative pain, anxiety, and opioid consumption [23, 24, 25]. A meta-analysis demonstrated that preoperative gabapentin significantly reduced postoperative pain scores and opioid requirements in patients undergoing various surgical procedures [23]. Similarly, our study found that gabapentin improved the quality of

anesthesia and recovery in rabbits, suggesting that its benefits may extend across species. These findings support the potential for translational applications of gabapentin in both veterinary and human anesthesia. Ketamine, a dissociative anesthetic, is commonly used in veterinary medicine due to its rapid onset of action, analgesic properties, and minimal effects on cardiovascular function [14, 26, 27, 26]. However, ketamine alone can cause inadequate muscle relaxation and analgesia, necessitating the use of adjuncts to optimize its effects [1]. In our study, the combination of gabapentin and ketamine resulted in a more stable anesthetic plane and improved recovery quality, which is consistent with findings in other species. For example, in dogs, the addition of gabapentin to ketamine anesthesia has been shown to reduce postoperative pain and improve recovery scores (Wagner et al., 2010).

Conclusions

A single oral dose of gabapentin (25 mg/kg) significantly enhances the quality of ketamine-induced general anesthesia in rabbits. Future studies should explore the use of gabapentin in other animal models and investigate its long-term effects on postoperative outcomes.

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