



A comparison between ketamine-xylazine and ketamine-midazolam or all of them to induce balance anesthesia in rabbits

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Abstract

The objective of this project was to study the induction of smooth anesthesia characterized by good induction (hypnosis), analgesia and good recovery with mild side effects caused by drugs. The effect of using Ketamine with both xylazine and midazolam KXM was investigated in adult rabbits and compared with the positive control group that was administered with ketamine alone K at 40 mg/kg i.m, and with ketamine - xylazine group KX at 40 and 4 mg/kg i.m respectively, and with ketamine - midazolam group KM also at 40 and 4 mg/kg i.m respectively. Administration of xylazine and midazolam each one alone at 4 and 2 mg/kg I.M induced analgesia in a dose-dependent manner through a significant elevation of the electrical voltage after injection when compared with its value before injection. A minimum doses of a mixture KXM at 20,2 and 2 mg/kg i.m respectively, induced good hypnosis with rapid induction and long duration with recovery periods without significant variations in vital physiological parameters (respiratory rate, heart rate, and rectal temperature) and some biochemical parameters (GPT and GOT and glucose level) comparing with groups K, KX and KM. The outcomes of this work were revealed to the induction of proficient general anesthesia that was described by effective hypnosis with analgesic efficacy throughout the administration a minimum doses of ketamine /xylazine /midazolam combination in rabbits.

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Introduction

Rabbits are broadly used as laboratory animals for experimental surgery procedures (1). Intubation of volatile anesthetic agents may be too complicated with inducing apnea and time consuming (2).

As a result of these reasons, an injectable technique is needed for use in rabbits that gives sufficient depth of anesthesia with the additional good quality and recovery, while being safer, easy and not required highly sophisticated equipment (3).

Several injectable agents have been used in rabbits, one of them is ketamine, which is broadly implicated in both human and veterinary medicine to induce anesthesia for surgical purposes by depression of the central nervous

system (CNS) by blocking the effect of the N-methyl D-aspartate receptor in the CNS, leading to reduce the quantity of calcium influx into the neurons, but when used as a sole anesthetic agent in rabbits it tends to cause skeletal muscle convulsion, poor analgesic reflex responses and violent recovery from anesthesia (3) consequently we used xylazine, an alpha 2 receptor agonist acting via stimulation of pre-synaptic adrenergic receptors that leads to minimized catecholamine releasing from nerve endings in combinations with ketamine to potentiate the anesthetic properties of ketamine in rabbits (3).

Xylazine has a potent analgesic and muscle relaxing properties than related agents used in anesthesia, in addition, it is widely used in veterinary medicine as pre-anesthetics to produce balanced anesthesia in different animals (4).

For the same reasons, we used midazolam (well-known GABA agonist drug) to increase influx of potassium ions into the neuron leading to depression of the brain with sedative and hypnotic effects to overcome ketamine side effects (4,5).

Electrical stimulation test is a painful assessment technique used in animals to measure the pain by using a voltage frequency set points (6). Because of the expansive use of these drugs in veterinary practices as sedative and analgesics agents alone or together with anesthetics, therefore the purpose of this work to evaluate some physiological changes and some biochemical parameters induced by ketamine alone and with a mixture of xylazine and midazolam in rabbits, in addition to, estimate the anesthetic properties as onset, duration and recovery periods for the above different mixtures in rabbits, also to explore the analgesic response in rabbits for the above different mixtures. The analgesic effect was estimated through electrical stimulation of pain induction in rabbits.

Materials and methods

Experimental animals

The study was carried out on clinically healthy adult male and female rabbits with body weight 1.8 ± 0.21 Kg (mean \pm SE), placed in the cages with a proper states of temperature, ventilation and constant lighting and fed with a commercial diet and water *ad libitum*. In the first week after their arrival, they were dewormed by ivermectine, the animals were judged to be healthy based on complete physical examination before starting the experiments. The animals were randomly dispersed into experimental groups with 5 rabbits for each one. They fasted a few hours before anaesthesia and standard clinical examination preceded general anaesthesia. Ethical consideration criteria were conducted through the follow-up and the scientific committee of the College of Veterinary Medicine, University of Duhok and have verified this exploration in addition to the use of experimental rabbits.

Medications

Ketamine 5% (Hameln pharmaceuticals, Germany), midazolam 500 μ g/10ml (Mercury pharma, from the United Kingdom) and xylazine 20 mg/ml (Laboratories Caller, Barcelona, Spain) were purchased. The effective dose of ketamine was selected depending on the previous test (7) while the xylazine dose was determined depending on another study in rabbits (8) and preliminary investigation for midazolam (9).

Study design

Four sets of randomized experiments were carried out on every rabbit with an interval of one week allowed between experiments to permit for complete metabolism and excretion of the medicines used.

Experiment 1: Determination of sub-analgesic dose of xylazine and midazolam in rabbits

The analgesic doses of xylazine and midazolam 4 mg/kg i.m for each one was chosen in accordance with previous trails in rabbits (8,9). We used this dose and sub-doses in this experiment expected as the initial step to determine the appropriate sub-analgesic dosage of xylazine or midazolam for induction good analgesia to be utilized in other experiments with ketamine. Electro-stimulation was utilized through electro-stimulator (Scientific and Research Ltd, England) for induce pain characterized by animal's head movement. The device is designed to assess the pain-dwelling feature of animals. Based on the initial experiments in the rabbits the electro-stimulator was set at the frequency of 50 Hertz with an electrical impulse amplitude of 5 Milli-Amperes (6).

To determine the sub-analgesic dose of each xylazine and midazolam, animals were divided randomly and equally in to four groups, each with 5 animals. 1st and 2nd group were treated with xylazine at 2 and 4 mg/kg I.M, respectively, while 3rd and 4th group were treated with midazolam also at 2 and 4 mg/kg I.M, respectively. The results recorded an induction, present pain, i.e., the voltage remained unchanged or decreased after the injection of drug when compared with the voltages measured before the injection. Whereas, the occurrence of analgesic effect is indicated when an expansion in the voltage is observed after infusion of the drug compared the voltage measured prior to injection (delta voltage).

Experiment 2: Assessment the effects of ketamine alone, ketamine with xylazine or with midazolam, or all agents together on some physiological changes in rabbits

Rabbits were divided randomly and equally into four groups with 5 rabbits. First group was administered ketamine alone K at 40 mg/kg I.M as positive control. The second group was given a mixture of ketamine 40 mg/kg with xylazine 4 mg/kg I.M KX. The third group was treated with a mixture of ketamine 40 mg/kg and midazolam 4 mg/kg I.M KM. Whereas the forth group was administered with a mixture of all above medicines KXM at 20, 2.2 mg/kg I.M., respectively.

These agents were injected into the femoral quadriceps muscle. The baseline recording in this experiment consisted of assessing the heart rate (beats/minute) determined by a stethoscope, and respiratory rate (breaths/minute) by visual observation of chest movement (9). and rectal temperature measured by using a digital clinical thermometer. The values were obtained within 0, 15, 30, 45, 60, 75, 90 and 120 minutes of drug administrations.

Experiment 3: Evaluation of analgesic effects of ketamine alone, ketamine with xylazine or midazolam, or all agents together on rabbits.

The same number of rabbits and their weight as in the earlier experiments were used for each group. Pain sensation

was applied by electro-stimulator. The induced- pain voltages have been measured before and then after 5, 15, 30, 45, 60 and 90 minutes of intramuscular application of ketamine alone K at 40 mg/kg as control group, or with xylazine at 4 mg/kg as 2nd group KX, or with midazolam 4 mg/kg as 3rd group KM, or with all agents together at 20, 2.2 mg/kg as 4th group KXM respectively.

The voltage was applied to the nasal mucosa by two probes, the nasal mucosa was suitable for sensation because of high levels of moisture than other sites. The voltage was increased until observing the head movement as an indicator of pain sensation in the rabbits (6).

Experiment 4: Estimating the anaesthetic effect (hypnosis) of ketamine alone, ketamine with xylazine or midazolam, or all agents together on rabbits

Four groups of 5 adult rabbits each were treated as the follows; ketamine alone (control group), the animals were treated with ketamine alone at 40 mg/kg, i.m. Ketamine and xylazine group: Animals were treated with ketamine at a dose 40 mg/kg with xylazine at 4 mg/kg, i.m respectively. Ketamine and midazolam group: Animals were treated with ketamine and midazolam at dose 40 mg/kg and 4 mg/kg, i.m., respectively. Ketamine, xylazine and midazolam group: Administration of ketamine, xylazine and midazolam at (20, 2 and 2 mg/kg i.m.) respectively.

The onset of anesthesia was recorded, which is the time interval (in minute) between the injection of medicine and loss of righting reflex of animal. The duration of anesthesia (hypnosis) is the time interval (in minute) between loss of correcting reflex (sleep) until the animal returned and corrected their body to normal (5), whereas the recovery time which is the period between a beginning of anesthesia to return the animals to the movement and normal activity (8).

Experiment 5: Measurement of serum GPT and GOT concentration in the rabbit treated with ketamine alone, ketamine with xylazine or midazolam, or all agents together

After 2 hours of treatment of our medicines to the groups as designed above the blood samples were collected from the heart for all groups by using gel tubes. They centrifuged at 3000 rpm for 15 minutes to obtain serum, and were chilled pending analysis during one day.

Serum GPT and GOT concentrations were determined (Units/L) with the specified kit (Biolabs, France) using the chemistry analyser device (Genotek, USA)

Statistical analysis

The SPSS program, version 21 was used for statistical analysis. The One Way ANOVA test was used to analyse results of the present study. $P < 0.05$ was considered to be statically significant. The data was expressed as mean \pm standard error (means). Least significant difference test (LSD) was used to test the difference between groups.

Results

Determination of sub-analgesic (Sedative) dose of xylazine and midazolam on rabbits

Intramuscular injection of xylazine or midazolam at 4 mg/kg body weight for each animal led to depression the central nervous system (sedation) and skeletal muscle relaxation represented by drooping of head, salivation, closed eyes, dyspnoea, loss of movement and recumbent animals with a poor response to external stimuli after 8 and 10 minutes of injection respectively.

For the animals treated with xylazine or midazolam 2 mg/kg (sub -sedative dose) the onset of mild sedation appeared within 14 and 18 minutes of injection respectively, represented by moderate head drooping and reduced animal movements.

On the other hand, a 4 mg/kg dose of each medicine led to a significant increase in pain threshold by electrical stimulation (analgesia) within the time intervals 30-45 and 30-60 minutes after injection respectively, compared with a dose 2 mg/kg or within time zero/other time in the same group (Table 1).

Table 1 additionally shows that the lowest and best dose of xylazine and midazolam, which acts as a sedative with moderate analgesics of 2 mg/kg i.m for each. Therefore, this dose is used in all subsequent experiments with ketamine to induce balanced anaesthesia.

Effects of ketamine alone, ketamine with xylazine or midazolam, or all agents together on some physiological changes in rabbits

Intramuscular injection of animals in the 1st group K at 40 mg/kg of body weight as a positive control led to significant increase in heart rate and respiratory rate within 30 to 90 minutes of injection compared with other times in the same group and then decreased gradually to the normal range. However, in 2nd and 3rd group (KX and KM) this led to significantly reduction of heart rate compared with time zero.

The 4th group KXM appeared less affected than other groups because there are no significant changes in heart rate and respiratory rate were induced within the period of experiment. This indicates that the sub-analgesic dose of mixture group KXM has minimum side effects on cardiopulmonary functions with the small drug doses used. (Table 2).

The rectal temperature manifested no changes in K group but decreased significantly in KX and KM groups especially after 45 minutes of drug administration compared with zero, 15 and 30 minutes of injection.

However, in group KXM, the rectal temperature did not change in any of the time periods with the exception at time 45 minutes after administration that returned to normal range after that time (Table 2).

Table 1: Determination of analgesic and sub-analgesics doses of xylazine and midazolam in rabbits

Group	Time (minutes)					
	0	15	30	45	60	90
Xylazine 4 mg/kg	7.8±0.6	8.1±0.4	9.3 ± 0.2 * a	8.4±0.4	8.3±0.8	8.0 ±0.5
Xylazine 2 mg/kg	8.0±0.3	7.9±0.4	8.1 ±0.4	8.3±0.1	8.0±0.2	8.1±0.6
Midazolam 4 mg/kg	8.0±0.7	8.2 ±0.3	9.7±0.5 * b	9.9±0.3	8.5±0.8	8.4±0.4
Midazolam 2 mg/kg	8.1±0.4	8.2±0.3	7.9±0.6	8.3±0.7	8.4±0.5	8.5±0.8

Values are the mean ± SE of five rabbits/group. *: Significantly different with time zero at same group at P<0.05. a: Significantly different with Xylazine at 2 mg/kg group at P<0.05. b: Significantly different with Midazolam at 2 mg/kg group at P<0.05.

Table 2: Effects of ketamine alone or with Xylazine or Midazolam and in combinations on physiological functions in Rabbits

Group	Time (min)	Heart rate (beat/min)	Respiration (rate/min)	Temperature (C°)
K group (control)	before	225.8 ±15.1	80±8.2	37.6±0.2
	15	233.4 ±10.2	85±7.8	37.4±0.2
	30	241.0 ± 12.4 *	94±7.7 *	37.5±0.3
	45	245.8 ± 17.0 *	99±4.1*	37.1±0.3
	60	244.4 ± 11.8 *	102±6.1*	37.6±0.3
	90	239.0 ±14.7 *	104±5.1*	37.5±0.3
	120	230.8± 12.6	89.9±2.9	37.7±0.4
KX group	before	217.0±14.1	83±6.0	37.5±0.7
	15	182.8±21.8	72±6.9	37.4±0.7
	30	163.0±9.2 *	65±5.5 * a	37.2±0.8
	45	156.0±12.4 *	62±9.4 * a	36.6±0.9 *
	60	174.0±10.8 *	67±7.3 * a	36.7±0.5*
	90	189.0±3.4	68±4.5 * a	35.8± 0.9 * +
	120	213.0±7.1	76±3.9	36.7±0.3 *+
KM group	before	227.0±10.9	85±4.2	37.6±0.3
	15	222.8±12.5	76±7.1	37.1±0.3
	30	203.0±9.1 *	52±9.9 * + #	37.2±0.8
	45	179.0±13.1 * +	49±4.8 * + #	36.3±0.9 *
	60	201.0±6.8	67.5.1 *	36.7±0.5 *
	90	214.0±6.9	70±5.7	35.7±0.5 * +
	120	231.1±6.2	79± 3.8	36.9±0.2 *+
KXM group	before	226.6±4.9	84±2.7	37.7±0.3
	15	216.0±7.3	79±7.6	37.5±0.7
	30	197.0±9.4	82±7.1 a b c	37.2±0.2
	45	196.1±9.9 a b	76±4.8 a b c	36.5±0.2 *
	60	211.2±5.5 a b	82±3.3 a b c	36.9±0.1
	90	221.6±4.1 a b	87±4.1 a b c	36.9±0.3
	120	228.0±10.6	84±3.7	37.1±0.4

Value represent the main± SE for five rabbits/group. *: Significantly different with the time zero at same group at P<0.05. +: Significantly different with the time 15 at same group at P<0.05. #: Significantly different with the time 120 at same group at P<0.05. a: Significantly different with K group at same time at P<0.05. b: Significantly different with KX group at same time at P<0.05. c: Significantly different with KM group at same time at P<0.05.

Estimating the anaesthetic effect (hypnosis) of ketamine alone, ketamine with xylazine or midazolam, or all agents together on rabbits

Animals in all groups suffered from hypnosis but there were significant differences between the groups in onset, duration of actions and recovery periods. Anesthesia started with all groups of animals within 1.1 to 3.1 minutes with

duration of 24.4 to 73.2 minutes, while the recovery periods were within 63.2 - 119.4 minutes after beginning of anesthesia (Table 3). Based on the current results there were significant differences between the ketamine group and other groups for start-up, duration and recovery periods from anesthesia. The start-up of anesthesia was reduced significantly in KXM groups compared with K group, while

the duration and recovery periods increased significantly compared with K group. On the other hand, there was no significant changes between KX and KM groups in onset, duration and recovery periods from anesthesia. This indicated rapid induction with long duration and recovery periods when ketamine was injected at 20 mg/kg with a mixture of xylazine and midazolam at a sub-analgesic dose 2 mg/kg of each with minimum side effects as well as, a small drug doses have been used (Table 3).

Evaluation of analgesic effects of ketamine alone, ketamine with xylazine or midazolam or all agents together on rabbits

Administration of ketamine alone K group at 40 mg/kg i.m did not induce good analgesia with unconsciousness represented with some of the reflexes such as tonic convulsions and eyes remaining open with permanence of corneal and pedal reflexes. However, the KX group was associated with good analgesia represented by elevating in delta voltage and significant increase in pain-induced voltage

mainly after 30 minutes of treatment compared to the time zero stat in the same group, and at the same time (30 minutes) with ketamine group and return to the normal value after 60 minutes of injection. The KM group induced a significant analgesia for short period at 30 and 60 minutes after injection compared with time zero. Excellent analgesia was obtained when ketamine was injected at a low dose of 20 mg/kg i.m, with mixture of xylazine and midazolam at a sub-analgesic dose 2 mg/kg i.m for each in a group KXM which showed significant elevation in delta voltage in all periods of the study compared to time zero in the same group and with other groups at the same time (Table 4).

Serum biochemical test

Table 5 shows that there are no any significant differences in serum GPT and GOT concentrations and glucose level with the group receiving Ketamine alone, and those treated with a combination of ketamine plus xylazine or plus midazolam, or all agents together.

Table 3: Effects of ketamine alone or with xylazine or midazolam and in combinations dose to induce hypnosis in rabbits

Groups	Onset/min	Duration/min	Recovery/min
K (Control)	3.1±0.7	24.4±2.9*	63.2±4.8*+
KX	2.7±0.2	57.1±2.1*	88.8±6.2*+
KM	2.8±0.1	49.6±7.1*	87.1±7.2*+
KXM	1.1±0.2abc	73.2±8.1*abc	129.4±9.1*+abc

Value are the main±SE for five rabbits/group. *: Significantly different with onset of action at same group P<0.05. +: Significantly different with duration of action at same group P<0.05. a: Significantly different with K group at P<0.05. b: Significantly different with KX group at P<0.05. c: Significantly different with KM group at P<0.05.

Table 4: Effects of ketamine alone or with xylazine or midazolam and in combinations dose to induce analgesia in rabbits

Groups	Time (minutes)			
	0	30	60	90
K (Control)	8.2±0.4	8.1 ±0.4	8.8 ± 0.8	8.5 ±0.3
KX	8.3± 0.7	9.8± 0.4 *a	8.8 ± 0.5	8.4 ±0.5
KM	8.8 ± 0.7	11.1±0.9 * a	10.5±0.5 * a	9.1±0.4 + #
KXM	8.8±0.6	12.2±0.7 * abc	11.7±0.7 * abc	11.4 ±0.6 * abc

Value are the main±SE for five rabbits/group. *: Significantly different with the time zero at same group P<0.05. +: Significantly different with the time 30 at same group P<0.05. #: Significantly different with the time 60 at same group P<0.05. a: Significantly different with K group at same time at P<0.05. b: Significantly different with KX group at same time at P<0.05. c: Significantly different with KM group at same time at P<0.05.

Table 5: Serum parameters to ketamine or with xylazine or midazolam and in combinations dose to induce analgesia in rabbits

Treated Groups	GPT (U/L)	GOT (U/L)	Glucose (mg/dL)
K (Control)	29.33 ± 0.95	38.87 ± 1.78	87.39 ± 2.66
KX	30.09 ± 0.89	39.67 ± 1.08	88.19 ± 1.96
KM	30.03 ± 0.72	39.17 ± 0.88	88.69 ± 1.36
KXM	29.05 ± 0.89	39.12 ± 0.93	89.09 ± 1.62

Value are the main±SE for five rabbits/group.

Discussion

Determination of sub-analgesic (sedative) dose of xylazine and midazolam in rabbits

Many articles have been published on drug combinations for induction of balanced anesthesia for human and animal medicine (10) such as ketamine with fentanyl (11), and ketamine with medetomidine (12), it has been demonstrated that these combinations of drugs acting on different receptors may produce super synergistic response. In this experiment, we used two analgesics, muscle relaxants with different mechanism of actions to determine the sedative and analgesic doses for each one alone in rabbits. The sedation was manifested by monitoring the animal after drug administration to calming signs as depression of central nervous system, dullness, ataxia, drooping of head and decrease of body activity (9), these signs had been very clear at a dose of 4 mg/kg of xylazine and midazolam each one alone but not very clear at lower doses for each one at 2 mg/kg IM in rabbits (dose dependent). While analgesic doses determined by an electrical stimulator device used to induce pain, then detected the analgesia induction and evaluate analgesic effect of xylazine or midazolam alone in rabbits. This device was used firstly by Al-Mashhadany to evaluate the analgesia by medetomidine in goats (6) and was also used to evaluate the analgesic effects of xylazine in chicks (13).

In this study was used an electrical stimulator device to evaluate the analgesic action of xylazine and midazolam and to detect the sedation symptoms with the best analgesic dose. The results indicate that xylazine and midazolam 4 mg/kg i.m, in rabbit relieve the pain sensation within the time periods 30-45 and 30-60 minutes after injection respectively, as dose-dependent response compared with time zero and with other times in the same group and with a dose 2 mg/kg. The results of xylazine were agreement with previous studies in rabbits (9), chicks (13) and horses (14). In addition, midazolam results were in agreement with previous studies in mice (15), chicks (16), rats (17) and rabbits (9). The sedative and analgesic effects of xylazine were due to activation of presynaptic alpha 2- adrenoceptors in the peripheral and central nervous system leading to a decrease of catecholamine release and turnover (7,8), but the sedative and skeletal muscle relaxant effects of midazolam results from high affinity to binding with GABA receptor in the CNS causing increased influx of potassium ions in to the neurons which leads to depression of brain, and sedative and hypnotic effects (9,15-18).

Assessment the effects of ketamine alone, ketamine with xylazine or midazolam, or all agents together on some physiological changes in rabbits

Balance anesthesia is induced by using multiple drugs in minimal doses to produce smooth induction and smooth recovery with minimum side effects. Using a combination of drugs with different mechanism of actions enhances the analgesic efficacy due to synergistic effects without

increasing the dose with little side effects compared with using individual medicines (19). Using ketamine as anesthetics is usually accompanied with significant side effects such as skeletal muscle rigidity, violent recovery in most species (20). The heart rate and respiratory rate were elevated significantly in K group at time 30 to 90 minutes after injection and return to normal value, while in KX and KM groups these parameters reduced significantly at the same time as above compared to other times, these results were in agreement with (20), they found the xylazine (alpha 2 agonist) and diazepam (GABA inducer) caused significantly decrease of cardiopulmonary activities when combined with ketamine but ketamine alone caused hyperactivity of cardio-pulmonary functions because ketamine can stimulate the central sympathetic outflow which in turn increases the heart and respiratory rates. In order to overcome these side effect, Ketamine must be combined with analgesics and muscle relaxants like xylazine and midazolam, because xylazine produces its effect by dual action, firstly, it has affinity to binding with pre-ganglionic alpha-2 receptors to reduce catecholamine release at nerve endings (21), secondly, it increases inhibitory neurotransmitters (glycine) within the spinal cord and in certain brain center (22). Since the respiratory and cardiac depression are not unique effects of using KX and KM but also occurs with other injectable anesthetics regiments in sheep (22), therefore, advisable to use oxygen therapy during anesthesia especially when using moderate or high doses of ketamine with midazolam (15). The best group results with mild effects for physiological functions was obtained with a sub-analgesic dose at 20, 2 and 2 mg/kg of mixture ketamine, xylazine and midazolam respectively. This treatment was safer than other groups because of no significant modifications in all times compared with time zero. These results agree with Al-Redah (22) who concluded the best mixture to be a combination of ketamine, midazolam and xylazine in sheep.

Assessment the anaesthetic effect (hypnosis) of ketamine alone, ketamine with xylazine or midazolam, or with all agents together on rabbits

In the hypnosis experiment the mixture of sub-analgesic dose of KXM group seemed to be the best group manifested a significant rapid induction with a long duration of action and recovery period compared with other groups by inducing balanced anesthesia (characterized by unconsciousness, good muscle relaxation, good loss of pain and hyporeflexia) in the rabbits with little unwanted effects, Therefore, these doses of mixture may be used in long surgical procedures in rabbits. These results agree with the findings in cats and dogs (23) due to the ketamine being a dissociative anesthetics by blocking the N-Methyl-D-Aspartate (N-MDA) receptor in the limbic system of the CNS causing a decline in the amount of calcium that entering into the neurons (4). When used with alpha-2 agonist or with GABA agonists at moderate or high doses, they will produce a balance anesthesia with prolonged

duration and recovery periods but may produce many side effects (3).

Evaluation the analgesic effects of Ketamine alone, ketamine with xylazine or midazolam, or all agents together on rabbits

In the present study we evaluated the analgesic effects of the interaction (synergism) between different drugs each producing individual actions by different mechanisms to produce super interaction as anti-nociceptive effects (3). In this trial an electrical stimulator was used to induce pain and estimate the analgesia of ketamine alone at 40 mg/kg i.m, or in combination with moderate or high doses of xylazine or midazolam at 4 mg/kg i.m for each one. In addition, combinations of ketamine at 20 mg/kg i.m with a mixture of sedative (sub-analgesic) doses at 2 mg/kg i.m of xylazine and midazolam were investigated to induce qualitative and quantitative effects in rabbits. The findings showed that significant analgesia effects were obtained at sub-analgesic dose of multi-drug mixture KXM group of rabbits to relieve nociception as a response to electrical stimulation via increase in delta voltage (an increase of pain threshold) compared with voltage at zero time and other groups at different times and persisted for more than 90 minutes after drugs administration, the results of ketamine with xylazine were in agreement with previous studies on rabbits (8) chicks (16), sheep (22) and with midazolam agree with other articles in rats (17) and rabbits (8) but not in agreement with Brown *et al.* (24) who used a small dosage of ketamine 15 mg/kg with midazolam 2 mg/kg in rabbits, that may have required higher doses of ketamine to produce analgesia. Serum GOT, GPT concentrations and glucose levels were near their normal values of rabbits, as reported elsewhere in Amin *et al.* (25) and there is evidently no significant liver or tissue damages between their combinations groups (depend on dose) in relation to serum GOT, GPT concentrations and glucose levels. This is another reason for utilizing this co-administration for enhance and prolong the narcosis in the rabbits.

We conclude in present study that a faster beginning and longer duration and recovery periods were achieved by sub-analgesic doses of KXM group when comparison with the other groups. This group KXM also appeared more safety in enhanced surgical procedures associated with excellent analgesics as a result of balance, reliable, and efficient anesthesia with minimum unwanted effects on cardio-pulmonary functions and other tissues when compared with other groups used in the rabbit model.

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Conflict of interest

No conflict.

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مقارنه بين إعطاء الكيتامين لوحده أو مع الزيلازين أو مع الميدازولام أو مع بعضهم لإحداث التخدير المتوازن في الأرانب

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الخلاصة

كان الهدف من هذه دراسة هو إحداث تخدير عام موزون والذي يتميز بفقدان منعكس وضع الجسم، وتسكين، ونقاهاة جيدين مع القليل من التأثيرات الجانبية عن طريق استخدام أدوية متنوعة في الية عملها وتأثيراتها وبجرع مختلفة في الأرانب. تم إعطاء من عقار الكيتامين مع عقار الزيلازين وعقار الميدازولام بالتعاقب وبجرع تحت السريرية ومقارنتها مع مجموعة السيطرة الموجبة التي عوملت فقط بعقار الكيتامين وبجرعه ٤٠ ملغم/كجم، ومع مجموعة الكيتامين - زيلازين عند ٤٠ و ٤ ملغم/كغم من وزن الجسم وعلى التوالي، ومع مجموعة الكيتامين - الميدازولام كذلك عند ٤٠ و ٤ ملغم/كغم على التوالي. أدى إعطاء الزيلازين وكذلك الميدازولام كل بمفرده وبجرعه ٤ و ٢ ملغم/كغم لكل منهما عن طريق الحقن بالعضلة إلى إحداث تسكين وبطريقة تعتمد على الجرعة من خلال الزيادة المعنوية في فولتية المحدثة للألم في الفترة ما بعد الحقن مقارنة بقيمته ما قبل الحقن. سببت الجرعات الواطئة في مجموعه مزيج الكيتامين مع الزيلازين و الميدازولام عند ٢٠ و ٢ و ٢ ملغم/كغم على التوالي إلى أحداث تخدير سلس ومتوازن مع قله في وقت بداية التخدير وإطالة معنويه في مدتا التخدير والإفاقة من دون أحداث اختلافات معنويه في المعايير الفسلجية الحيوية (معدل التنفس، معدل ضربات القلب، ودرجة حرارة المستقيم) وكذلك في بعض معايير الكيمياء الحياتية (أنزيم ناقله أمين الالنين وأنزيم ناقله أمين الاسبارتيت ومستوى الكلوكونز) مقارنة بالمجموعات الكيتامين لوحده و مجموعة الكيتامين مع الزيلازين ومجموعه الكيتامين مع الميدازولام. أشارت نتائج هذه الدراسة إلى إحداث تخدير عام متوازن تميز بنوم مريح مع تسكين جيد للألم من خلال إعطاء جرعات واطئة من مزيج كل من الكيتامين/الزيلازين/الميدازولام في الأرانب .