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COMPARISON OF SEDATIVE AND TRANQUILIZER DRUGS WITH KETAMINE HYDROCHLORIDE FOR GENERAL ANAESTHESIA IN RABBITS

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ABSTRACT
The aim of the present study was to compare the effect of (detomidine 150 mg/kg) mixed (Ketamine 35mg/kg) in one syringe with (Acepromazine 2mg. /Kg B. W.) mixed (Ketamine 35mg/kg) in one syringe. First protocol uses detomidine and Ketamine in one syringe administered intramuscularly and the second protocol uses acepromazine and ketamine in one syringe administered intramuscularly. Data were collected immediately before administration of drugs (zero time) as control data. Parameters included clinical measures: Heart rate, respiratory rate, rectal temperature, analgesia at time 5, 20, 15, 20, 25, 30, and 50 minutes. The results revealed that detomidine has sedative and analgesic effects. Whereas the acepromazine ketamine protocol shows that the acepromazine has mild to moderate tranquillization and muscle relaxation, but adverse effects do not have a property of analgesia. Last protocol shows a weaker analgesia and unconsciousness as compared with first protocol which was stronger analgesia and deep unconsciousness. Both protocols showed a decrease in the plus rate, respiratory rate and body temperature. The two protocols were analyzed in terms of analgesia and sedation level, and duration of anesthesia. In conclusion, the injection of (detomidine Ketamine) is suitable to from an injection of (acepromazine ketamine), because induction period is shorter and more surgical anesthesia, with long period of recovery time.

KEYWORDS: detomidine, acepromazine, ketamine, general anesthesia, rabbits.

INTRODUCTION

Rabbits are popular pets and are often accessible to veterinarians for assessment of medical treatment. Anesthesia in exotic pets is required for many diagnostic and surgical procedures and is associated with a higher perioperative risk in rabbits when compared with dogs and cats[1]. Rabbit is often considered as a difficult laboratory animal to anesthetize successfully. The rabbit has strong reflexes which are difficult to suppress during general anesthesia apparent sensitivity of the rabbit's respiratory center to an anesthetic agent, and the variety of observed secondary effects relate to stress, including death[2-4]. Rabbits attempt to escape during the examination; this will affect various hormonal pathways and physiological processes, notably to a rise of catecholamine and the slowdown of the digestive system activities[5]. The rise of catecholamine can have a dramatic effect on the cardiac and respiratory activities which lead to secondary adverse complication such as altered response to surgical anesthetic drugs[6]. Indications of general anesthesia in rabbits are numerous (*e.g.* Dental work, wound cleaning, otitis treatment, ovariohysterectomy and castration). Sedatives and Tranquilizers drugs are commonly used in veterinary practice as premedication before general anesthetic. Detomidine is very potent Alpha-2 adrenocepter agonist of the non-opioid group produces sedative and analgesic effect**[7],** via binding to Alpha-2receptor in the locus ceruleus on the Pons and lower in the brainstem and spinal cord[8]. It's developed to provide similar clinical effect as xylazine but without some of the associated side effects[7]. Acepromazine (ACP) phenothiazine derivative is a potent neuroleptic agent with relatively low toxicity. It induces mild to moderate tranquillization, muscle relaxation and a decrease in spontaneous activity attributable principally to central dopaminergic antagonism[9]. Acepromazine produces numerous effects such as peripheral vasodilation, hypotension, hypothermia and behavioral modifications. Ketamine is the most popular injectable anesthetic drug using in Veterinary Medicine. It binds to the phencyclidine receptor site in the N_methyl-D-aspartate receptor complex (NMDA), which located within the ion channel so it's blocking the transmembranous ion flux this makes ketamine a non-competitive (NMDA) receptor antagonist, NMDA-receptor are calcium –gated channel receptors [10]. The objectives of the study to determine and evaluating the effects of anesthetic protocols, by detomidine or acepromazine with ketamine for induction of general anesthesia in rabbits. Also effect of the additives on the vital signs (heart rate, respiratory rate, body temperature, analgesia, muscle relaxation). And finding the most suitable mixture used as a general anesthesia for rabbits.

MATERIALS & METHODS

Twelve adults (12-18 months old) local breed rabbits of both sex weighting from (1400-2000) gm were used in this study. Rabbits were divided into two equal groups six in each group. Animals were maintained in individual houses in animal house of College of Veterinary Medicine and exposed to the same environment including climate, management and feeding. Clinical examination was done to animals before administration of any sedative or

anesthetic agent. The animals in group DK were received detomidine hydrochloride (ORION pharmaceuticals, ESPOO, FILND) at dose 150 µg/kg IM, mixed with ketamine hydrochloride (ASTRAPIN pharmaceuticals, GERMANY) at dose 35 mg/kg. The animals in group AK were injected with mixture of Acepromazine maleate (Alfasaan Company, Holland) at a dose of 2 mg/Kg. with Ketamine hydrochloride (ASTRAPIN pharmaceuticals, GERMANY) at dose 35 mg/kg. The induction time, surgical anesthesia and recovery time, respiratory rate, heart rhythm, body temperature and degree of analgesia were recorded. The following parameters recorded at zero time (before injection of drugs) as control data and after 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 minutes. Than results were expressed as M± SE. Parametric data were analyzed using two way analysis of variance (ANOVA) continued with Least Significant Difference (LSD), and $p< 0.05$ was considered significant used Statistical Package for Social Sciences (SPSS)[11].

RESULTS

Animals in group DK caused rapid induction within 120-150 second after the IM injection of detomidine mixed with ketamine hydrochloride at dose 150µg/kg, 35 mg/kg B.W. Respectively as anesthetic protocol (Table 1). In group AK rabbits were anesthetized by IM injection of a mixture of Acepromizine 2 mg/kg B.W. And ketamine hydrochloride 35 mg/kg B.W the induction was delayed and occur with 3–8 minutes. Group AK was appearing significant difference with DK in spate of the ketamine cause rapid induction. The induction of anesthesia by DK protocol was provided, good general anesthesia in all rabbits about 50 ±10 minutes and caused good muscle relaxation with complete unconsciousness and complete disappearance of all reflexes**.** In the group AK protocol was not provide muscles relaxation, sedation and analgesia the anesthetic time 40 ±10 minutes. The two protocols which provide not significant differences in time of anesthesia except the animal in group AK was response to stimulation. The uses of ketamine in this tow protocol are responsible for time of anesthesia. Recovery of the animals were smooth and ranged between 65-75 minutes in group DK while in group AK was lesser and ranged between 40 -60 min. The reflexes of limbs were returned at 25 ±5 minutes in group AK and 40 ±10 minutes in group DK. The recovery was smooth, free of convulsion, the return of pedal reflex at the end of anesthesia was marked as a time of recovery, but animal at this time still at lateral recumbency and the animals were required more than 15 to return to Sternal recompense in AK but later in group DK to 25 minutes (Table 1).

TABLE 1: the incidence time of general anesthesia by detomidine or acepromazine with ketamine in rabbits

Group	Induction time Min	Anesthetic time (Minutes)	Recovery time (Minutes)
(DK)	2.5± 0.102 b	47± 2.813	70±1.825 a
(AK)	5.8± 0.945 a	44 ±5.540	49±5.540b

Small latter revealed significant difference in between groups $p<0.05$

TABLE 2: Shows the effect of DK or AK and CO_2 on heart rats (beat/min), Respiratory rate (breath/minute) and rectal body temperature °C

GROUP	Time of experiment Minutes										
	Control	5	10	15	20	25	30	35	40	45	50
D.K	210 ±	147.3±	141.3±	138±	135.3±	128±	124±	123.3±	124.6±	123.6±	123.3±
H.R	11.301	6.565	6.504	5.537	8.849	9.743	11.123	10.141	10.141	10.663	10.852
	A	Bb	Bb	Bb	BCb	Cb	Cb	Cb	Cb	Cb	Cb
A.K	206±	198.5±	185±	189±	186.5±	190±	192±	196.5	199±	200±	200±
H.R	13.613	11.577	9.559	7.055	8.432	10	10.583	±8.027	8.407	9.219	9.309
	A	Aa	Aa	Aa	Aa	Aa	Aa	Aa	Aa	Aa	Aa
D.K	164±	80.6±	78.6±	72.6±	76±	72±	68.6±	66±	64.6±	64.6±	69.6±
RES	4.844	10.999	9.503	7.825	12.176	7.155	4.997	3.966	4.055	4.055	4.013
	A	B	B	B	B	Ba	B	BC	BC	BC	B
A.K	158.8±	64.3±	63.6±	62±	61.3±	59.3±	62±	66±	64.8±	65.6±	70.5±
RES	17.679	10.124	10.255	5.240	5.232	5.206	5.537	3.966	3.310	3.169	4.014
	A	B	B	B	BC	BCb	B	B	B	B	B
D.K	38.2 ±	38.1 ±	38±	37.9±	37.6±	37.6±	37.3±	37±	36.8±	36.8±	36.8±
TEMP	0.228	0.203	0.209	0.196	0.172	0.172	0.248	0.276	0.285	0.285	0.285
	A	A	A	A	AB	AB	AB	B	B	B	B
A.K	38.7±	38.6±	38.3±	38±	37.9±	37.5±	37.3±	37.2±	37.1±	37.2±	37.4±
TEMP	0.197	0.175A	0.22	0.305	0.253	0.284	0.319	0.249	0.184	0.155	0.147
	A		AB	B	B	B	B	B	B	B	B

Small different letters denoted that significant differences between period at ($p<0.05$). Capital different letters denoted that significant differences between groups ($p<0.05$)

The animals in the DK group showed decreasing in heart rate beats about 147 ±6.565 during the first five minutes and continue till 20 min and appear stabile after this time, and revealed significant differences in control with other time and 5, 10 and 15 min with 25min to the end. While group AK showed stability in the heart rate beats compared with the DK group and revealed non-significant differences. The statistical analysis in between groups were revealed that significant differences at the level of ($P<0.05$) from 5 minutes to the end of the study (Table 2).

The statistical analysis of respiratory rate showed significant differences at the ($p< 0.05$) between controls with other period in both groups. There was a significant difference at 25 minutes in between the groups. The result of core body temperature was showed a continuing decrease at the end of the study. The statistical analysis showed significant differences at the ($p < 0.05$) between control, 5, 10, and 15 min with 35 min and above in DK groups. While in AK group control and 5 min appear to significantly decrease with 15 min and above (Table 2).

DISCUSSION

This study was designed to compare the sedative and analgesic effects of two alpha-2 adrenergic agonist detomidine (150µg/kg) and acepromazine administered intramuscular mixed with ketamine 35 mg/kg BW in rabbits and to evaluate the safety. These results of sedation are in agreement with others who found a dose dependent effect of alpha-2 agonist on the onset of sedation in rabbits. The first 3 hours of termination of the anesthesia were the most common time for rabbits die (4 and 12). In all that combination of detomidine or Acepromazine with ketamine was safe and not death occurs in any animals in both groups. The increase in time of recovery in group DK may be due to use of high dose of detomidine cause deep sedative effect and synergistic inhibition effects with ketamine to the CNS. Detomidine is a potent α2-adrenoceptor agonist that induces sedation, analgesia and muscle relaxation[7]. Its mechanism of action is similar to that of xylazine, which causes sedation and analgesia by stimulating central presynaptic α2– adrenoceptors, resulting in inhibition of norepinephrine release from adrenergic nerve terminals. Detomidine has been successfully combined with ketamine for anesthesia in a range of species of animals including rabbits [13]. The level of analgesia was in group DK only because detomidine induced dose dependent Sedative and analgesic effect is produced via binding to Alpha-2receptor in the locus ceruleus on the Pons and lower in the brainstem and spinal cord [8], And the Analgesic effect usually parallels with sedation at the beginning, but as the drugs effect decreases, analgesia disappears before sedation. In general analgesia is about 30 to 60 minutes in duration but acepromazine lack any generalized hypnotic effect and do not produce analgesia[14,15]. The differences between both groups in heart rate beats might be due to the effect of detomidine was causing bradycardia effect in the DK group compared with the AK group[7]. The major side effects of α2- adrenoreceptor agonists on the cardiovascular system have contributed to the sharp decline in heart rate in DK anesthetic regimen [16]. Afshar *et al.*,2005[17] revealed that ketamine may increase the heart rate by the increased sympathetic activity and decreased vagal tone, but both the groups were appeared conflicting results and respiratory rate was not increased. In stead of detomidine dominates these effects by the excitatory carotid baroreceptor reflex induced by hypotension and decreased sympathetic and increased vagal activity,The result of heart rate in the animals of AK group was conformed with Amarpal, *et al.*,2010[18] who revealed that combination between acepromazine with ketamine was little effect and appeared non-significant in heart rate. The result of respiratory rate was agreed with another researcher who revealed that all anesthetic techniques commonly used in rabbits depress ventilation [19, 20]. Mild to moderate respiratory depression has been recorded in ketamine administration, but not interfere with a tidal volume of lung [17&21].But using high doses could lead to serious respiratory depression including apnea in rabbits[22]. On the other hand, detomidine as a member of adrenoceptor agonist may produce tachypnoea[7]. sRabbits are prone to hypoxia due to their small lung capacity and restricted nasopharynx. Their tidal volume is 4-6mls/kg. Hypoxia can be caused by anesthetic agents that cause a drop in oxygen tension (*e.g.* Medetomidine), respiratory depression, breath holding, occlusion of the airway caused by poor positioning, increased weight of viscera on the diaphragm, pre-existing lung disease or firm restraint around the chest. The decrease in rectal temperature observed in rabbits after the administration of detomidine or acepromazine with ketamine might have been caused by sedation, reduced metabolism, muscle relaxation and depression of the CNS as suggested by Kinjavdekar *et al*., 2000[23]. In addition, all phenothiazine derivatives, including acepromazine have also been reported to cause a decrease in body temperature[7]. It is concluded that determine and acepromazine mixed with ketamine are safe to be used in rabbits in the field. These detomidine with ketamine drugs produce a rapid and reliable sedation and analgesia in the rabbits In contrast to acepromazine with ketamine was little sedative and analgesic effect.

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