Evaluation of general anesthesia induced by propofol, ketamine protocol in rabbits premedicated with diazepam

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Summary

The present study was designed to evaluate the efficacy of diazepam-propofol-Ketamine protocol for induction of general anaesthesia in rabbits. The experiment was conducted on seventeen healthy male adult local rabbits weighting 0.9-1.5 kg. Rabbits were given protocol, Diazepam 1mg/kg B.W. by intramuscular injection then 15 minutes later propofol 10 mg/kg B.W. as bolus slow intravenous injection and ketamine 25 mg/kg BW by intramuscular injection. Several parameters included respiratory rate, body temperature and heart rate were recorded before injection of drugs and after giving the anesthetic protocol at 0, 5, 10, 15, 20, 30, 45, 60, 75 and 90 minutes. The results showed that the anaesthesia with diazepam, propofol and Ketamine protocol in rabbits was suitable as it produced reliable surgical anaesthesia, good analgesia and muscle relaxation with minimal changes on the wave morphology of the cardiac muscle.

Keywords: Diazepam, propofol, ketamine, general anaesthesia, electrocardiogram, rabbit.

Introduction

Rabbits are the third most anesthetized animal species in the world, either as pets or as research model. This gives these animals the opportunity to conduct basic research with direct application to the species and translation to other species (1). Although rabbits have more risks of anesthetic-related death when compared to other species and they are easily stressed by handling, and when excited may struggle vigorously, this may lead to musculoskeletal trauma, severe stress, shock and cardiac arrest, in part due to difficulty in endotracheal intubation, and also due to their susceptibility to respiratory arrest once adequate surgical anaesthesia has been achieved (2 and 3). A variety of different anesthetic techniques have been recommended to overcome the various problems in rabbit anaesthesia such as handling associated stress and breath hold during induction with volatile anaesthetic agent, apnoea is accompanied by marked bradycardia, hypercapnia and hypoxia and is not prevented by pre - anaesthetic medication (4). General anaesthesia can be induced by using a variety of drugs and techniques, a single drug can be given to produce all the required features of general anaesthesia. Giving several drugs in combination, at relatively low dose rates, can often result in less effect on major body systems than that following induction of anaesthesia using a single anaesthetic agent (5). Injectable anesthesia is more reliable than inhalation anesthesia in clinical setting used protocol of propofol and ketamine administered for each can be reduced the dose of other. Propofol is an alkylphenol, hypnotic drug while ketamine is a dissociative non-barbiturate anaesthetic agent. The administration of propofol with ketamine is producing a more stable hemodynamic and respiratory profile (6). Premedication with different sedative, hypnotic and muscle relaxant drugs (e.g. diazepam which it is classified as sedative, hypnotic and muscle relaxant drugs of benzodiazepines derivative), potentiates the effects of other anesthetic agent in rabbits and facilitates a smooth induction and recovery (7). The object of this study was to evaluate the efficacy of diazepam-propofol-Ketamine protocol for induction of general anaesthesia in rabbits.

Materials and Methods

The study was performed on 17 local breed adult males' healthy rabbits. These rabbits weight range from 0.9-1.5 kg, mean weight was 1.24±0.04 kg, their ages ranged between 12-18 months. Animals were maintained in an animal house and exposed for the same

environment including climate, management and feeding for 1 week to acclimatization and adaptation on the place. Rabbits had free access to water and food. Local anaesthetic gel Lidocaine 2% was applied to the rabbits´ ears for 5 mins to prevent pain during catheter insertion (catheter gauge 27 was placed in the marginal ear vein) and connected to a syringe before induction of anesthesia. Prior to induction of anaesthesia the animal was premedicated with diazepam 1.0 mg/kg B.W. I.M. (pharmaceutical industries. Aleppo-Syria). After 15 minutes to induction of anaesthesia by I.V. Propofol injection 10 mg/kg B.W. (Dong Kook pharmaceutical /Korea) via marginal ear vein followed by Ketamine (TEKAM 50, Gracure pharmaceuticals Ltd, India) 25 mg/kg B.W. I.M. The evaluation of the anesthetic protocol was basically evaluated depending on the monitoring of the following parameters which recorded before injection of any drug as control data and at zero, 5, 10, 15, 20, 30, 45, 60, 75 and 90 minutes. Monitoring continued until the animal regained its righting reflex. Anesthetic period was estimated from the induction time of injection the anesthetic agent to a satisfactory immobilization until recovery. The recovery period was estimated from the time of reappearance of the reflex until complete consciousness (complete righting reflex) (8). Degree of analgesia was evaluated by (9): + (Mild degree of the analgesia) ++ (Moderate analgesia) +++ (Deep analgesia). Pinching toe-web region in the hind limbs was alternatively pinched with hemostatic forceps to the first, second and third ratchet-lock for 5 sec, and was evaluated at 0, 5, 10, 15, 20, 30, 45, 60, 75, and 90 min from anesthetic injection. Depth of anesthesia was going to be evaluated according to the following data (Table 1).

Table, 1: Depth of anesthesia based on the clinical signs and the respective attributed numerical scale.

Numerical scale of anesthesia	Clinical signs	Anesthetic state
0	Fully awake and alert	Awake
1	Relaxed but still responsive to stimulation and with righting reflex present	Sedated
2	Lost its righting reflex but still responds to any stimulation	Shallow anesthesia
3	Only responds to painful stimulation	Medium anesthesia
4	Does not respond to painful stimulation, but still has corneal reflex	Surgical anesthesia
5	Without corneal reflex, mean arterial blood pressure below 40 mmHg; Apneic.	Very deep level

The Eyes reflexes were evaluated according to the palpebral and reflexes corneal Presence (–), absent (+) and size of pupil: Contracted (Myosis – Mo), dilated (Mydriasis – Md). Hind leg muscle relaxation was evaluated by hind leg muscle tone by flexion and extension of the hind limb of rabbit: present of the relaxation (+), absence of the relaxation (–). Respiratory rate (breath/min) was measured. Rectal temperature (◦C) was measured. Saturated oxygen pressure (Spo_2%) was measured by using medical monitor (Omni II infinium, USA). Heart rate was measured by using medical monitor with aiding of electrocardiogram (ECG). Heart rhythm by using ultrasonic (sonoket, Korea). Electrocardiograph (ECG) was recorded by using medical electrocardiogram. ECG recorded before the beginning of experiment which was considered basal heart rate. ECG was possibly the first diagnostic signal to be studied with the purpose of automatic interpretation by computer programs. There are two characteristics for interpretation in the ECG: the morphology of waves and complexes which compose a cardiac cycle; and the timing of events and variations in patterns over many beats. In this way, the analysis of the ECG waveform supports identifying a wide range of heart diseases. The characterization of each cardiopathy manifests itself by specific modifications on the

characteristics (10). Preparation of rabbit for recording of ECG by using clip electrodes which were attached to the skin at the triceps brachi muscle (coputlongum and coputlaterale) of the right and left limbs and biceps femurs muscle of the right and left hips. Electrode gel was rubbed into the skin in the area where the clips were attached to act as a decreasing agent and thereby decrease the resistance of the skin. The rabbits were immobilized by wrapping light cotton around them and then placed on a wooden table. It waited about 5 min. for rabbits to get calm. ECGs were recorded by a direct writing electrocardiograph with a chart speed of 50 mm/sec. Leads I, II, II, aVR, aVL and aVF were recorded before and after anesthetic protocol was given. The morphological changes of the waves on the trace were observed in all limb leads to detect any effect of the anesthetic protocol on these cardiac waves. The Statistical Analysis was used to detect the effect of factor (group) in study parameters. The least significant difference (LSD) test and chi-square test were used at the comparative between means and percentage in this study (11).

Results and Discussion

The anaesthetic duration was 32.88±2.33 min. This result might due to inhibition effects of CNS mediated by effect of diazepam, propofol, and ketamine induced by deep sedative effect mediated by diazepam and anesthetic effects of propofol and ketamine resulting in inhibition of CNS depression mediated by inhibition of intranural transmission of impulses. This result agreed with (2). The recovery period was 42.27±1.95 min. Although this protocol is safe, it produces a relatively long recovery period due to effect of diazepam which is classified as sedative, hypnotic and anticonvulsant muscle relaxant properties drugs of benzodiazepines derivative (12). The surgical anaesthesia was evaluated according to the (Table, 1) in which the anesthetic status was based on clinical signs and the respective attributed numerical scale, scale 4 in which rabbit status was characterized by not responding to painful stimulation, but still has corneal reflex. The surgical anaesthesia (25 min duration) extendes from 5 min to 30 min, the optimum was at 15 min and there was significant ($P<0.01$) difference between 0 time and 10–20 min, and there was significant ($P<0.05$) difference between the 0 time and 30 min, but there was non-significant ($P>0.01$) difference between the 0 time and 5, 45 min. The total response percentage about 29% in diazepam, propofol, and ketamine as in (Table, 2).

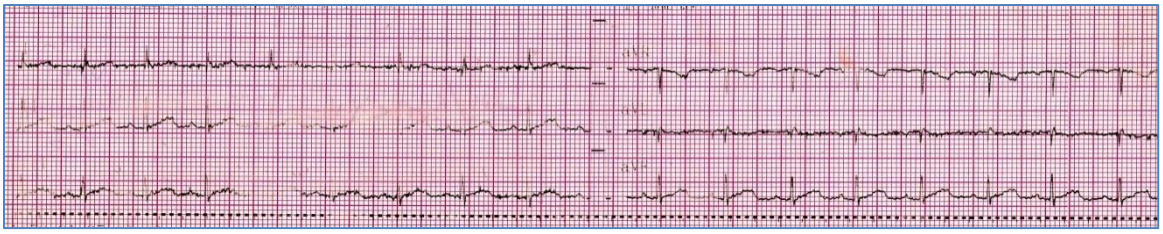
Table, 2: The effect of protocol (diazepam, propofol, and ketamine) on different parameters at ten time points.

parameter	Time / Minutes										significant difference
	0	5	10	15	20	30	45	60	75	90	
R R (bth/min)	(c) 37.82± 5.13	(c) 39.82± 4.33	(c) 43.00± 3.26	(bc) 46.29± 2.99	(bc) 51.47± 3.40	(abc) 60.64± 5.57	(ab) 69.52± 6.85	(a) 76.76± 7.73	(a) 79.53± 7.17	(a) 77.82± 6.52	23.91 *
Spo2(%)	(abc) 88.88 ± 1.18	(bc) 85.35 ± 1.40	(c) 85.11 ± 1.97	(a) 90.70 ± 1.52	(abc) 87.76 ± 1.72	(abc) 88.23 ± 1.30	(abc) 87.88 ± 2.18	(bc) 85.70 ± 1.42	(ab) 89.47± 1.05	(abc) 89.23± 0.76	4.272 *
Temp(◦C)	(a) 37.98 ± 0.17	(ab) 37.84 ± 0.17	(abc) 37.67 ± 0.17	(abc) 37.57 ± 0.18	(bc) 37.39 ± 0.19	(c) 37.26 ± 0.19	(c) 37.14 ± 0.18	(c) 37.03 ± 0.19	(c) 7.09 ± 0.25	(c) 37.15 ± 0.23	0.579 *
H.R. (bt/min)	(a) 252.76 ± 7.86A	(a) 248.23± 10.04	(a) A248.58± 10.31	(a) 248.82 ± 8.65	(a) 244.47 ± 9.65	(a) 240.88 ± 7.64	(a) 237.94 ± 8.81	(a) 234.3 ± 7.09	(a) 238.12 ± 6.63	(a) 230.29 ± 4.80	22.684 NS
Analgesia (scale 3)	(e) 0	(de) 5.88	(c) 47.06	(a) 82.35	(b) 58.82	(d) 11.76	(d) 0	----	----	----	11.65**
Anesthesia scale (4)	0 (c)	5.88 (ef)	47.06 (c)	82.35 (a)	58.82 (b)	11.76 (de)	0 (c)	----	----	----	11.91**
Muscle relaxation (present)	(a) 100	(a) 100	(a) 100	(a) 100	(a) 100	(a) 100	(a) 100	(a) 100	(b) 5.29	(c) 23.53	16.72**
Size of pupil (md)	(c) 29.41	(a) 100	(a) 100	(a) 100	(a) 100	(a) 94.12	(b) 58.82	(c) 23.53	(d) 5.88	(d) 0	12.40**

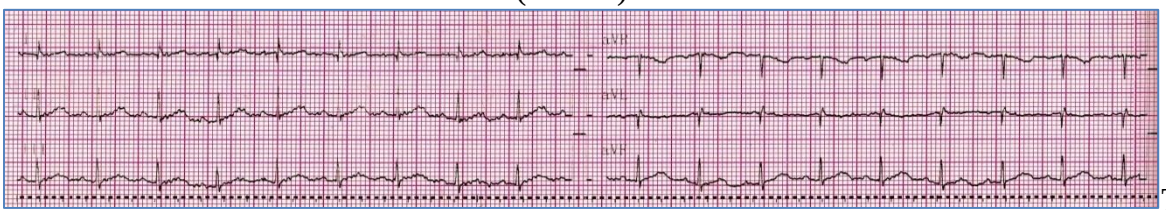
NS – non significant, small letters within group/rows are significantly different at ** (P<0.01), * (P<0.05). DPK (diazepam + propofol + ketamine), R.R. (respiratory rate-breath/minute), bth-breath/minute, Spo_2 (saturated pressure of oxygen-%), Temp (rectal body temperature -◦C), ◦C- centigrade degree, H.R. (heart rate-beat/minute), bt- beat/minute, md (mydriases-dilatation in the eye pupil).

The degree of analgesia at scale (3) which means no sense of pain extended from 5 min to 30 min, the optimum was at 15 min, and there was significant ($P<0.01$) difference between the 0 time and 10, 15, 20, and significant difference ($P<0.05$) between the 0 time and 30 min, but there was non-significant ($P>0.01$) difference between the 0 time and 5 min. The total response percentage about 29% as in (Table, 2). Propofol in clinical doses was weak at controlling pain and had no analgesic effect (13), unless combined with analgesic drug (14). The analgesic effects of ketamine were thought to be mediated by binding of the drug to N-methyl-D-aspartate (NMDA) receptors which results in inhibition of these receptors which mean inhibition of excitatory glutaminergic transmission at spinal and supraspinal sites (15). Although ketamine acts on nicotinic and muscarinic receptors; it blocks sodium channels in the peripheral and human central nervous system and interacts with opioid receptors, μ, δ and κ and with calcium channels (16). Combination with drugs such as diazepam is to improve analgesia and muscle relaxation of anesthetic regimes (17). It is important to ensure that additional analgesic agents used when painful procedures are required (18). The degree of muscle relaxation started early after the animal was premedicated with diazepam and reached to the optimum degree in time control (the time of propofol injection) extending to 60 min, while it was minimal at 75, 90 min until loss of muscle relaxation at 105 min. There was significant ($P<0.01$) difference between the zero time and 75, 90, 105 min but there was non-significant ($P>0.01$) difference between the 0 time and 5 min to 60 min. It had a significant response in anesthetic protocol. This result was in agreement with (19) which revealed the use of diazepam with ketamine aids muscle relaxation. The total response percentage about 87%. In general benzodizepines can be used to augment sedation and muscle relaxation in combination with other anaesthetic (e.g. ketamine). Muscle relaxation effect of diazepam was mediated through depression of polysynaptic musculoskeletal reflexes (20). Propofol has been shown to possess anticonvulsant activity and antiseizure properties (18) and inhibit calcium to entry in muscle cells (21). Ketamine is always administered in combination with diazepam to eliminate the muscle rigidity, which occurs when ketamine is used alone (22). The eye reflexes (palpebral and corneal reflexes) were never abolished completely. It became nearly sluggish at 5 min to 30 min. These results were in agreement with (23), the palpebral and corneal reflexes may be consistently abolished only immediately before fatal respiratory arrest. The pupil size was dilated from time 0 and extended to 75 min and it was found ($P<0.01$) significantly dilated at at 5 min to 45 min. There was significant ($P<0.01$) difference between the 0 time and 5 min to 45 min and at 75, 90 min, but there was non-significant ($P>0.01$) difference between the 0 time and 60 min of the observation. This result was consistent with (24). The total response percentage was about (61%) in DPK as (Table, 2). This result may be due to the effect caused by central inhibition of parasympathetic tone to the iris and/or direct sympathetic stimulation of alpha-2 adrenoceptors located in iris and C.N.S. The respiratory rate (breath/min) was decreased by the effect of anesthetic protocol and this result was in consistency with (25). The decreasing of respiratory rate was from zero time, then it increased gradually from 5 min. to 75 min. then minimal decline at 90 min at the end of the observation. There was significant ($P<0.05$) difference between the 0 time and 45 min to 90 min but there was non-significant ($P>0.05$) difference between the 0 time and the time of 5 min to 30 min as in (Table, 2). Benzodiazepine did not significantly alter respiratory rate (26). Ketamine administration causes minimal depression of respiratory rate (15), moderate respiratory depression (5), bronchodilation (15) and high doses could lead to serious respiratory depression including apnea (27). The effect of anesthetic protocol on the saturated pressure of oxygen was (SPO_2%): It was decreased in time 5 min, 10 min and fluctuating between the increasing and decreasing to the end of the observation. There was non-significant ($P>0.05$) difference between the 0 time and the other times to the

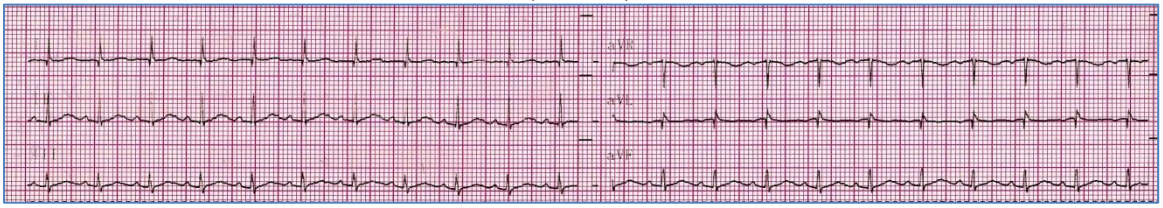
end of the experiment as in (Table, 2). From the observation, it was concluded that saturated pressure of oxygen was not affected by this protocol with high degree. Anesthetized rabbits with propofol, macroscopic findings of the lungs at necropsy included lung enlargement and congestion and pinky frothy edema fluid effusing from lung sections and filling the tracheal cannula. The lungs had also a milky tincture and histological examination revealed interstitial pneumonia and pulmonary edema. This last finding was suggested as the most probable cause of death, and the potential for pulmonary embolism (28) are believed to be due in large part to its oil-in-water emulsion formulation (29). The effect of anesthetic protocol on the body rectal temperature (◦C): It was gradually decreasing in body rectal temperature in time zero to 60 min then gradually increasing after 60 min to the end of the experiment. There was significant ($P<0.05$) difference between the zero time and 20 min. to 105 min., but there was non-significant ($P>0.05$) difference between the zero time and the time of 5 min to 15 min as in (Table, 2). From the observation, it was concluded that body rectal temperature was affected by sedative effect of diazepam which induced reduction in metabolism, muscle relaxation and depression of the CNS which agreed with the study of other authors (30). Reduction in cutaneous heat losses, in contrast to the consistent reductions in body temperature reported with the use of other anesthetic agents that induce vasodilatation (31). The heart rhythm was significantly regular and this appeared from ECG paper. There was minimal decreasing in heart rate from 5 min to the end of the experiment (Table, 2). From this observation, cardiovascular and autonomic side effect of diazepam is negligible and it has antiarrhythmic action due to decrease catecholamine release, which has proven useful in treating certain kinds of myocardial hyper excitability (32). Diazepam causes mild decrease in heart rate (33).



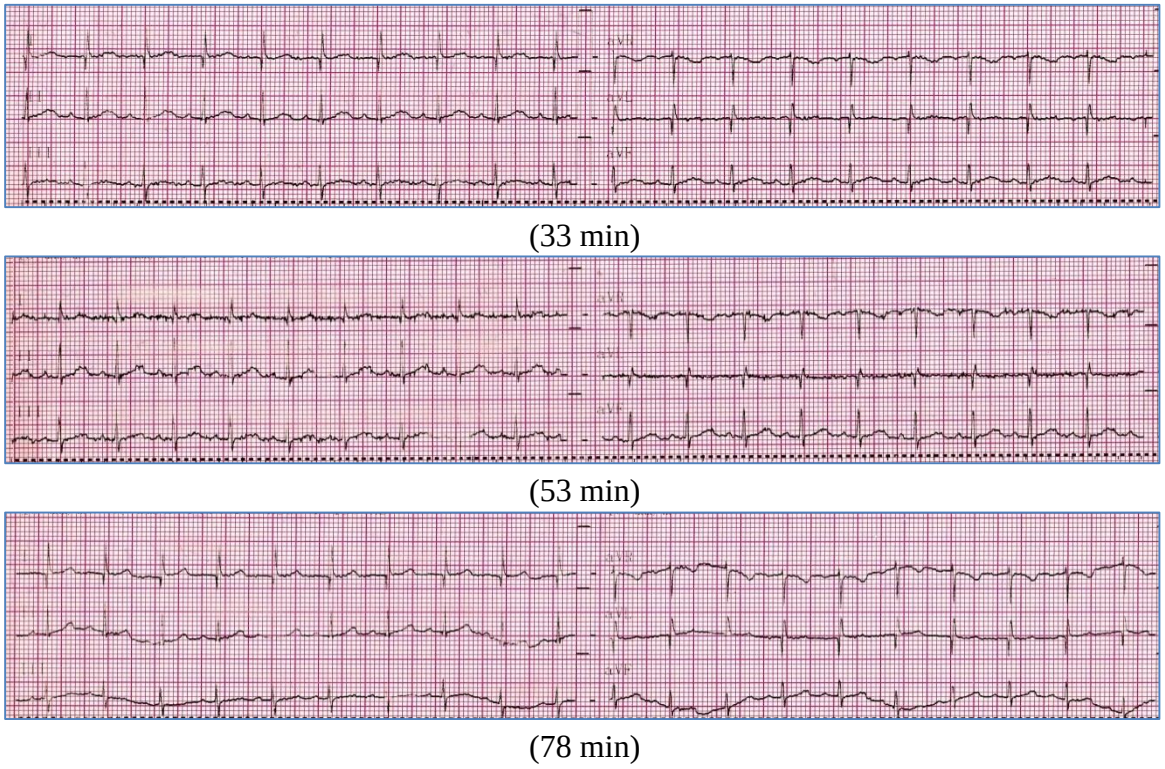
T1 (control)



T2 (11 min)



T3 (26 min)



Figure, 1: Electrocardiography results of anesthetic protocol, for local male rabbit in different times (T): T1 (control), T2 (11 min), T3 (26 min), T4 (33 min), T5 (53 min) and T6 (78 min) at the end of experiment.

The electrocardiogram (limb leads) of rabbits in (Fig. 1), T wave in lead I showed mild flatten after 26 minute (T3) comparing to control (T1) and 11 min (T2) in the same protocol. In addition there was a rise of QRS complex wave peak in lead I and AVR lead at 26 min (T3), 33 min (T4), 53 min (T5), and 78 minute (T6) as compared to control (T1) and 11 min (T2). The T wave is generated by myocardial voltage gradients during the repolarization phase of cardiomyocyte action potentials (34). Myocardial ischemia may cause T wave changes and abnormally tall T waves (35). The majority of intraoperative ischemic episodes occur in the absence of hemodynamic aberrations, such as tachycardia, hypertension, or hypotension. This implies that many of the episodes of intraoperative myocardial ischemia occur because of a decrease in myocardial oxygen supply rather than an increase in myocardial oxygen demand (36). Modern anesthetic interventions may help control ischemic episodes during the intraoperative period (37). The QT interval consists of two components: the QRS complex and T wave interval (38), Prolongation of the QT interval may be a consequence of an unfavorable balance between sympathetic and parasympathetic activity. It has been noted that imbalance in cardiac autonomic function (increased or decreased sympathetic activity) shortens or prolongs the QT interval of the electrocardiogram (39). It was found from the results that the study protocol is safe on the cardiac muscle contractile because the changes are minimal in the electrocardiogram.

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تقييم برنامج التخدير العام عن طريق البروبوفول مع الكيتامين في الأرانب المعالجة تمهيدياً بالديازيبام

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الخلاصة

تم تصميم هذه الدراسة لتقييم كفائة استعمال برنامج ديازيبام – البروبوفول – والكيتامين لغرض إحداث التخير العام في الأرانب. أجريت التجربة على سبعة عشر من ذكور الأرانب البالغة ذات صحة جيدة ومن النوع المحلي, يتراوح وزنها 0.9 – 1.5 كجم. تم حقن الأرانب بالبرنامج المتكون من الديازيبام 1 ملغم/كغم وزن الجسم عن طريق الحقن العضلي وبعد 15 دقيقة تم حقن البروبوفول 10 ملغم / كغم وزن الجسم عن طريق الحقن البطئ في الوريد و الكيتامين 25 ملغم / كغم وزن الجسم عن طريق الحقن العضلي. تم تسجيل مجموعة من القياسات قبل حقن الأدوية ومن ثم بعد إعطاء البرنامج التخديري بالدقائق 0, 5, 10, 15, 20, 30, 45, 60, 75, 90 على التوالي. أظهرت النتائج أن التخدير مع البرنامج المتكون من الديازيبام و البروبوفول و الكيتامين في الأرانب كان مناسب من حيث التخدير الجراحي، جيد في التسكين واسترخاء العضلات مع تغيرات طفيفة على الشكل الموجي لعضلة القلب.

الكلمات المفتاحية: ديازيبام، بروبوفول، كيتامين، تخدير عام، تخطيط كهربائي للقلب، أرانب.