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Comparison of different regimens of nerulepanesthesia in rabbits

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Abstract

The study was intended to compare the efficacy of different anesthetics combinations for induce general anesthesia in rabbits. Eighteen adult (12-18 months) local breed rabbits of either sex weighting from (980-1800) gm were used in this study. Rabbits were divided into three equal groups (3 males - 3 females) in each group. The study include induce general anesthesia by intramuscular injection of different drugs as following: droperidol (1.25mg/kg)+fentanyl 0.025mg/kg+ketamine 25mg/kg (D+F+K) group (A). xylazine (2.5mg/kg) + fentanyl 0.025mg/kg + Ketamine 25mg/kg (D+F+K) group (B). Diazepam 1mg/kg + fentanyl 0.025mg/kg + ketamine 25mg/kg (D+FF+K) group (C). The rectal temperature, respiratory rate, heart rhythm, degree of analgesia, degree of muscle relaxation and eyes reflexes (palpebral and corneal reflexes, size of pupil, were recorded before the i.m. injection of the drugs (time zero) as a control data and after 5, 10, 15, 20, 30, 45, 60, 75 minutes of injection respectively until the rabbit response to external stimuli, the induction time, anesthesia time and recovery time were recorded. An orthopedic surgery (femur periosteum elevation) was done to estimate the efficiency of the anesthetic programs. There were no significant difference in induction time, while the anesthesia time in X+F+K group was significantly longer than in the other groups. The recovery time in D +F+K group was seen significantly longer than in the other groups. The analgesia and muscle relaxant were seen superior in X+F+K group. In conclusion mixture of (X+F+K) seem to be superior asrental general anesthestic drug in rabbits.

Keywords: Neruleptic, Anesthesia, Deperidol, Diazepam, Ketamie, Fentanyl, Xylazine, Rabbits.
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مقارنة برامج مختلفة من النيروليبتك كمخدر عام في الارانب

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الخلاصة

هدفت الدراسة الى تقييم ثلاثة انواع من المخدر العام في الارانب أستخدمت في الدراسة 18 أرنب بالغ (١٢–١٨ شهر) من النوع المحلي و من كلا الجنسين و تراوحت اوزانها بين (٨٩٠– ١٨٠٠ غم)، قسمت الأرانب الى ثلاثة مجاميع وتم احداث التخدير العام وكما يلي: في المجموعة A اعطي مزيج مكون من الدروبريدول ١,٢٥ ملغم/كغم + الفنتانيل ٠,٠٢٥ ملغم/كغم +الكيتامين ٢٥ ملغم/كغم. اما في المجموعة Bفقد اعطي مزيج مكون من الزايلزين ٢,٥ ملغم/كغم +الفنتانيل ملغم/كغم +الكيتامين ٢٥ ملغم/كغم. في حين اعطي للمجموعة C مزيج الديازيبام ١ ملغم/كغم +الفنتانيل ٠,٠٢٥ ملغم/كغم +الكيتامين ٢٥ ملغم/كغم. أعتمدت المعايير الأتية لتقييم برامج الدراسة مثل درجة الحرارة, معدل التنفس, نسق القلب, درجة التسكين، درجة أرتخاء العضلات, منعكسات العين (الجفن، القرنية، حجم البؤبؤ) سجلت هذه المعايير قبل الحقن بالعضلة (الوقت صفر) واعتبرت كقيم لمجموعة السيطرة و بعد الحقن في الاوقات ٥، ١٠، ١٥، ٢٠، ٣٠، ٤٥، ٦٠، ٧٥ دقيقة حتى أستجابة الأرنب للمؤثرات الخارجية، بالاضافة الى كل هذه المعايير تم تسجيل وقت أحداث التخدير, طول فترة التخدير الجراحي، وقت الافاقة بالنسبة الى مجاميع المقلدات العصبية التخديرية. كما تم تقييم كفاءة المقلدات العصبية التخديرية سريريا وذللك بأجراء عملية رفع سمحاق العظم. لم يلاحظ فرق معنوي في وقت احداث التخدير في

حين كان هناك فرق معنوي في طول فترة التخدير في مجموعة الزايلزين +الفنتانيل + الكيتامين حيث كانت أطول من المجوعتان الباقيتين. أيضا لوحظ هناك فرق معنوي في طول فترة الأفاقة مجموعة الديازيبام +الفنتانيل+الكيتامين حيث كانت أطول من المجوعتان الباقيتان. كانت درجة التسكين و أرتخاء العضلات عالية و متفوقة في مجموعة الزايلزين +الفنتانيل + الكيتامين عند التقييم السريري بأجراء العملية الجراحية. يستنتج من هذه الدراسة ان مزيج الزايلزين الفنتانيل كيتامين اظهرتفوق واضح على بقية الانواع.

Introduction

Rabbits are used widely in biomedical research and it has also gained increasing popularity among urban families as a domestic pet, Rabbits are easily stressed by handling and when excited, may struggle vigerously, this may lead to musculoskeletal trauma, severe stress, shock and cardiac arrest. A safe anaesthetic method is there fore needed both for surgeon undertaking research and fore practicing veterinarian. But there use in surgery is limited due to problems encountered during anaesthesia. Rabbits are often considered to be the most difficult laboratory animal to anesthetized successfully, in part due to difficulty in endotracheal intubation, and also due to their susceptibility to respiratory arrest once adequate surgical anaesthesia has been achieved (1,2).

Many complications still arise when anaesthetizing rabbits and there are possible reasons. The margins of safety between anaesthetic and lethal doses are less than those found in other animal and there is wide individual variation in response to anaesthetic and ancillary agents. The rabbit has strong reflexes which are difficult to suppress during general anaesthesia (3).

Inhalation anaesthesia has gained wide acceptance as a method for providing moderate to long periods of anaesthesia in man and many animal. The anatomical conformation of the oral cavity of rabbits impedes visualization of the larynx, intubation is difficult. Therefore, parenteral anaesthetic are often preferred in this species (4). The present study was intended to compare the efficacy of use one of the anesthetics/ analgesics combinations.

Materials and methods

Eighteen adult (12-18 months) local breed rabbits of either sex weighting from (980-1800) gm were used in this study. Rabbits were divided in to three equal groups (3 males- 3 females) in each group. Animals were maintained in individual kennels in an animal house and exposed for the same environment including climate, management and feeding for 1 week to acclimatize and adaptation on the please.

Clinical examination always precede administration of any sedative or anesthetic agent. Tthe following parameters recorded at zero time (before injection of drugs) as control data and after 5, 10, 15, 20, 30, 45, 60 and 75 minutes respectively until the rabbit response to external stimuli. the induction time, surgical anesthesia and recovery time also recorded, respiratory rate (by the movement of chest and abdominal muscles), heart rhythm (by auscultation using a stethoscope), degree of analgesia (by pinch the digit of rabbit mild degree of the analgesia + moderate analgesia ++ and deep analgesia +++) (1, 2, 4), degree of hind leg muscle tone (by flexion and extension of the limb of rabbit minimal degree of the relaxation + moderate relaxation ++ and marked relaxation +++) (1). eyes reflexes palpebral (by touch the medial canthus) and corneal by (touch it through the digit by using sterile cotton moisted with antibiotic) (pesence 0, mild -1, sluggish -2, absent -3), size of pupil (cntracted 0, dilated 1).

Drugs injection

Droperidol (Dehydrobenzperidol (2.5mg/ml) The Vial contain 10ml, JANSSEN Pharmaceutica), Fentanyl (Fentanyl-Janssen 2ml (0.05mg/ml fentanyl) The Vial contain 2ml, JANSSEN Pharmaceutica), Ketamine (TEKAM 50 (50mg/ml) The Vial contain 10ml, HIKMA Pharmaceuticals, Amman, Jordan) group (Dro + F + K) (group A). Droperidol in 1.25 mg/kg B.W. was injected intramuscularly. After 5 min the Fentanyl was injected in 0.025 mg/kg B.W., Ketamine was injected in 25mg/kg B.W. after 5 min post Fentanyl injection.

Xylazine (SETON 2% (20mg/ml) The Vial contain 25ml, LABORATORIOS CALIER, S.A., SPAIN) + Fentanyl + Ketamine group (X + F + K) (group B). Xylazine in 2.5mg/kg B.W. was injected intramuscularly. After 5 min the Fentanyl was injected in 0.025 mg/kg B.W., Ketamine was injected in 25mg/kg B.W. after 5 min post Fentanyl injection.

Diazepam (Diazepam (10mg/2ml) The ampoule contain 2ml, Rasht – Iran) + Fentanyl + ketamine group (Dia + F + K) (group C). Diazepam in 1mg/kg B.W. was injected intramuscularly. After 5 min the Fentanyl was injected in 0.025 mg/kg B.W., Ketamine was injected in 25mg/kg B.W. after 5 min post Fentanyl injection.

Orthopedic surgery

Priosteum elevation was done to estimate the efficiency of anesthetic programme.

Statistical Analysis

The values were expressed as mean ± SE the data was analyzed using the complete random design (CRD). The comparisons between the means of the group in each

parameter (examination) were tested by Duncan's test. A probability was considered significant (at ***=P≤0.01% and **=P≤0.05%) (5).

Results

Induction time, anesthesia time and recovery time

The time of injection anesthetic drug (ketamine), the induction time in all the neuroleptanaesthetic groups were nearly similar to each other the mean of induction time was 3.5, 3.1 and 3.3min. in Dro+F+K, X+F+K and Dia+F+K groups respectively.

The anaesthesia time was short 16.67 min. in Dia+F+K group, 20 min. in Dro+F+K group and 32 min. in X+F+K group, it was significantly longer at P<0.01 in X+F+K group among the other two groups of experiment.e recovery time ranging from 51.66 min., 55.33 min. and 83.5 min. In Dro+F+K, X+F+K and Dia+F+K groups respectively, it was significantly at P<0.01 longer in Dia+F+K group fig. (1).

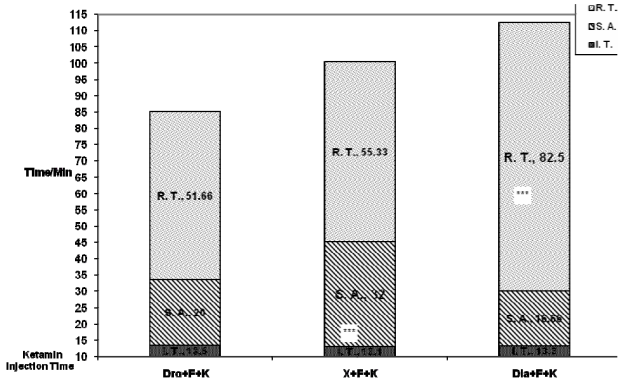

Figure 1: I.T.: Induction time. S.A.: Length of surgical anesthesia. R.T.: length of recovery time. To all neuroleptanesthetic groups. Dro+F+K. X+F+K. *** = P<0.01%.

Degree of analgesia

There was a mild analgesia starting from 10 min. after IM injection in all neuroleptanaesthetic groups, which developed to deep analgesia extending from 15-30 min, then gradually decreased to moderate at 45 min. in X+F+K group, and finally to mild at 60 min. until loss of analgesia fig. (2).

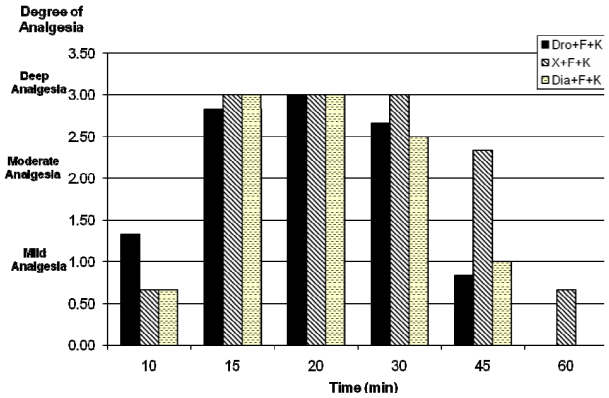

Figure 2: The analgesic effect of IM injection of Dro+F+K, X+F+K and Dia+F+K: (Dro: Droperidol in 1.25 mg/kg, F: Fentanyl 0.025 mg/kg, X: Xylazine 2.5 mg/kg, Dia: Diazepam 1 mg/kg, K: Ketamine 25 mg/kg).

Degree of muscle relaxation

The muscle relaxation started early in the Dro+F+K group but it was moderate, while it was below minimal in the other two groups of experiment. The muscle relaxation was marked in all the neuroleptanaesthetic groups extending from 15-45 min. of the starting of IM injection of the drug, then return to moderate and minimal at 60, 70 min. respectively until loss of muscle relaxation fig. (3).

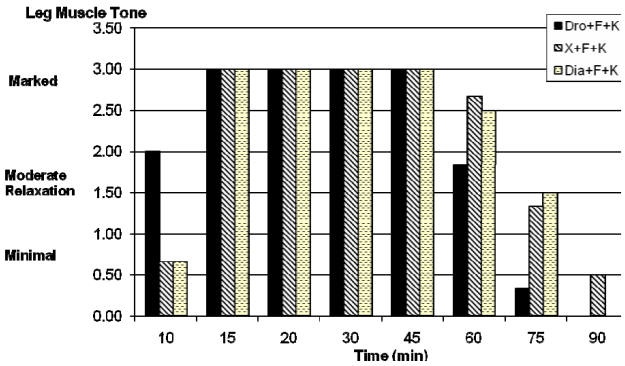

Figure 3: The effect of IM injection of Dro+F+K, X+F+K and Dia+F+K on the muscle relaxation: (Dro: Droperidol in 1.25 mg/kg, F: Fentanyl 0.025 mg/kg, X: Xylazine 2.5 mg/kg, Dia: Diazepam 1 mg/kg, K: Ketamine 25 mg/kg).

Eye reflexes (palpebral, corneal and size of pupil)

The eye reflexes (palpebral and corneal reflexes) were never abolished completely in all the treatment groups, while it becomes nearly sluggish at 20 min. of observation. The pupil size reflex was found significantly contracted at P<0.01 in Dro+F+K group, while it was directed toward contraction in the other two groups figs. (4, 5 and 6).

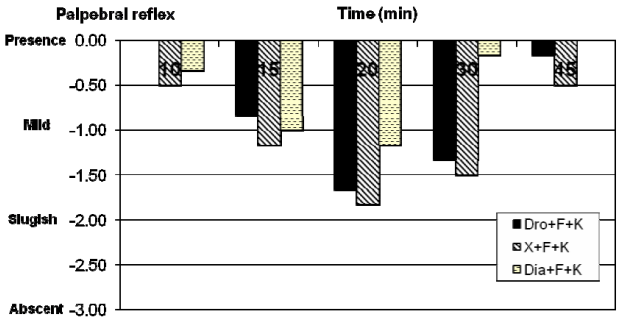

Figure 4: The effect of IM injection of Dro+F+K, X+F+K and Dia+F+K on the palpebral reflex: (Dro: Droperidol in 1.25 mg/kg, F: Fentanyl 0.025 mg/kg, X: Xylazine 2.5 mg/kg, Dia: Diazepam 1 mg/kg, K: Ketamine 25 mg/kg).

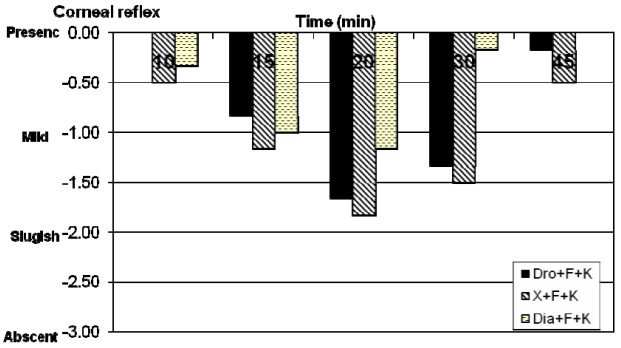

Figure 5: The effect of IM injection of Dro+F+K, X+F+K and Dia+F+K on the corneal reflex: (Dro: Droperidol in 1.25 mg/kg, F: Fentanyl 0.025 mg/kg, X: Xylazine 2.5 mg/kg, Dia: Diazepam 1 mg/kg, K: Ketamine 25 mg/kg).

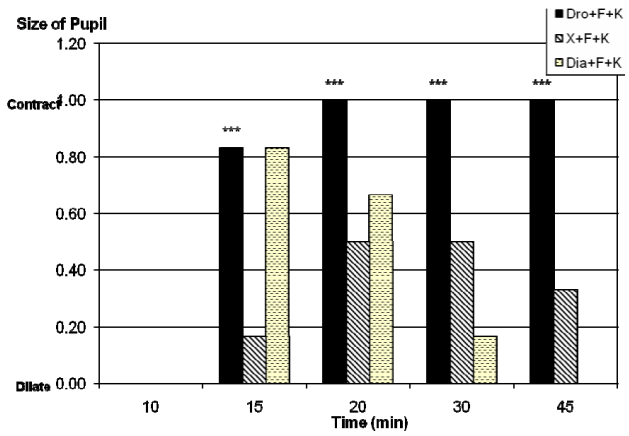

Figure 6: The effect of IM injection of Dro+F+K, X+F+K and Dia+F+K on the size of pupil: (Dro: Droperidol in 1.25 mg/kg, F: Fentanyl 0.025 mg/kg, X: Xylazine 2.5 mg/kg, Dia: Diazepam 1 mg/kg, K: Ketamine 25 mg/kg).

Respiratory rate

The respiratory rate was slowly decreased through the first 10 min. from the starting of drug injection in tow groups while it was decreased below the half of time zero in X+F+K group at that time. From the 15-30 min. time of observation there was sharply decreased of respiratory rate in all groups where it reached below 20 breath/ min, then slowly increased from 45 min. to 75 min. where it reached near half of normal respiratory rate fig. (7).

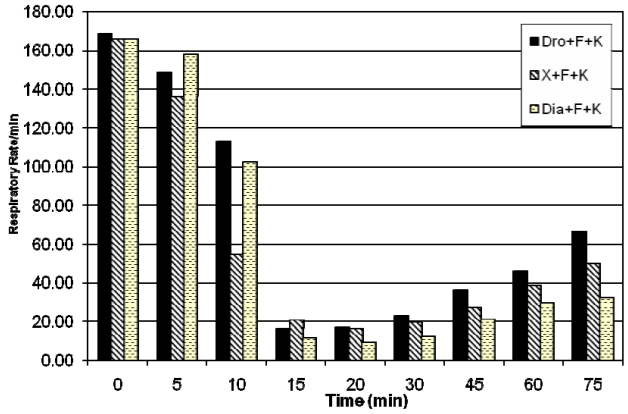

Figure 7: The effect of IM injection of Dro+F+K, X+F+K and Dia+F+K on the respiratory rate (per/min): (Dro: Droperidol in 1.25 mg/kg, F: Fentanyl 0.025 mg/kg, X: Xylazine 2.5 mg/kg, Dia: Diazepam 1 mg/kg, K: Ketamine 25 mg/kg).

Temperature

The rectal temperature of animals remain within normal values ranging from 39.3 C°, 39.5 C° and 40 C° in Dia+F+K, X+F+K and Dro+F+K groups respectively at the beginning of the injection, then gradually decreased to reached 38.8 C°, 38.9 C° and 39.7 C° in Dia+F+K, X+F+K and Dro+F+K groups respectively fig. (8).

Heart rhythm

The heart rhythm it was significantly regular at $P<0.05$ in Dia+F+K group it remain regular almost all the observation time, in reverse to Dro+F+K group where has irregularity at 5 min. extended to 15 min. then return to normal (regular) 20-30 min. then again directed toward irregularity till the 75 min. The X+F+K group remain stable (near to regular) from the beginning to the end of experiment fig. (9).

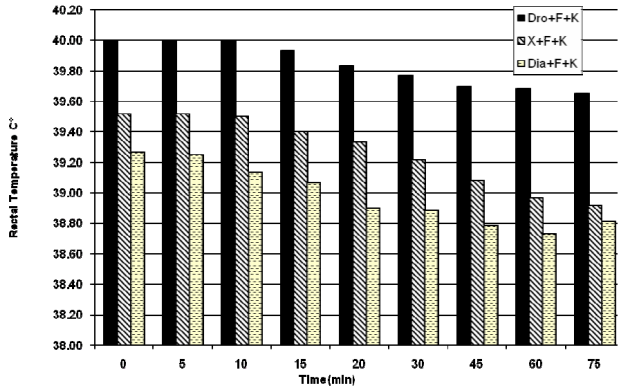

Figure 8: The effect of IM injection of Dro+F+K, X+F+K and Dia+F+K on the rectal temperature ºC: (Dro: Droperidol in 1.25 mg/kg, F: Fentanyl 0.025 mg/kg, X: Xylazine 2.5 mg/kg, Dia: Diazepam 1 mg/kg, K: Ketamine 25 mg/kg).

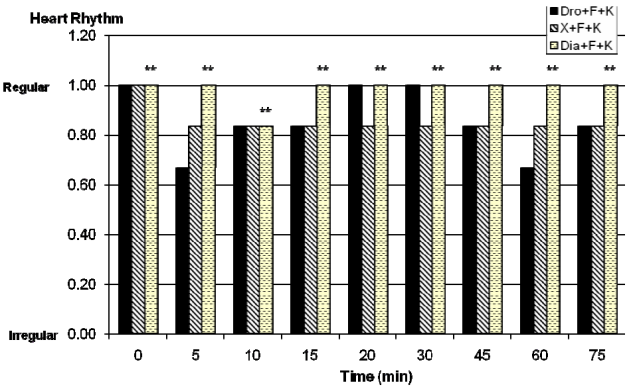

Figure 9: The effect of IM injection of Dro+F+K, X+F+K and Dia+F+K on the heart ryrhem: (Dro: Droperidol in 1.25 mg/kg, F: Fentanyl 0.025 mg/kg, X: Xylazine 2.5 mg/kg, Dia: Diazepam 1 mg/kg, K: Ketamine 25 mg/kg).

Discussion

Although inhalant anesthetics are generally safer than injectable anesthetics, their use may be limited by lack of equipments, facilities or experience of anesthetist.

The X+F+K group has good length of anesthesia (32 min) when compared with the other two groups of experiment. This result was in agreement with (2,3). This length of surgical anesthesia was sufficient to do a short duration of surgical operation in rabbtis.

The recovery time for X+F+K group (55.33 min.) was good when compare with Dia+F+K group. The relatively long surgical anesthesia and convenient recovery time make this combination reliable to use in rabbits. The short duration time of anesthesia in Dro+F+K (20 min.) and Dia+F+K (16.67 min) groups and the relatively long duration of recovery time specially in Dia+F+K group (82.5 min) made this combination not suitable to do any surgical operation in rabbits. The analgesia started after 15 min. of IM drugs injection and extended approximately from 15-45 min. These result in consistence with (6) using xylazine-kitamine, or ketamine-diazepam, or fentanyl-droperidol in rabbits. But it was incompatible with (3; 9; 10; 11; 2; 12; 13). Using different mixtures in different doses in rabbits. The variation may be due to the difference in the doses. The analgesic effect of our combination was mediated through alpha 2-agonists drugs which produce analgesia by stimulating receptors at various sites in the pain pathway within the brain and spinal cord (14). In some binding of either alpha 2-agonists or Mu-opioid agonist to their receptors results in activation of the same signal transduction system (membrane associated G proteins), which induces a chain of events that open potassium channels in the neuronal membrane. Active of potassium channels in the postsynaptic neuron leads to hyper polarization of the cell, which ultimately the cell unresponsive excitatory input effectively severs the pain pathway (15).

The analgesic effects of ketamine are thought to be mediated by binding of the drug to N-methyl-D-aspartate (NMDA) receptors (16). Butyrophenones act as allosteric inhibitors at postsynaptic receptors sites to decrease the neurotransmitter activity of dopamine (16). Good muscle relaxation was gained in the starting after 15 min from the IM injection and extended for 35 min in all groups These results were in agreement with (1) using xylazine +ketamine in rabbits.

The ketamine produce profound analgesia but with tonic-colonic spasm and without muscle relaxation of limb muscle (17). The muscle relaxation gained comes from the complementary drugs e.g. xylazine, diazepam, droperidol, and fentanyl. Xylazine muscle relaxant effect was by inhibition at the alpha 2- adrenoreceptor at the interneuron of the spinal cord (18,19). Generally muscle relaxation produce by benzodiazepines is probably mostly central in origin although some of this action is also attributable to direct activity at the postsynaptic neuromuscular junction (20).

Droperidol is may cause muscle tremors, hyper excitability. This may be the cause for short duration of muscle relaxation in this group (21).

The palpebral and corneal reflexes were never abolished completely, it become nearly sluggish at 20min of observation. These results were in agreement with (6,7), using X+K and Dia+X. also same results were found using barbiturate and several combinations for anesthesia (8,9), (22) observes the persistence of the corneal reflex with using Innovar-Vet (droperidol + fentanyl combination) as anesthetic in rabbits. The palpebral and corneal reflexes

were difficult to suppress (3). These reflexes may be consistently abolished only immediately before fatal respiratory arrest (8,9). These result in agreement with the fact said that the rabbits have strong reflexes which is difficult to suppress during analgesia and general anesthesia (3).

The pupil size was found significantly contracted in Dro+F+K group and directed toward contraction in Dia+F+K and X+F+K groups. This may be due to the presence of opioid substitute in the combination of mixtures. Miosis is often considered an effect of opioid administration during anesthesia (23). Fentanyl induce miosis and impairment of extraocular muscle control. Droperidol constrict the pupil and block the pupillary dilation brought about by nociceptive stimuli (24). Mydriasis is commonly observed after xylazine administration, this effect is 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 (25).

The respiration was shallow between 15-30 min. of observation, and respiratory rate was decreased promptly between 15-45 min. where it reached the least levels at that time. These results were in agreement with (2, 6 and 13) using X+K, K+Dia, M+F+Mz mixtures as anesthetic drugs. The most prominent effect on respiration was seen attributed to the opioid constituent (26). Generally opioid (naturally and synthetic) causes respiratory depression by inhibition of the brain-stem respiratory center (27). Sedation with alpha 2-agonist result in a reduction in respiratory rate for varying periods. Respiratory depression occur secondary to the C.N.S depression produced by alpha 2-adrenoreceptor stimulation; however the degree of depression with alpha 2-agonists alone is less than that with other sedative, even at sub lethal doses (15,28). The rectal temperature were decreased slowly toward the end of experiment at 75 min. This decrease was mild and remains within the normal rang of the body temperature. These results were in agreement (3,6,29). Diazepam (10mg/2ml) The ampoule contain 2ml, Hypothermia is the dominant body temperature response to morphine in rabbit, dogs and monkeys, Where as hyperthermia usually occurs in cats, goats, cattle and horses. In general, reduction in temperature with alpha 2-agonist can be attributed to C.N.S depression, in combination with a reduction in muscle activity (30,31). Alpha 2-agonist may allow for better maintenance of body temperature due to the peripheral vasoconstriction and central redistribution of blood, with a consequent reduction in cutaneous heat losses, in contrast to the consistent reductions in body temperature reported with the use of other anesthetic agents that induce vasodilation (8,15). The heart rhythm become irregular. Although subject to controversy, low doses droperidol has recently been suspected to induce cardiac arrhythmias (32).

Xylazine appear to sensitize the myocardium to catecholamine, thus making dysarhythmias more likely (21). The regularity of heart rhythm were seen in may due to the effect of Ketamine which found in all groups, the cardiovascular action of Ketamine is characterized by indirect cardiovascular stimulation (17,18).

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