

## **MAGNESIUM SULFATE, KETOROLAC, PROPOFOL, KETAMINE, AND XYLAZINE ANESTHETIC PROTOCOL IN RABBITS**

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### **ABSTRACT**

The study aimed to evaluate the combination of Magnesium sulfate (Mg), ketorolac (Kr), Propofol (P), Ketamine (K), and Xylazine(X) anesthetic protocol in anesthesia and analgesia of rabbits. Twenty healthy male rabbits, weighing ( $1.300 \pm 0.200$  kg) were used in the study. All rabbits were randomly assigned to four groups of five rabbits injected with the different protocols (G1(p<sub>10</sub>k<sub>50</sub>mg<sub>50</sub>), G2(p<sub>10</sub>k<sub>50</sub>kr<sub>10</sub>), G3(p<sub>10</sub> k<sub>50</sub> kr<sub>10</sub>mg<sub>50</sub>), and G<sub>4</sub>(p<sub>10</sub> k<sub>50</sub> kr<sub>10</sub>mg<sub>50</sub>X<sub>5</sub>)) of anesthesia intravenously in the marginal ear vein. The heart rate (HR), respiratory rate (RR), rectal temperature (RT) were taken before giving the drugs (Time 0 (control reading)), and then after 5,10,15,20,30,45,60,and 75 minutes of giving anesthesia. The induction time, duration of anesthesia, degree of analgesia, muscle relaxation and recovery time were recorded also.

The anesthetic protocol in G<sub>3</sub> (p<sub>10</sub> k<sub>50</sub> kr<sub>10</sub>mg<sub>50</sub>) is seen suitable for short operations (gives 24.2 minutes of surgical anesthesia), and the anesthetic protocol in G<sub>4</sub> (p<sub>10</sub> k<sub>50</sub> kr<sub>10</sub>mg<sub>50</sub>X<sub>5</sub>) is seen suitable for long operations (gives 43.5 minutes of surgical anesthesia), and no signs of pain with the intravenously injection of propofol.

### **INTRODUCTION**

Rabbits are the third most commonly anesthetized species of animals, but have at least seven times more risks of anesthetic-related death compared to dogs and cats (1). Currently, advanced diagnostic and surgical procedures requiring safe and adequate anesthesia are routinely performed on rabbits. Tracheal intubation of rabbits and use of inhalation anesthetic can be quite complicated and time consuming (2). Intubations can cause trauma to the larynx, laryngospasm and tracheal lesions (3). In small

laboratory animals, most anesthetics are administered intramuscularly because of the difficulty in obtaining intravenous (IV) access. The introduction of short acting hypnotic drugs like propofol prompted the development of alternative methods to inhalation anesthesia, i.e. total intravenous anesthesia (TIVA) (4). The most commonly used injectable agents in veterinary medicine are ketamine, diazepam, propofol, xylazine and medetomidine for animals. Certain combinations of these agents improve their anesthetic properties (5, 6).

Propofol (2, 6-diisopropylphenol) is a potent intravenous hypnotic drug widely used for induction of anesthesia, short-term anesthesia, and for longer-term sedation. Clinical observations indicate that long-term propofol use can be a safe alternative to opiates (7). Ketorolac in combination with propofol for sedation associated with a rapid recovery, low postoperative pains cores, and an absence of side effects (8).

Magnesium sulfate has anesthetic, analgesic and muscle relaxation effects and significantly reduces the drug requirements of propofol during anesthesia (9).

Ketamine is a phencyclidine derivative NMDA receptor antagonist used in clinical practice for anesthesia and analgesia (10, 11).

Xylazine hydrochloride is a typical  $\alpha_2$ -adrenoreceptor agonist of the non-opioid group having, analgesic, sedative, and muscle relaxant effects and is used commonly in clinical practice (12). The combination of ketamine and xylazine has been used for many species over the years and remains a popular combination for intramuscular and intravenous anesthesia in animals including rabbits (13, 14).

The study aim to evaluate the combination between these drugs as I/V anesthetic protocol in rabbits.

## **MATERIALS AND METHODS**

Twenty healthy male rabbits, weighing ( $1.300 \pm 0.200$  kg) were used in the study. All rabbits were randomly assigned to four groups of five rabbits injected with the different protocol, of anesthesia intravenously in the marginal ear vein.

**Group 1**(P<sub>10</sub> K<sub>50</sub> Mg<sub>50</sub>), was injected by a mixture of propofol (10 mg/kg), ketamine ( 50 mg/kg ) and magnesium sulfate ( 50 mg/kg ), BW, I/ V. **Group 2** ( P<sub>10</sub> K<sub>50</sub> Kr<sub>10</sub>):was injected by a mixture of propofol (10 mg/kg ), ketamine (50 mg/kg ) and ketorolac ( 10 mg/kg ),BW, I/ V. **Group 3**( P<sub>10</sub> K<sub>50</sub> Kr<sub>10</sub>Mg<sub>50</sub> ) was injected by a mixture of propofol (10 mg/kg ), ketamine (50 mg/kg ), ketorolac (10 mg/kg ) and magnesium sulfate (50 mg/kg ),BW, I/ V. **Group 4** ( P<sub>10</sub> K<sub>50</sub>

Kr<sub>10</sub>Mg<sub>50</sub>X<sub>5</sub> ), was injected by a mixture of propofol (10 mg/kg ), magnesium sulfate (50 mg/kg ), ketorolac (10 mg/kg ), ketamine(50 mg/kg) and xylazine ( 5 mg / kg ),BW, I/V .

The heart rate (HR), respiratory rate (RR), and rectal temperature (RT) were taken before injection of the drugs (Time zero reading, and consider as control reading of that animal), then after 5, 10, 15, 30, 45, 60 and 75 min. after injection. The induction time, duration of anesthesia, degree of analgesia, muscle relaxation and the time of recovery were recorded also.

## **RESULTS**

The heart rate ( HR ) in G1(p<sub>10</sub>k<sub>50</sub>mg<sub>50</sub> ) at 0 time was (274.0 ± 5.09 beats / minutes), then significantly decreased with an irregularity at the 5 minutes, where it reached to the least reading at 15 minutes (163.0 ± 2.59 beats / minute ), then that increased slowly and reached at 60 minutes (204.0 ± 2.44 beats / minute) at the end of observation. In G2 ( p<sub>10</sub> k<sub>50</sub>kr<sub>10</sub> ) the HR at 0 time was (274.0 ± 4.0 beats / minute), significantly sharply decreased at (5 – 10 )minutes to reach in the 15 minutes to ( 147.0 ± 2.0 beats / minute ) then increased gradually but not reach to the normal at the end of observation. In G3( p<sub>10</sub> k<sub>50</sub> kr<sub>10</sub>mg<sub>50</sub> ) the HR at 0 time was ( 276.0 ± 2.44 beats / minute ) then, significantly sharply decreased to reach to ( 141.0 ± 4.30beats / minute ) at 20 minutes then, increased gradually but not reach to the normal at the end of observation. In G4(p<sub>10</sub> k<sub>50</sub> kr<sub>10</sub>mg<sub>50</sub>X<sub>5</sub>) the HR at 0 time was ( 285 ± 5.09 beats / minute ) significantly decreased sharply more than other groups to reach at 30 minutes to ( 134 ± 1.22 beats / minute ) then increased gradually but not reach to the normal at the end of observation (Fig.1).

The respiratory rate ( RR ) in G1 at 0 time was ( 77 ± 1.37 breaths /minute ) then sharply decreased to reach the least reading (41 ± 1.87 breaths / minute) at 15 minutes, then the ( RR ) increased gradually to the end of observation . In G<sub>2</sub> the (RR) at 0 time was ( 82 ± 3.74 breaths / minutes ) where sharply decreased to reach the least reading ( 39 ± 1.87 breaths / minute ) at 20 minutes then increased gradually to the end of observation . In G<sub>3</sub> the ( RR ) at 0 time was ( 86 ± 2.91 breaths / minute ) where sharply decreased to reach the least reading at 20 minutes ( 35 ± 0.44 breaths / minute ) then increased gradually to the end of observation. In G4 the ( RR ) at 0 time was ( 87 ± 3 breaths / minute ) where sharply decreased to reach the least reading at 20 minutes ( 34 ± 0.48 breaths / minute ) then increased gradually to the end of

observation . The respiratory rate was decreased significantly in all groups between (5- 15 minutes) in G1, (5 – 20 minutes) in G2 and G3, and (5-40 minutes) in G4 (Fig.2).

The rectal temperature in all groups remains near normal through all the times of observation. There was no significant difference ( $P < 0.05$ ) of RT in all groups (Fig. 3).

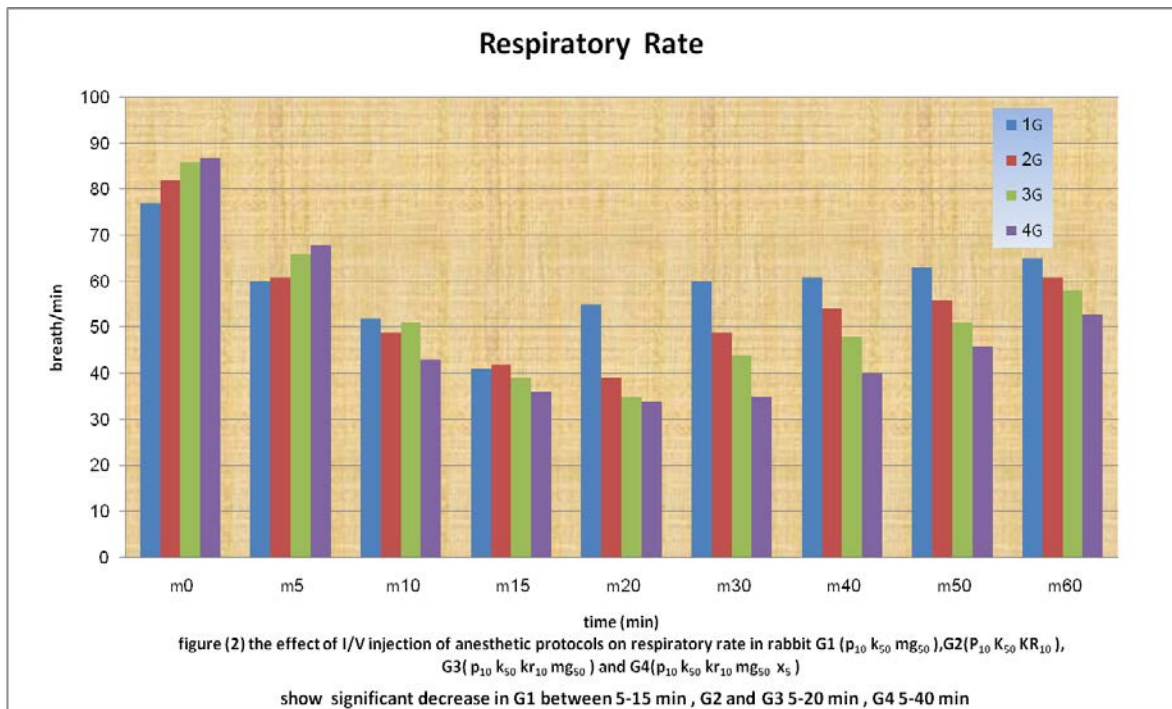
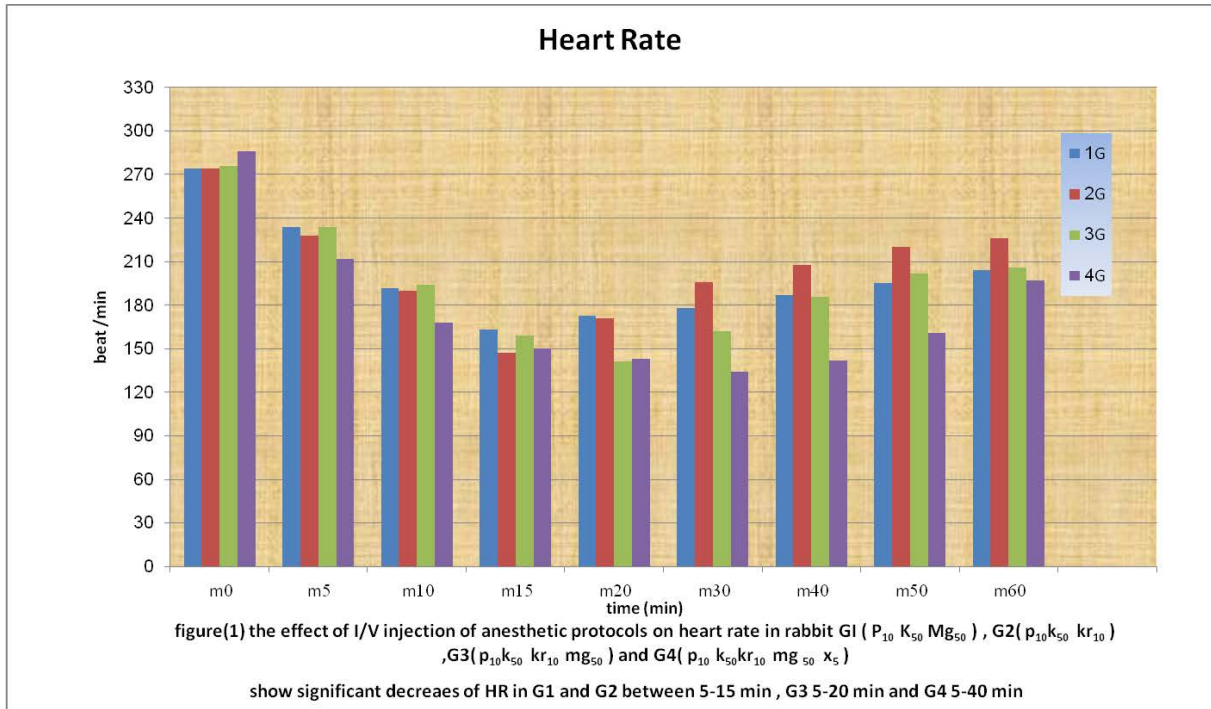
The degree of analgesia in G1, G3 and G4 was significantly deep in G1 between 5 - 10 minutes, G3 between 5-20 minutes and G4 between 5-40 minutes, which reduced to moderate analgesia in G1 at 15 minutes, G4 at 50 minutes, then reduced to mild analgesia in G1 at 20 minutes, G3 at 30 minutes, and in G4 at 60 minutes. In G2 the analgesia remains moderate between 5 -20 minutes and become mild at 30 minutes (Fig.4). There was no sign of pain in the site of injection of propofol in all animals during injection and after recovery of animal from anesthesia.

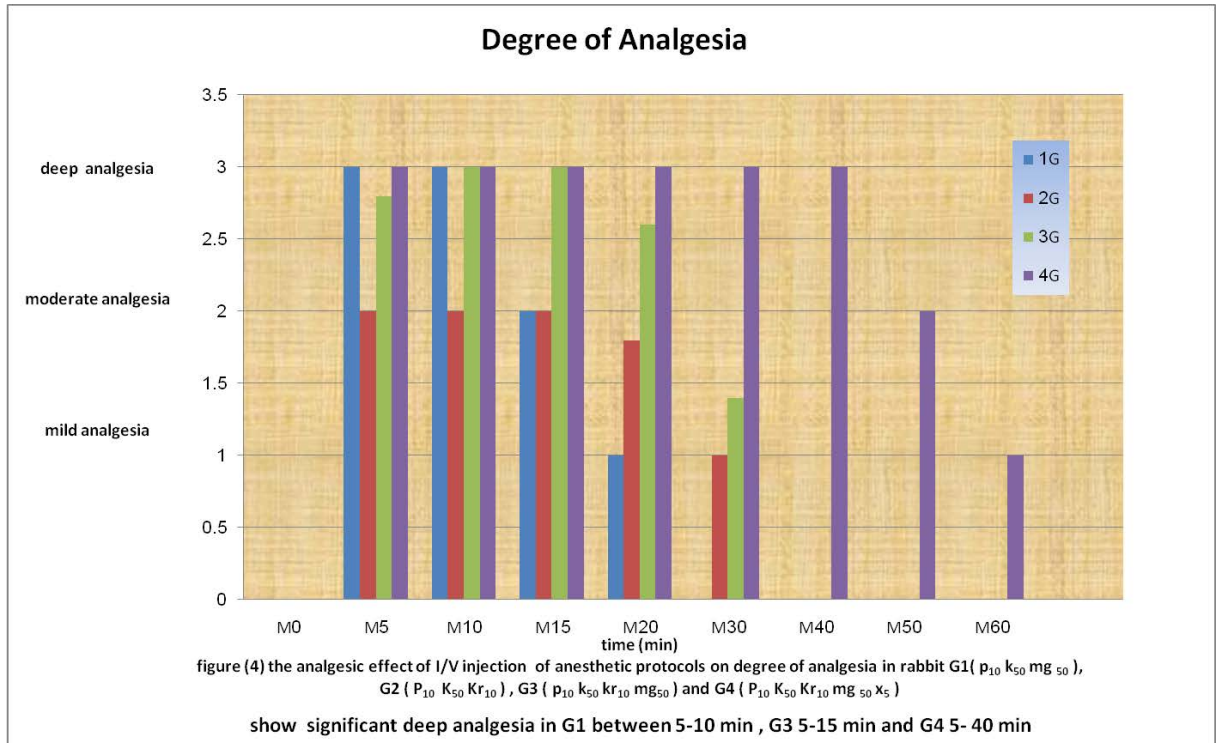
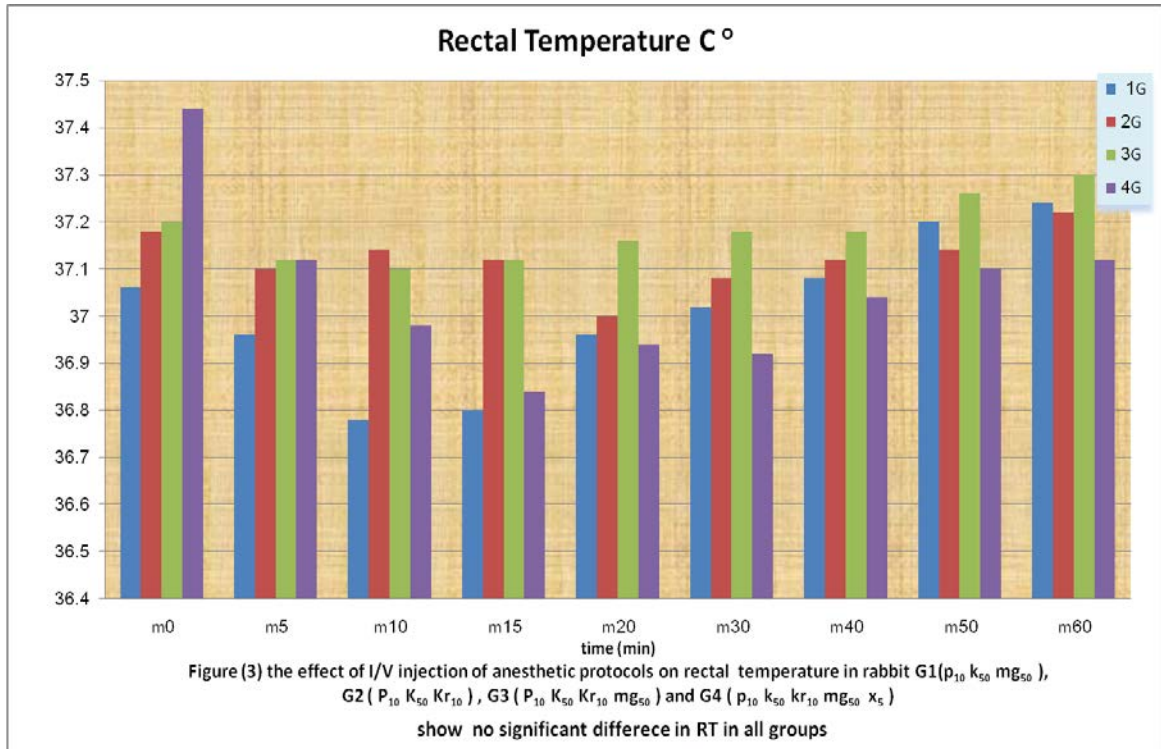
The muscle relaxation was significantly deep in G1, G3 and G4. In G1 between 5 - 10 minutes, G3 between 5-20 minutes and G4 between 5-40 minutes, which where reduced to moderate muscle relaxation in G1 at 15 minutes, G4 at 50 minutes, and it reduced to mild muscle relaxation in G1 at 20 minutes, at 30 minutes in G3, and at 60 minutes in G4, (Fig 5). The muscle relaxation in G2 was moderate between 5-15 minutes and reduced to mild at 30 minutes.

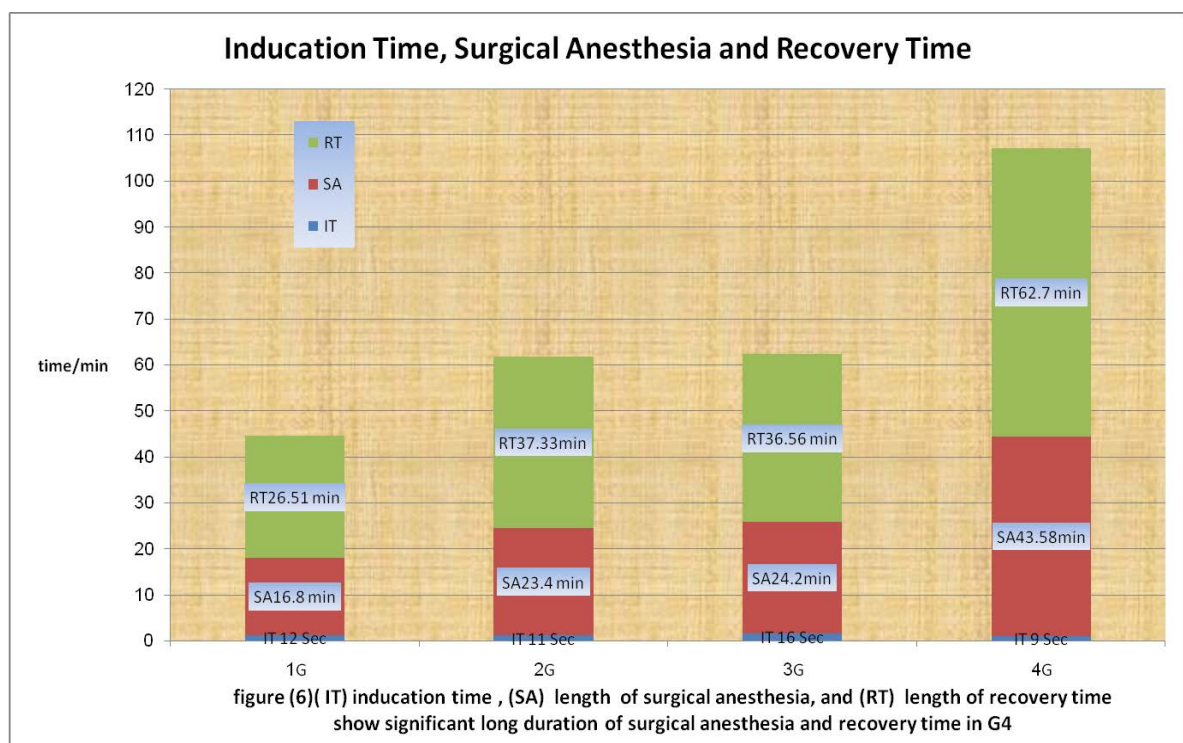
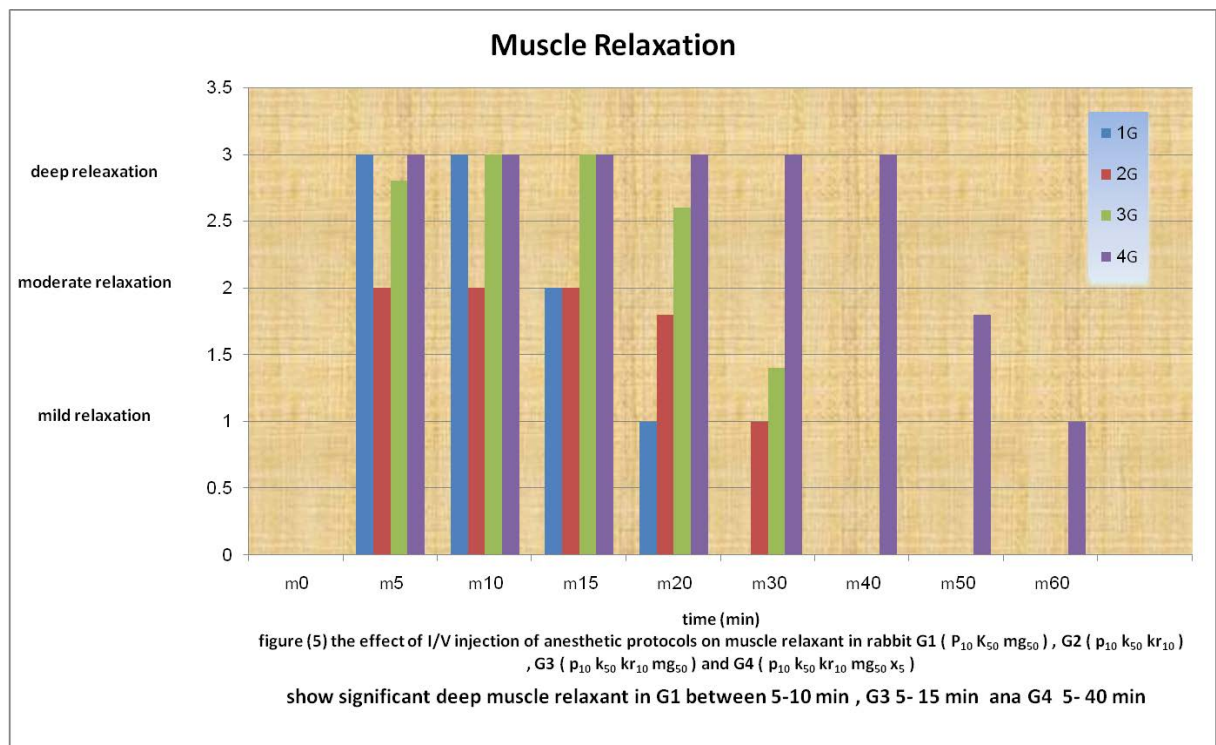
The induction time in all groups was fast, ranging between (  $11 \pm 2.1$  second ) in G1, G2, (  $16 \pm 2.2$  second ) in G3, and (  $9 \pm 1.1$  second ) in G4. There was no significant difference ( $P < 0.05$ ) between all groups (Fig. 6).

The duration of anesthesia in G1, G2, G3 and G4 was  $16.8 \pm 1.35$ ,  $23.4 \pm 2.45$ ,  $24.2 \pm 2.58$ , and  $43.58 \pm 3.76$  minutes respectively. The duration of anesthesia was significantly long ( $P < 0.05$ ) in G4 (Fig. 6).

The recovery time of all animals in all groups was smooth, with no signs of pain at the site of I/V injection of propofol. The duration of recovery time was (  $26.51 \pm 2.4$  minutes ), (  $37.33 \pm 3.2$  minutes ), (  $36.56 \pm 3.1$  minutes) and (  $62.7 \pm 4.2$  minutes) in G1 , G2 ,G3 and G4 respectively ( Fig.6 ) The recovery time was significantly longer (  $P < 0.05$  ) in G4 .







## DISCUSSION

In all groups there is marked significant decrease in heart rate. In G1 and G2 the decrease reached the least reading at 15 minutes, while in G3 the decrease least reading at 20 minutes, and in G4 at 30 minutes. These results are consistent with

previous studies (15, 16). All of these studies show that Propofol infusion is decrease both heart rate and heart rate variability, predominantly by a reduction in cardiac parasympathetic tone in rabbits, dogs, rats, sheep and horse .propofol can also induce cardiovascular depression, manifested primarily by decreased arterial blood pressure (17), due to inhibition of the sympathetic nervous system (18). Magnesium has been shown to cause central arteriolar vasodilatation and to act against vasospasm in the central nervous system (19). The heart rate in G4 decreased more than other groups due to the addition of Xylazine which also causes decreased myocardial contractility, bradycardia and decreased cardiac output, decreased heart rate, systolic and/or diastolic blood pressure (20, 21, and 22). Ketamine-xylazine a IV combination in of 35 mg/kg (K) and 5 mg/kg (X) induced a drop of blood pressure, significant increase in vessel diameter and heart rate significantly decreased, while mean arterial blood pressure initially increased in rabbits (23).

In all groups there is significant decrease in respiratory rate (RR) between 5 – 30 minutes reading time, this decreased of respiratory rate comes from mixing more than one of anesthetic drugs which causes inhibition of brain stem respiratory center and alteration in blood flow (24), or due to the depression of central nervous system by propofol lead to depression in muscular activity, then reducing air flow rate. The present fact is supported by (25). Propofol causes bradypnea which may conduct to apnea, as a main undesirable effect (26). All anesthetic techniques commonly used in rabbit anesthesia depress ventilation, and as companion rabbits may have a degree of lung pathology, it is advisable to administer oxygen during anesthesia (27).

The rectal temperature (RT) in all groups is not affected during the period of observation after giving the drugs .There is no significant difference ( $P < 0.05$ ) in RT in all groups. The results are in agreement with (28, 29) they show no significant difference in RT in all groups when used different anesthetic protocol in rabbit, and disagreement with (30) which show increase rectal temperature when use xylazine alone. While in cattle (31) show decrease in rectal temperature observed after the administration of xylazine, acepromazine or medetomidine with ketamine. In G1, G3 and G4 there is significant deep analgesia, and muscle relaxation between 5 -40 minutes. reduced to moderate analgesia and muscle relaxation in G1 at 15 minutes, G2 between 5 -20 minutes,G3 at 30 minutes and G4 at 50 minutes, then reduced to mild analgesia and muscle relaxation in G1,G2 and G4 between 20- 60



minutes. These results consistence with (32). The combinations of mgso4 in these protocols increase the effect of analgesia.

In all groups the induction time is fast and rapid; it's ranging between (9 to 16 second). There is no significant difference ( $P < 0.05$ ) between all groups. The present result in agreement with (33, 34). The fast induction time seem due to the effect of propofol. (33) Suggesting that rapidly uptake the propofol from CNS tissues due to its lipid solubility caused rapid cross of the drug to the blood brain barrier. Propofol is a short acting anesthetic drug, rapidly redistributed from the brain and metabolized from blood (35). Propofol induced loss of righting reflex immediately more rapidly when the drug is administered by I/V route compared with other route of administration (35).

The duration of anesthesia is significantly longer ( $P < 0.05$ ) in G4 than the other groups. Adding ketorolac to propofol and ketamine in G2, show the duration of anesthesia become longer than that G1, with poor degree of analgesia. These results consistence with (27).

The recovery time in all animals of all groups is smooth, with no signs of pain at the site of I/V injection of propofol. The recovery time is significantly longer ( $P < 0.05$ ) in G4. The present result in agreement with (36), who observed prolongation of the recovery seen in hamster receiving the Xylazine-Ketamine combination. The long recovery time may need more intensive care to the animals.

### استخدام المغنيسيوم سلفيت و الكيتورولاك والبروبوفول والكتامين والزيلازين كبرنامج تخدير في الأرانب

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#### الخلاصة

أجريت الدراسة لتقييم خلط المغنيسيوم سلفيت (M) و الكيتورولاك (Kr) و البروبوفول (P) والكتامين (K) والزيلازين (X) كبرنامج تخدير في الأرانب . استخدمت في هذه الدراسة (20) ذكر أرنب وزنها ( $0,200 \pm 1,300$  كغم). قسمت الأرانب بشكل عشوائي إلى أربع مجاميع كل مجموعة خمسة أرانب وحقنت كل مجموعة بخطة تخدير مختلفة ورديا في الوريد الاذني . المجموعة 1 (P<sub>10</sub>K<sub>50</sub>Mg<sub>50</sub>) ، المجموعة 2 (P<sub>10</sub>K<sub>50</sub>Kr<sub>10</sub>) ، المجموعة 3 (P<sub>10</sub>K<sub>50</sub>Kr<sub>10</sub>Mg<sub>50</sub>X<sub>5</sub>) ، والمجموعة 4 (P<sub>10</sub>K<sub>50</sub>Kr<sub>10</sub>Mg<sub>50</sub>X<sub>5</sub>). تم قياس معدل ضربات القلب HR ومعدل التنفس RR ودرجة حرارة المستقيم RT ودرجة التسكين ودرجة ارتخاء العضلات قبل إعطاء خليط العقار ( عند وقت الصفر، واعتبرت قراءة السيطرة لذلك الحيوان ) وبعد

إعطائه في الفترات 5 ، 10 ، 15 ، 20 ، 30 ، 45 ، 60 ، 75 دقيقة ولكل حيوان ، بالإضافة إلى تسجيل وقت أحداث التخدير وطول فترة التخدير والتخدير الجراحي ووقت الإفاقة بعد إعطاء العقارات . أظهرت النتائج أن برنامج التخدير في المجموعة الثالثة ( P<sub>10</sub> K<sub>50</sub> Kr<sub>10</sub>Mg<sub>50</sub>) كان مناسباً للعمليات الجراحية ذات المدة القصيرة (حيث أعطى تخدير جراحي لمدة 24.2 دقيقة) . أما برنامج التخدير في المجموعة الرابعة ( P<sub>10</sub> K<sub>50</sub> Kr<sub>10</sub>Mg<sub>50</sub>X<sub>5</sub>) ظهر أنه مناسب للعمليات الجراحية ذات المدة الطويلة (حيث أعطى تخدير جراحي لمدة 43.5 دقيقة) ، مع عدم وجود علامة للألم في منطقة الحقن الوريدي للبروبوفول .

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