

## Evaluation of Midazolam and Ketamine Preceding by Xylazine as General Anesthesia in Rabbits

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### Summary

The present study was designed to evaluate the efficacy of use xylazine hydrochloride 5mg/kg BW as premedication and a mixture of midazolam and ketamine 3mg/kg BW, 40 mg/kg BW respectively. The effects of combination was estimated before injection drug as control and each 15 min until 90 min, on the induction of anesthesia, degree of analgesia, respiratory rate, body temperature and type of recovery. Ten local breed rabbits were used in this study; all animals were done surgical operation (splitting Achilles tenotomy) to evaluate surgical anaesthesia. The result of this combination is reflected good induction of anaesthesia and good analgesia to animals and smooth recovery with minor complications.

**Keywords:** general anesthesia, midazolam, ketamine, xylazine, rabbits.

### Introduction

General anaesthesia in rabbits can be induced by using a variety of drugs and techniques of injection. Combination of two drugs or more can be given to produce all the required features of general anaesthesia. The rabbit is widely used as a laboratory animal for experimental surgery (1). Anesthesia in Rabbits is very critical because rabbits are high risk anaesthetic patients, with a mortality risk 14 times higher than in dogs (2).

The margins of safety between anaesthetic and lethal doses in rabbits are less than those found in other animals and there is wide individual variation in response to anaesthetic agents (3 and 4). Combinations of several injectable drugs are used to produce most suitable general anesthesia in rabbits. Many investigators have studied the effects of different anaesthetic drugs in rabbits but there appears to be an increasing popularity of ketamine-based combinations for rabbit anaesthesia (5-7). When ketamine is used as a single anaesthetic agent it causes hyper tonus, poor muscle relaxation, persistent pain reflex responses and violent recovery from anaesthesia in many species (8). To counteract these undesirable side effects, various drugs such as xylazine, or other  $\alpha_2$ -agonist compound, have been used in combination with ketamine (1, 9 and 10), Ketamine combined with xylazine has been reported to produce good anaesthesia in the

rabbits (9, 11 and 12). But other researcher show that this companions is failed to achieve complete anaesthesia in rabbits (5 and 13). The benzodiazepines, is widely use in clinical anaesthesia, the main effects are sedation, hypnosis, centrally mediated muscle relaxation and anti-convulsive activity. Adding diazepam to this combination is safe in comparison with other techniques; it produces a relatively long recovery period (8 and 14). The duration of action of all benzodiazepines is strongly dependent on the route of the administration (15).

The objective of this study was to improve the general anaesthesia produce by combination of ketamine/ xylazine in rabbits.

### Materials and Methods

The study was conducted on 10 apparently healthy young rabbits of both equal sexes, there ages ranged from 8-10 months and weighing 0.7 - 1.5 kg. The rabbits were housed indoors at same condition. Previous to anesthesia and surgery, the animals had free access to water. Baseline data of respiratory rate and temperature were obtained prior to injection of any drugs. Rabbits were received xylazine as premedication at dose rate of 5mg/kg BW (VMD Belgium 2%). Five minutes later a mixture from midazolam (Duramed, 5 mg in 1 ml, AL- saad pharmaceuticals, Syria) and ketamine (Ketamine, 5%, Alsaad pharmaceuticals,

Syria) were used for induction of anesthesia at a dose rate of 3mg/kg and 40 mg/kg B.W., respectively. The doses of xylazine and ketamine were estimated according to (16). But midazolam dose was obtained by pilot study.

Experiments were conducted between 9 and 12 am. The rabbits were placed on a big operation table after the injection of pre-anaesthetic and were observed for the parameters. The time from the injection of pre-anaesthetic to the onset of signs of drowsiness was recorded once weakly.

The time from the injection of the midazolam- ketamine to the time when the animal was unable to attain sternal recumbency was recorded as a righting reflex. Status of the pedal reflex was recoded as intact or abolished at 3 minute intervals up to 15 minutes and each 15 minutes by applying pressure to finger and hind paw. Time of pedal reflex was recorded after loss of righting reflex. The time of loss of pedal reflex was considered as the time of onset of analgesia as mentioned by (17).

Respiratory rate and body temperature were measured prior to injection of any drug (zero minute), and then at 15, 30, 45, 60, 75 and 90 minutes post injection of pre-anaesthetic drug.

Body temperature was recorded, using a digital thermometer (Beurer Company), was put in mouth. Then, ten minutes after the injection of mixture of midazolam and ketamine, the animals were subjected to surgery which involved splitting tenotomy. If the animal responded to surgical incision, the depth of anaesthesia was considered.

The nature of recovery was observed from the time of reappearance of the reflex until complete return to normal position. The results were expressed as means (M)  $\pm$  stander error (SE). Parametric data were analyzed by one ways Analysis of Variance (ANOVA) continued with Least Significant Difference (L.S.D.), and  $p < 0.05$  was considered to be significant. Statistical Package for Social Sciences (SPSS) was used (18).

## Results and Discussion

The combination of xylazine as premedication and the use of a mixture of midazolam and ketamine in this protocol were providing a good general anesthesia to perform bilateral tenotomy in all rabbits. Induction occurred without excitation or apnea, it was smooth and not required additional dose to optimum anaesthesia. The righting reflex was lost within  $3.00 \pm 1.00$  minutes. The present mixture caused delay in down time and time to loss of righting reflex (5 and 19).

The combination was provided  $49 \pm 2.333$  minutes as anaesthetic time; the anaesthesia was optimum at 15 minutes after injection of the mixture and the pedal reflex was disappeared at this time. The increase in time of anaesthesia by this combination may be due to use of high dose of midazolam and synergistic inhibition effects of CNS mediated by effect of combination induced by deep sedative effect of xylazine and midazolam and anesthetic effects of ketamine.

The recovery was smooth free of convulsion, the return of pedal reflex at the end of anesthesia was marked as time of recovery but animal at this time still at lateral recumbency for  $10.00 \pm 2.00$  minutes, then the animal tries to raise head while remaining quiet for  $35.00 \pm 5.00$  minutes after this time the animal return to sternal position. The increase in the recovery time may be due to the sedative and hypnotic effects of high dose of midazolam. Midazolam was caused smooth recovery when use in combination with ketamine because its half-life longer than ketamine (20 and 21). Although midazolam has the shortest recovery profile compared with other benzodiazepines (15). The first 3 hours of termination of the anaesthesia was the most common time for rabbits die (1 and 2). For all that combination of xylazine, midazolam and ketamine was safe with a documented no death of any animal.

The respiratory rate was sharply decreased after the injection of midazolam and ketamine. All rabbits were showed tachypnea before induction, this result was similar to other researcher (1 and 9). Tachypnea may be ascribed to frightening and excitement of the

animal, this phenomena caused elevation in the respiratory rate when compared with normal  $139.6 \pm 3.373$ . In addition, there were significant differences with other time to the end of recovery (Table 1). All anaesthetic techniques commonly used in rabbit anaesthesia depress ventilation (5). Rabbits have a large abdominal cavity in relation to the thoracic cavity, and pressure from the intestinal mass may interfere with respiration during anaesthesia (22). Use xylazine 5mg /kg premedication have cause respiratory depression more than other  $\alpha_2$  agonist

drug (1, 16 and 23). Result agree with Kavosi, *et al.*, (17) demonstrated that using xylazine 5 mg / kg BW and ketamine 40 mg /kg BW combination causes decrease in respiratory rate in rabbits. In general; Respiratory rate alone is not induction of decreased arterial oxygen tension. Orr *et al.*, (5), whom to advised administration oxygen during general anaesthesia. In addition, midazolam causes bradypnea when associated with ketamine because this drug depresses the respiratory centers of the brain (24).

**Table, 1: Effect of general anesthesia regime on some clinical parameters in (10) rabbits**

parameter	Time minutes						
	zero	15	30	45	60	75	90
Respiratory rate	139.6±	30.5±	24.5±	23.9±	24±	30.5±	60.7±
Breath/minute	3.373	0.957	0.401	0.233	0.149	0.654	0.257
	A	C	D	D	D	C	B
Body temperature (°C)	38.75±	38.3±	37.89±	37.3±	36.6±	36.27±	37.2±
	0.108	0.114	0.122	0.147	0.180	0.152	0.123
	A	A	B	C	D	D	C

Different in the capital letters refers to significant differences ( $P < 0.05$ ) between time.

Body temperature was recording from mouth of animal. Its essay compared with measurement with rectum because the animal is young and difficult put thermometer in rectum and repeated measurement causes injury to animals.

Temperature was show significant decrease at the level of  $P < 0.05$  after anesthesia, it was continues decrease until 75 minutes than increase in 90 minutes but stall below normal.

General anaesthesia was causes decrease in body temperature due to reduction in metabolic rate and limited movement of animal (25). But Wyatt *et al.* (26) did not find any significant changes in body temperature after ketamine-xylazine administration in rabbit. However' mild hypothermia in rabbits is improves survival and cardiac systematic function and protects lung from injury (27). In conclusion the adding of midazolam at the dose 3 mg / kg to the ketamine xylazine which improve the combination in the type of induction, time of anaesthesia, recovery and little effect on clinical parameter.

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### تقييم التخدير العام بحقن مزيج من الميدازولام والكيثامين المسبوق بالزايلازين في الأرانب

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#### الخلاصة

تم تصميم هذه الدراسة لتقييم فعالية استخدام زيلازين هيدروكلوريد 5ملغ / كغم من وزن الجسم كعلاج تمهيدي واحداث التخدير بواسطة خليط من ميدازولام والكيثامين 3 ملغ / كغم و 40 ملغ / كغم من وزن الجسم على التوالي. تم تسجيل تأثيرات المزيج قبل حقن ادوية التخدير كسيطرة وكل 15 دقيقة حتى 90 دقيقة على احداث التخدير، ودرجة ازالة الالم، معدل التنفس، درجة حرارة الجسم ونوعية الافاقية. استخدمت عشر ارانب من السلالة المحلية في هذه الدراسة، اجريت عملية جراحية لجميع الحيوانات لتقييم التخدير الجراحي. اظهرت النتائج ان استخدام هذا المزيج احدث تخدير جيد وفترة التخدير الجراحي جيدة لإجراء عملية جراحية في وتر (بضع الوتر) للحيوانات وكانت الافاقية سلسلة مع قليل من المضاعفات.

الكلمات المفتاحية: التخدير العام, الميدازولام, الكيثامين, الزايلازين, الارانب.