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Evaluation of general anaesthesia by using Propionylpromazine, Xylazine and Ketamine in rabbits

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SUMMARY

Safe and effective anaesthetic regimens have been described for use in rabbits, partially because of the susceptibility of this species to fatal respiratory arrest. The present study was conducted to evaluate the efficacy of anesthetics, analgesics combinations an anesthesia in twenty five local breed rabbits. Rabbits were injected intramuscularly by: Propionylpromazine 0.5mg/kg B.W. as premedictation, after 10minutes later Xylazine and Ketamine Hydrochloride at a dose of 20mg/kg, 50mg/kg respectively. The results of the physiological parameters of the control group at the period of zero time concerning rectal body temperature, respiratory rate, heart rate were 38.00±0.29 ºC; 96.36 ±3.33bpm; and 147.20±6.46/minutes respectively. While in treated group at the periods 10, 20, 35, 50, 65, 80 and 95 minutes were 37.76 ±0.61; 37.34± 0.28; 37.00± 0.29; 37.00±0.35; 36.92±0.38; 35.80±0.40; 34.92± 0.53 ºC; 96.36±3.33; 41.00±1.37; 45.00±2.01; 45±2.01; 40.00±1.31; 40.00±1.31; 39.20±1.01 bpm; and 147.20±6.46; 142.00±3.73; 145.00±3.26; 144.48±3.31; 130.00±4.18; 140.00±3.49; 138.68 ±2.93 beats/minutes. The results of biochemical tests: Glucose, ALP, GPT, GOT in control group (zero time) were: (137.40±1.97 mg/dl; 53.09±2.13 U/L; 51.48±4.31 U/L; 116.9±09.82 U/L) respectively. And in treated group at the periods (10, 20, 35, 50, 65, 95 minutes and 24 hours) respectively were 139.60±0.79; 207.60±5.00; 222.20±7.42; 359.20;±18.89; 341.60±15.30; 337.7±76.39 and 199.92±9.14 mg/dl; 39.74±2.74; 42.55±3.29; 39.65±4.13; 42.48±2.62; 56.56±2.16; 47.41±3.61 and 42.84±4.16 U/L; 46.17±3.92 ; 39.34±3.01; 44.69±3.05; 49.98±3.16; 51.65±4.03; 47.22±2.54 and 72.63±4.98 U/L, and 94.72±8.24; 86.22±5.59; 90.82±6.89; 76.65±4.12; 82.70±4.69; 100.6±7.39 and 126.6±7.77 U/L. The conclusion of this study investigate that the lose of righting reflex was 4.760±0.421 minutes; induction time was 8.44±1.05, the time to complete muscle relaxation was 3.920±0.321 minutes, surgical time 41.48±2.11 minutes, and recovery time was 45.76±2.43 minutes; in which the surgical period was enough for the most of surgical interference, while the recovery period was smooth and short in comparison with another anaesthetic regimen.

تقييم مزيج التخدير العام باستخدام البروبونيل برومازين ، زايلازين والكيتامين في الأرانب

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الخلاصة

تم وصف العديد من أنظمة التخدير الآمنة والفعالة في الأرانب وذلك بسبب تحسس هذه الحيوانات وقابليتها على الإصابة بتوقف التنفس المميت. إن الدراسة الحالية صممت لغرض تقييم كفاءة مزيج المخدرات،

مسكنات الألم كمزيج تخدير في خمس وعشرين أرنبا محليا. تم حقن الأرانب عضليا بـ(0.5 ملغم / كغم من وزن الجسم) بالبروبونيل برومازين وبعد مرور عشرة دقائق تم حقنها بالزايلازين والكيتامين وبجرعة 20 ملغم / كغم من وزن الجسم و 50 ملغم /كغم من وزن الجسم على التوالي. إن نتائج المعايير الفسلجية لمجموعة السيطرة عند وقت الصفر و المتعلقة بدرجة حرارة الجسم، معدل التنفس، ومعدل ضربات القلب كانت (38.00 ± 0.29 °م ، 96.36 ± 3.33 تنفس بالدقيقة، و 147.20 ± 6.46 / دقيقة على التوالي. في حين سجلت نتائج مجموعة المعاملة بمزيج التخدير وعند الأوقات 10، 20، 35،50 ،65،80 و95 دقيقة (37.76 ± 0.61، 37.34 ± 0.28، 37.00 ± 0.29 ، 37.00 ± 0.35، 36.92 ± 0.38، 35.80 ± 0.40، 34.92 ± 0.53) °م ، (96.36 ± 3.33 ، 41.00 ± 1.37 ، 45.00 ± 2.01 ، 45.00 ± 2.01 ، 40.00 ± 1.31 ، 40.00 ± 1.31 ، 39.20 ± 1.01 نفس /الدقيقة و (147.20 ± 6.46، 142.00 ± 3.73 ، 145.00 ± 3.26 ، 144.48 ± 3.31 ، 130.00 ± 3.49 ، 138.68 ± 2.93) دقة / دقيقة. وكانت نتائج اختبارات الفحوصات الكيمياحيوية التي شملت قياس مستوى جلوكوز الدم (سكر الدم)،الفوسفاتيز القاعدي ، أنزيمات الكبد ((جاما جلوتامايل ترانسفيرازوكلوتاميك – بايروفيك ترانساميناز) في مجموعة السيطرة (وقت الصفر) (GPT) و (GOT) كالأتي: 137.40 ± 1.97 ملغرام/دسي لتر ، 53.09 ± 2.13 L /U ، 51.48 ± 116.9 ± 09.82 L/U على التوالي في حين كانت النتائج لمجموعة المعاملة بمزيج التخدير وعند الأوقات 10، 20، 35،50 ، 65،80 ، 95 دقيقة و 24 ساعة على التوالي كالآتي: (139.60 ± 0.79 ، 207.60 ± 5.00 ، 222.20 ± 7.42 ، 395.20 ± 18.89 ، 341.60 ± 15.30، 337.7 ± 76.39 و 199.92 ± 9.14) ملغم / دسي لتر، (39.74 ± 2.74 ، 42.55 ± 3.29 ، 39.65 ± 4.13 ، 42.48 ± 2.62 ، 56.56 ± 2.16 ، 47.41 ± 3.16 و 42.48 ± 4.16) L/U ، (46.17 ± 3.92، 39.34 ± 3.01 ، 44.69 ± 3.16 ، 51.65 ± 4.03، 47.22 ± 2.54 و 72.63 ± 4.98) L / U و (94.72 ± 8.24 ، 86.22 ± 5.59 ، 90.82 ± 6.89 ، 76.65 ± 4.12 ، 82.70 ± 4.69، 100.6 ± 7.39 و 126.6 ± 7.77) L/U وقد استنتجت هذه الدراسة إن اختفاء منعكس الاستقامة كان خلال (4.760 ± 0.421) دقيقة ، في حين استغرق وقت الإحداث (8.44 ± 1.05) دقيقة، أما الوقت الذي ظهر فيه ارتخاء كلي للعضلات فقد كان (3.920 ± 0.321) دقيقة، أما وقت التداخل الجراحي فقد استغرق (41.48 ± 2.11) دقيقة آما وقت الأفاقة فقد استغرق (45.76 ± 2.43) دقيقة وان هذا الوقت هو كاف لمعظم التداخلات الجراحية أما الإفاقة فقد كانت سلسة وقصيرة مقارنة بأنظمة تخدير أخرى.

INTRODUCTION

Rabbits are often considered as difficult in relation to anaesthesia. This probably relates to the fact that the dosage needed to induce anaesthesia and those producing toxic effect are close (1). So many complications still arise when anaesthetizing rabbits and there are several possible reasons. The margins of safety between anesthetic and lethal doses are less than those found in other animals and there is wide individual variation in response to anaesthetic and ancillary agents. The rabbit also has strong reflexes which are difficult to suppress during general anaesthesia. Other problems may occur because of the relatively small diameter of the respiratory tract and difficulty with tracheal intubation due to the small glottis being hidden by

the base of the tongue (2). Therefore a safe anesthetic method is required both for surgeons undertaking research and for practicing veterinarians since the intubation of the rabbit and use of volatile anesthetic agents may be too complicated and time consuming(3).

The aim of this study was to evaluate of general anaesthesia by using injectable anaesthesia of Propionylpromazine, Xylazine and Ketamine Hydrochloride in rabbits as a new combination.

MATERIALS AND METHODS

Twenty five adult local breed rabbits from both sexes were used. Weighing 1.1101±0.0614 Kg. They were housed indoor to accommodate the place of experiments. The following physiological parameters, rectal body temperature, respiratory and heart rate) were recorded before the intramuscular injection of the drugs - (zero time) - as a control group. Rabbits were injected intramuscularly by: Propionylpromazine (Combelen®, Bayer Group, Germany) 0.5 mg/kg B.W as premedication, after 10min. Xylazine 2% (Rumpon®, Bayer Group, Germany) and Ketamine hydrochloride 5% (Rotexmedica, Germany) at a dose of 20 mg/kg 50mg/kgB.W,respectively. 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 group after intramuscular injection of the drugs at periods of 10, 20, 35, 50, 65, 80 and 95 min. in addition to the lose of righting reflex and time to complete muscle relaxation degree. 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.

Bio-chemical values were measured during general anesthesia: Glucose (blood glucose levels were measured via routine work (Accu-check/Roche group, Ireland) Alkaline phosphatase enzyme (ALP) (Kit from bioMerieux®sa - France), GOT and GPT (Kit from bioMerieux®sa - France).l Blood samples were taken directly from the heart and collected in tubes without EDTA at the periods (10, 20, 35, 50, 65, 95 minutes and 24 hours).

The complete Randomized Design (CRD) within the SAS (2001) program was used to the effect of difference treatments in study traits, and the Least Significant Differences (LSD) test was used to the comparison between means. The ANOVA 1-way was applied to the data of and $p<0.05$ was considered to be significant **(4)**.

RESULTS

The lose of righting reflex, induction period complete muscle relaxation; surgical anesthesia and recovery time were summarized in table (1) as the following:

Table (1): Mean values (±Standard Error) of subjective scores qualifying anesthesia (Time to of loss righting reflex, Time of complete muscle relaxation)/minute

Time / Rabbit No.	Lose of righting reflex	Induction period	time to complete muscle relaxation	Surgical period	Recovery period
n= 25	4.760 ± 0.421	8.44 ± 1.05	3.920 ± 0.321	41.84 ± 2.11	45.76 ± 2.43

The righting reflex lost within 4.760±0.421 minutes, while the induction period lasted for 18.44±1.05 minutes, time to complete muscle relaxation was 3.92±0.321, the surgical period lasted for 41.84±2.11 minutes, while recovery lasted for 45.76±2.43 minutes as in table (1).

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, the pricking by needle test was applied to all animals, absolutely all animals not respond to this test.

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

Table (2): Rectal body temperature before, during and after general anesthesia administration in rabbits (ºC)

(P<0.05):

Time / Rabbit No.	0	10	20	35	50	65	80	95
n = 25	38.00± 0.29 A	37.76± 0.61 A	37.34± 0.28 A	37.00± 0.29 A	37.00± 0.35 A	36.92± 0.38 AB	35.80± 0.40 BC	34.92± 0.53 C
LSD	1.1371*							

Means having different letters (Capital Letters among treatment/column and small letters within group/rows) are significantly different

0= Control group

Results of rectal body temperature should no significant changes between control group (zero time) and treated group during the periods lasted from the injection of combelen until 65 minutes after injection of anesthetic combination, while at 80 and 95 minutes there was a significant decrease in rectal body temperature. (Table-2).

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

Time / Rabbit No.	0	10	20	35	50	65	80	95
n = 25	96.36± 3.33 A	96.36± 3.33 A	41.00± 1.37 B	45.00± 2.01 B	45.00± 2.01 B	40.00± 1.31 B	40.00± 1.31 B	39.20± 1.01 B
LSD	5.9673*							

* (P<0.05)

Means having different letters (Capital Letters among treatment/column and small letters within group/rows) are significantly different.

0= Control group

The respiratory rate significantly unchanged 10 minutes after combelen injection, while 20 minutes after xylazine, ketamine injection the respiratory rate decrease significantly and this decrease continues to be decreased till recovery period, although there was no significancy noticed among the periods lasted from 20minutes till 95 minutes (Table-3).

Table (4): Heart rate before, during and after general anesthesia administration in rabbits (beats/minute "bm")

Time / Rabbit No.	0	10	20	35	50	65	80	95
n = 25	147.20± 6.46 A	147.40± 6.87 A	142.00± 3.73A B	145.00± 3.26 A	144.48± 3.31 A	130.00± 4.18 B	140.00± 3.49 AB	138.68± 2.93 AB
LSD	12.577*							

* (P<0.05)

Means having different letters (Capital Letters among treatment/column and small letters within group/rows) are significantly different

0= Control group

Heart rate showed significant decrease at 65 minutes in treated group in comparison with control group (zero time), the heart rate should variable changes although they were not significant as shown in (table -4).

The results of bio-chemical tests of glucose, alkaline phosphatase (ALP), Glutamic -Pyruvic Transaminase activity GPT (U/L), and Glutamic -Oxaloacetic Transaminase activity GOT (U/L) were mentioned respectively in tables (5,6,7 and 8).

Table (5): Mean values (±Standard Error) of Glucose level (mg/dl)

Time / Rabbit No.	Time/minutes							time/hrs
	0	10	20	35	50	65	95	24
N=25	137.40± 1.97 C	139.60± 0.79 C	207.60± 5.00 B	222.20± 7.42 B	359.20± 18.89 A	341.60± 15.30 A	337.76± 76.39 A	199.92± 9.14 B
LSD	30.982*							

* (P<0.05)

Means having different letters (Capital Letters among treatment/column and small letters within group/rows) are significantly different.

0= Control group.

A significant increase were noticed at periods lasted from 50 to 95 minutes in comparison with control group (zero), after 24 hours from the injection of these drugs a significant decrease were noticed in comparison with the periods lasted from 50 to 95 minutes, although this value still significantly increased in comparison with control group (zero) as shown in (table -5).

Table (6): Mean values (±Standard Error) of Alkaline Phoshatase level (ALP (U/L)

Time / Rabbit No.	Time/minutes							time/hrs
	0	10	20	35	50	65	95	24
	53.09± 2.13 A	39.74± 2.74 C	42.55± 3.29 C	39.65± 4.13 C	42.48± 2.62 C	56.56± 2.16 A	47.41± 3.61 C	42.84± 4.16 C
LSD	8.9138*							

* (P<0.05)

Means having different letters (Capital Letters among treatment/column and small letters within group/rows) are significantly different.

0= Control group.

The level of ALP enzyme significantly decrease after Propionylpromazine injection (10 minutes), and Xylazine, Ketamine injection during the periods (10, 20, 35, and 65 minutes) in comparison with control group (zero), these levels return back to increase significantly at 65 minutes period, while during the periods of 95 minutes and 24 hours the level of ALP return to decrease significantly as shown in (table-6).

Table (7): Mean values (±Standard Error) of GPT level (U/L)

Time / Rabbit No.	Time/minutes							time/hrs
	0	10	20	35	50	65	95	24
	51.48± 4.31 B	46.17± 3.92 BC	39.34± 3.01 C	44.69± 3.05 BC	49.98± 3.16 B	51.65± 4.03 B	47.22± 2.54 BC	72.63± 4.98 A
LSD	10.332*							

* (P<0.05)

Means having different letters (Capital Letters among treatment/column and small letters within group/rows) are significantly different

0= Control group.

Significant decrease were recorded at 20 minutes from the injection of anesthetic combination in comparison with control group (zero), after 24 hours the level of GPT was significantly increase as mentioned in (table -7).

Table (8): Mean values (±Standard Error) of GOT level (U/L)

Time / Rabbit No.	Time/minutes							time/hrs
	0	10	20	35	50	65	95	24
	116.90± 9.82 AB	94.72± 8.24 CD	86.22± 5.59 CD	90.82± 6.89 CD	76.65± 4.12 D	82.70± 4.69 CD	100.6± 7.39 BC	126.6± 7.77 A
LSD	19.661*							

* (P<0.05)

Means having different letters (Capital Letters among treatment/column and small letters within group/rows) are significantly different

0= Control group.

The level of GOT enzyme showed variable changes start after 10 minutes from the injection of Propionylpromazine, 95 minutes , but after 24 hours the level of GOT was increase significantly, although this increase was not significant in comparison with control group (zero) as shown in (table -8).

DISCUSSION

The results of the depth of anaesthesia (41.84±2.11) and the determination of analgesic effect of the anesthetic combination agree with other workers (**5**). In this study showed that the surgical period was enough for the most surgical interference. The recovery period of this regimen was smooth and short in comparison with other anesthetic regimens (6). Also the rapid onset of complete muscle relaxation could be due to the effect of Propionylpromazine which appear its increased the duration of sleep in psychogeriatric subjects(7).

The slight decrease of rectal body temperature after 80 min. (Table, 2) of anesthetic period may be due to the large heat losses occurred on transfer to the recovery room, where the total heat produced increased rapidly and was unrelated to shivering; and slight decrease in rectal body temperature is a common problem in

patients having surgery, this agree with (6), Researchers estimate that 50% to 90% of surgical patients experience hypothermia during surgery (8).

The results of respiratory rate values of control group (Table-3) was not completely in accordance with the results of other works (Hedenqvist, 2008 and Kowalska *et al*., 2008) (9 and 10) and 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 20 minutes from injection of the anesthetic mixture, and this depression was significant, but it became non significant within periods started after 20minutes until 95 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 (11) 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 (12).

The result of heart rate at zero time (control group) agree with (13) who reported that the normal values of heart rate which ranged between 130-325 beats/minutes, while after 20 min. from anesthetic combination injection a significant decrease in heart rate could be noticed with variable degrees as shown in (table-4) this could be due to bradycardiac effect of xylazine (14).and these results were also agreed with (15).

Generally the decrease of respiratory and heart rate probably was due to xylazine component of the mixture, this agree with other workers (12).

The significant increase in glucose level (table -5) could be due to the secretion of insulin which is stimulated by beta-adrenergic stimulation. The beta - adrenergic stimulation induced a slight decrease in insulin secretion. If the rabbits were under some stress, the sympathoadrenomedulaary system and exogenous catecholamine might strongly suppress insulin secretion. It is well known that beta - adrenergic stimulation caused hyperglycemia greater than alpha-adrenergic stimulation (15) and it well known that Xylazine is an alpha-2 adrenergic agonist used as a sedative, analgesic, and muscle relaxant in veterinary medicine and in addition to its role in general anesthesia, xylazine was used to induce a temporary, but sustained (up to 12 hrs), hyperglycemia in rats (16). Moreover, ketamine probably induces catecholamine and this stimulates hepatic glycogenolysis, inhibits insulin secretions and consequently increases plasma glucose concentrations (17).Liver is most important metabolic organ with high anabolic and catabolic capacity. Metabolic activity within the liver is controlled by enzymes. In case of small necrosis within the liver parenchyma there is marked increase in the activity of enzymes present within the liver, therefore duration and intensity of action may be increased in the presence of liver disease (18 and 19).

Alkaline phosphatase enzyme (ALP) is present in almost all tissues and fluids. The small intestine, bone, lactating mammary gland and kidney are particularly rich sources. Elevated levels in disease are almost confined either to bone disease with increased osteoblastic activity, or to disease of the hepatobiliary system (20 and 21). Glutamic -Pyruvic Transaminase (GPT) levels remain within normal values or may

show slight increase (marginal increase) because the increase of GPT 's of cardiac muscle represent a small part of the total amount of the whole GPT enzyme. Also these enzymes have a wide distribution in animal tissues and are present in small quantities in the serum of all animals as a consequence of normal tissue destruction and subsequent enzyme release. Since these enzymes have their principle functions within the cell, increases observed in the serum are often a reflection of cellular destruction or disease (20).

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