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Evaluation of Two General Anesthetic Regimes by Use Xylazine and Ketamine with atropine and diazepam in Rabbits

تقيم نظامين للتخدير العام باستخدام الزايلازين والكيتامين مع الاتروبين والديازيبم في الارانب

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SUMMARY

The present study was assigned to evaluate and compare two regimes of general anesthesia in rabbits. Twelve adult local breed rabbits from both sexes weighing (1.1-1.6)Kg. were divided equally into two groups each group consisted of six animals. Group(A) was injected intramuscularly by atropine1% at a dose 0.5mg/kg B.W as premedication, after 10min. the animals were injected xylazine 2% and ketamine hydrochloride 10% at a dose of 10 mg/kg, 50mg/kg B.W, respectively. Group(B) were injected intramuscularly by diazepam 10% at a dose 1mg/kg B.W. as premedication, after 10min. the animals were injected as same in group (A). The results of the physiological parameters of the self control at the period of zero time concerning heart rate, respiratory rate and rectal body temperature in group(A) were 147.3±0.577beats/minute; 130±0.577 breath/minute; 38.1±0.577 ºC respectively, while in group(B) were 151.6±0.57 beats/minute; 153.3±0.57 breath/minute; 38±0.57 ºC respectively. The results of physiological parameters at periods 10, 20, 35, 50, 65, 80, and 95minutes in group(A) were 154.1±5.77; 144.6±0.577; 128±0.577; 132.2±0.64; 128±0.577; 124.1±0.577; 132.6±0.577 beats/minute; 47.8±0.577; 47.6±0.577; 41.6±0.577; 39.3±0.577; 41.3±0.577; 39 ±0.577; 47±0.577 breath/minute; 39±0.577; 38.9±0.577; 38.5±0.578; 38.1±0.577; 37.8 ±0.577; 37.5±0.577; 37.2±0.577 ºC, while in group(B) were 157.5±0.57; 150±0.57; 150.6±0.57; 153.3±0.57; 153.8±0.57; 151.7±0.33; 152±0.57 beats/minute; 54±0.57; 49±0.57; 43.3±0.57; 42.3±1.73; 42.8±2.3; 45.6±0.57; 47.6±0.57 breath/minute; 38.8±0.57; 38±0.57; 37.6±0.57; 36.6±0.58; 36.5±0.57; 35.9±0.57; 35.9±1.15 ºC. The results of biochemical tests of GPT and GOT at zero time (self control) in group(A) were 53.1±0.577; 120.6±0.577 U/L, while in group(B) were 51.1±0.57; 118.8±0.57 U/L respectively, and the results at periods 20, 50, 95minutes and 24hours in group(A) were 44.1±0.577; 47.6±0.577; 65.1±1.186; 78.5±0.577 U/L, 109.5±0.577; 96.6±3.52; 109.3±1.154; 141±0.577, while in group(B) were 45.5±0.57; 42.1±0.57; 48±0.57; 69.1±0.57 U/L, 119±0.57; 111±0.57; 110±1.73; 139.8±0.57 U/L, respectively. The conclusion of this study investigate that the induction time, surgical time and recovery time in group(A) and group(B) were 5.8±0.577; 5.1±1.15; 56.6±0.577; 51.5±0.577; 71.6±0.577; 95.3±1.15minutes respectively in which the surgical time was enough for the most of surgical interference, while the induction time and recovery time were smooth in both group when comparison with another anesthetic regimes. From our results it may concluded that use of atropine with xylazine and ketamine exceptional from use diazepam with xylazine and ketamine.

المستخلص

صممت الدراسة الحالية لتقييم ومقارنة نظامين من التخدير العام في الارانب. استخدمت اثنى عشر ارنباً من السلالة المحلية من كلا الجنسين وبوزن يتراوح بين 1.1 الى 1.6 كغم. قسمت الحيوانات بالتساوي الى مجموعتين كل مجموعة تضم ستة حيوانات. المجموعة (A) حقنت عضليا بالاتروبين بتركيز 1% وبجرعة 0.5 ملغم / كغم من وزن الجسم كممهد للتخدير، حقنت الحيوانات بعد 10 دقائق بالزايلازين بتركيز 2% والكيتامين هايدروكلورايد بتركيز 10% وبجرعة 10ملغم /كغم من

وزن الجسم و50 ملغم/كغم من وزن الجسم على التوالي. حقنت المجموعة (B) عضليا بالديازيبام بتركيز 10% وبجرعة 1ملغم/كغم من وزن الجسم كممهد للتخدير وحقنت الحيوانات بعد 10 دقائق كما في المجموعة (A). وكانت نتائج المعايير الفسلجية لمجموعة السيطرة (A) (وقت الصفر) لضربات القلب ومعدل التنفس وحرارة المستقيم 147.3 ± 0.577 دقة/دقيقة، 130± 0.577 نفس/دقيقة ،38.1± 0.577مº على التوالي، بينما مجوعة السيطرة(B)(وقت الصفر) كانت 151.6± 0.57 دقة/الدقيقة ،153.3± 0.57 نفس/دقيقة ،38± 0.57 مº على التوالي. وكانت نتائج المعايير الفسلجية في الفترات الزمنية 10،20 ، 35 ،50، 80 و95 دقائق في المجموعة (A) (151.1±0.577، 144.6±0.577، 128±0.577، 123.2±0.64، 128±0.577، 124.1±0.577، 132.6±0.577) دقة/الدقيقة ، (47.8±0.577، 47.6±0.577، 41.6±0.577، 39.3±0.577، 41.3±0.577، 39±0.577، 47±0.577) نفس/دقيقة، (39± 0.577، 38.9±0.578، 38.5±0.577، 38.1±0.577، 37.8±0.577، 37.5±0.577، 37.2±0.577)مº بينما المجموعة(B) (157.5±0.57، 150±0.57، 150.6±0.57، 153.3±0.57، 153.8±0.57، 151±0.33، 152±0.57) دقة/الدقيقة، (54±0.57، 49±0.57، 43.3±0.57، 42.3±1.73، 42.8±2.3، 45.6±0.57، 47.6±0.57) نفس/دقيقة، (38.8±0.57، 38±0.57، 37.6±0.57، 36.6±0.58، 36.5±0.57، 35.9±0.57، 35.9±1.15) مº على التوالي. وكانت نتائج الفحوصات الكيمياحيوية لانزيمات الكبد(جاما جلوتامايل ترانسفيرازوكلوتاميك و بايروفيك ترانساميناز) لمجموعة السيطرة (A) (وقت الصفر) (GPT) و (GOT) (53.1±0.577، 120.6±0.577) U/L على التوالي بينما مجموعة السيطرة (B) (وقت الصفر) كانت 51.1±0.57، 118.8±0.57 U/L على التوالي. وكانت نتائج الفحوصات الكيمياحيوية لانزيمات الكبد في الفترات الزمنية 20، 50، 95 دقيقة و24 ساعة في المجموعة (A) (44.1±0.577، 47.6±0.577، 65.1±1.186، 78.5±0.577 و 109.5±0.577، 96.6±3.52، 109.3±1.154، 141±0.577) U/L على التوالي. بينما المجوعة (B) (45.5±0.57، 42.1±0.57، 48±0.57، 69.1±0.57 و 119±0.57، 111±0.57، 110±1.73، 139.8±0.57) U/L على التوالي. وقد استنتجت هذه الدراسة الاحداث، وقت التداخل الجراحي ووقت الافاقة في المجموعة (A) والمجموعة (B) كانت (5.8±0.577، 5.1±1.15، 56.6±0.577، 51.5±0.577، 71.6±0.577، 95.3±1.15) دقيقة على التوالي وان هذا الوقت هو كافي لمعظم التداخلات الجراحة اما الاحداث والافاقة فكانت سلسة مقارنة بأنظمة تخدير اخرى. من خلال النتائج نستنتج ان استخدام الاتروبين مع الزايلازين والكيتامين افضل من استخدام الديازيبم مع الزايلازين والكيتامين.

INTRODUCTION

Rabbits are often considered as difficult in relation to anesthesia. This probably relates to the fact that the dosage needed to induce anesthesia and those producing toxic effect are close (1). So many complications still arise when anaesthetizing rabbits and there are several possible reasons. The margins of safety between anesthetic and lethal doses are less than those found in other animals and there is wide individual variation in response to anesthetic and ancillary agents. The rabbit also has strong reflexes which are difficult to suppress during general anesthesia other problems may occur because of the relatively small diameter of the respiratory tract and difficulty with tracheal intubation due to the small glottis being hidden by the base of the tongue (2).

The use of anticholinergic agents are controversial and their efficacy varies greatly with species (3,8). They provide beneficial effects by preventing bradycardia and accumulation of salivary secretions that can occur during anesthesia and surgical manipulations. They are often recommended in studies using laboratory animals although there is limited information on efficacy in these species (3,8). Prevention of bradycardia is particularly important during lengthy surgical and experimental procedures involving these laboratory animals Alpha-2-adrenergic agents, such as xylazine, which are a common component of injectable anesthetic combinations in laboratory animals, produce severe depression of heart rate in rodents and rabbits (5,8).

The aim of the present study was to evaluate and compare between two anesthetic regime, using injectable anesthesia (Atropine, Xylazine and Ketamine) and(Diazepam, Xylazine and Ketamine) in rabbits .

MATERIALS AND METHODS

Twelve adult local breed rabbits from both sexes weighing (1.1-1.6)Kg. were divided equally into two groups they were housed indoor to accommodate the place of experiments. The following physiological parameters (heart rate, respiratory rate and rectal body temperature) were recorded before the intramuscular injection of the drugs for each group (zero time) as a self group.

Group (A) were injected intramuscularly by :Atropine 1% (Norvel, India) 0.5 mg/kg B.W as premedication, after 10min. Xylazine 2% (alfasan, Holland) and Ketamine hydrochloride 10% (alfasan, Holland) at a dose of 10 mg/kg, 50 mg/kg B.W, respectively.

Group (B) were injected intramuscularly by: Diazepam (Hameln, Germany) 1mg/kg B.W. as premedication, after 10min. the animals were injected as same in group (A). The induction time recorded from the time of injection of Ketamine to the complete loses of consciousness.

The same physiological parameters was taken as mention in control after intramuscular injection of the drugs at periods of (10, 20, 35, 50, 65, 80 and 95) min.

The surgical anesthesia recorded from the time of complete lose of sensation until the rabbit response to external stimuli, recovery time were also recorded from the time of response to the external stimuli until returned to its normal condition (complete consciousness). Pinching by artery forceps was used to determine the analgesic effect of the anesthetic combination and make sure for the entrance to the surgical stage, in addition to that pricking by needle test were also used.

Bio-chemical values were measured during general anesthesia: GOT and GPT (Kit from bioMerieux®sa - France) Blood samples were collected via heart puncture and put in tubes without anticoagulan at the zero time as control and periods (20, 50, 95) minutes and 24 hours.

The complete Randomized Design (CRD) within the SAS (2001) program was used to the effect of difference treatments in study traits, and the Least Significant Differences (LSD) test was used to the comparison between means. The one–way ANOVA with replication was applied to the data of and $p<0.05$ was considered to be significant (9).

RESULTS AND DISCUSSION

The induction time, surgical anesthesia and recovery time were summarized in table (1) as the following:

Table(1): Mean values (±Standard Error) of subjective scores qualifying anesthesia (induction time, surgical anesthesia and recovery time)/minute

Time / Group	Induction time	Surgical time	Recovery time
Group A n= 6	5.8 ± 0.577	56.6 ± 0.577	71.6 ± 0.577
LSD	1.77	1.77	2.177
*P<0.05			
Group B n= 6	5.1 ± 1.15	51.5 ± 0.577	95.3 ± 1.15
LSD	3.24	2.17	2.99
*P<0.05			

The induction time lasted for 5.8±0.577 minutes and 5.1±1.15 minutes for group A and B respectively, while surgical time and recovery time for group A were 56.6±0.577 minutes and 71.6±0.577 minutes while group B were 51.5±0.577 minutes and 95.3±1.15 minutes respectively as in table(1).

The analgesic effect of anesthetic drugs combination in both groups were determine by scratched by artery forceps, in order to confirm for the entrance to the surgical stage, generally all animals not response to these test.

Results of table(1) were highly significant changes between two groups.The results of surgical anesthesia in group (A) was (56.6±0.577) and in group (B) was (51.5±0.577) that agree with (10).

In this study showed that the surgical period was enough for the most surgical interference in both groups.

The recovery period of both anesthetic regimes were smooth when comparison with other anesthetic regimes (11). The recovery time in group (A) was (71.6±0.577) that agree with (12), while in group (B) was (95.3±1.15) that agree with (2).

Results of physiological parameters of heart rate, respiratory rate and rectal body temperature were summarized in tables (2,3 and 4) respectively as the following:

Table (2): Heart rate before, during and after general anesthesia administration in rabbits (beats/minute "bm")

Time / Group	0	10	20	35	50	65	80	95
Group A n= 6	147.3 ± 0.577 A	154.1 ± 0.577 B	144.6 ± 0.577 C	128 ± 0.577 D	123.2 ± 0.64 D	128 ± 0.577 D	124.1 ± 0.577 D	132.6 ± 0.577 C
LSD	1.75	* (P<0.05)						
Time / Group	0	10	20	35	50	65	80	95
Group B n= 6	151.6 ± 0.57 A	157.5 ± 0.57 B	150 ± 0.57 A	150.6 ± 0.57 A	153.3 ± 0.57 B	153.8 ± 0.57 B	151.7 ± 0.33 A	152 ± 0.57 A
LSD	1.657	*(P<0.05)						

Means having different letters (Capital Letters among treatment/column) are significantly different

0= Self control.

The heart rate significantly changed at all the times from (10-95) minutes in group A compare with self control (zero time), while in group B the times(10, 50 and 65) minutes were significantly changed, and (20, 35, 80 and 95) minutes unchanged compare with self control (zero time) as in table(2).

Olson,1993;etal demonstrate that atropine causes a brief period of elevated heart rate in unanesthetized rats and only weakly controls the heart rate depression in ketamine: xylazine or ketamine: detomidine anesthetized rats. Conversely glycopyrrolate was more effective in preventing the heart rate depression in anesthetized rats. This may be attributed to a reduced rate of hydrolytic degradation and a higher anticholinergic activity in rats.

Atropine sulfate in rabbits did not elevate the heart rate at either dosage used.

These rabbits were outbred stock from a single supplier with a high level of serum atropine esterase in 20% of the animals.

The result of heart rate at zero time (self control) agree with (14) who reported that the normal values of heart rate which ranged between 130 -325 beats/minutes, while after 20 min. from anesthetic combination a significant decrease in heart rate could be noticed in group (A) this could be due to bradycardiac effect of xylazine (1 5) and these results were also agreed with (16).

Table (3): Respiratory rate before, during and after general anesthesia administration in rabbits (breath/minute "bpm")

Time / Group	0	10	20	35	50	65	80	95
Group A n= 6	130 ± 0.577 A	47.8 ± 0.577 B	47.6 ± 0.577 B	41.6 ± 0.577 B	39.3 ± 0.577 B	41.3 ± 0.577 B	39 ± 0.577 B	47 ± 0.577 B
LSD	1.731	*(P<0.05)						
Time / Group	0	10	20	35	50	65	80	95
Group B n= 6	153.3 ± 0.57 A	54 ± 0.57 B	49 ± 0.57 B	43.3 ± 0.57 B	42.3 ± 1.73 B	42.8 ± 2.3 B	45.6 ± 0.57 B	47.6 ± 0.57 B
LSD	3.4	*(P>0.05)						

Means having different letters (Capital Letters among treatment/column) are significantly different
0= Self control.

The respiratory rate significantly decreased at (10) minutes until (95) minutes in group A and group B respectively as in table(3).

Respiratory rate values which are taken before administration of general anesthesia was not completely in accordance with the results of past works(17,18); and this could be due to many reasons concerning the animals themselves such as: breed, age, sex, individual variations and due to ambient conditions occurred during each experiment.

Two groups(A and B) suffered respiratory rate depression that persisted till recovery or shortly after recovery, this result in line with(1) which found that the rate of respiration depends on the used anesthetic.

Decreased respiratory effort due to the effects of the anesthetic agents can lead to passive collapse of diseased airways the decline of respiratory rate in rabbits had been showed previously by(19).

Generally the decrease of respiratory and heart rate probably was due to xylazine component of the mixture, this agree with other workers (19).

Table (4): Rectal body temperature before, during and after general anesthesia administration in rabbits (ºC)

Time / Group	0	10	20	35	50	65	80	95
Group A n= 6	38.1 ± 0.577 A	39 ± 0.577 A	38.9 ± 0.578 A	38.5 ± 0.577 A	38.1 ± 0.577 A	37.8 ± 0.577 A	37.5 ± 0.577 A	37.2 ± 0.577 A
LSD	1.732	*(P<0.05)						
Time / Group	0	10	20	35	50	65	80	95
Group B n= 6	38 ± 0.57 A	38.8 ± 0.57 A	38 ± 0.57 A	37.6 ± 0.57 A	36.6 ± 0.58 A	36.5 ± 0.57 A	35.9 ± 0.57 A	35.9 ± 1.15 A
LSD	3.4	*(P<0.05)						

Means having different letters (Capital Letters among treatment/column) are significantly different
0= Self control.

Results of rectal body temperature were no significant changes compare with self control (zero time) in group A and B as in table (4).

Normal body temperature is regulated by a center in the hypothalamus, which ensures a balance between heat loss and heat production (20). When body temperature becomes high, the temperature regulatory system, which is governed by a nervous feedback mechanism, dilates the blood vessels and increases sweating to reduce the temperature. When the body temperature becomes low, hypothalamus protects the internal temperature by vasoconstriction (21).

The reason of hypothermia during anesthesia could be due to release of monoamines in the anterior hypothalamus, since the noradrenaline lowers and 5-hydroxytryptamine (5-HT) raises body temperature, when acting on the anterior hypothalamus. It is well known that anesthetics produce a fall in body temperature; this fall in temperature was explained by release of noradrenaline; also release of 5-HT was not excluded but the action of noradrenaline was thought to be predominate (22).

The results of biochemical test of Glutamic -Pyruvic Transaminase activity GPT (U/L), and Glutamic -Oxaloacetic Transaminase activity GOT (U/L) were mentioned respectively in tables (5 and 6).

Table (5): Mean values (±Standaed Error) of GPT level (U/L)

Time / Group	Time/minutes				Time/hrs
	0	20	50	95	24
Group A n= 6	53.1 ± 0.577 A	44.1 ± 0.577 B	47.6 ± 0.577 B	65.1 ± 1.186 C	78.5 ± 0.577 C
LSD	2.33	*(P<0.05)			
Time / Group	0	20	50	95	24
Group B n= 6	51.1 ± 0.57 A	45.5 ± 0.57 B	42.1 ± 0.57 B	48 ± 0.57 AB	69.1 ± 0.57 AB
LSD	1.81	*(P<0.05)			

Means having different letters (Capital Letters among treatment/column) are significantly different
0= Self control.

Significant decrease were recorded at (20 and 50) minutes from injection of anesthetic combination in comparison with self control (zero time) while increased in (95) minutes and (24) hours in both groups as in table (5).

GPT is a specific cytosol liver enzyme, and its increase in the blood plasma is specific for changes in the liver, but GPT activity in pigs, horses, goats, sheep and cattle is not specific for the liver, in order to have a diagnostic significance (23). GPT activity is significantly elevated during liver damage caused by drug toxicity and infection while the total protein level remains constant (24). Increase in the plasma GPT values during anesthesia. The increase in GPT values could probably be due to alteration in cell membrane permeability which may permit these enzymes to leak from cells with intact membrane (25).

Table (6): Mean values (±Standard Error) of GOT level (U/L)

Time / Group	Time/minutes				Time/hrs
	0	20	50	95	24
Group A n= 6	120.6 ± 0.577 A	109.5 ± 0.577 B	96.6 ± 3.52 C	109.3 ± 1.154 B	141 ± 0.577 D
LSD	5.4	*(P<0.05)			
Time / Group	0	20	50	95	24
Group B n= 6	118.8 ± 0.57 A	119 ± 0.57 A	111 ± 0.57 B	110 ± 1.73 B	139.8 ± 0.57 C
LSD	2.93	*(P>0.05)			

Means having different letters (Capital Letters among treatment/column) are significantly different

0= Self control.

The level of GOT enzyme showed variable changes start after (20 and 95) minutes but after (24) hours the level of GOT was highly increase significantly in group A, while in group B the level of GOT enzyme showed variable changes start after (50 and 95) minutes but after (24) hours the level of GOT was significantly increased as in table (6).GOT is present in most tissue and increases with muscle injury especially cardiac muscle, as well as hepatocellular injury, also present in kidney, pancreas and erythrocytes.

Thus GOT assay should be run in conjunction with other enzymes assay, especially GPT when evaluating liver function. Increased GPT with normal to mildly elevated GOT may indicate reversible liver damage. Marked elevation in GPT andGOT indicate hepatocellular necrosis. Increased GOT with normal GPT may indicate that the source of GOT is not the liver (26 and 27).Thus GOT has also been used as a cardiac marker (28). From our results it may concluded that use of atropine with xylazine and ketamine exceptional from use diazepam with xylazine and ketamine.

References

1- Praag, E. V. (2003). Anesthesia of the rabbits. Part II: Intra-anesthetic period, and its monitoring. Surgery in Rabbits -Anesthesia.P1-7.From MediRabbit.

2- Peeters, M. E.; Gil, D.; Teske, E.; Eyzenbach, V.; Brom, W. E.; Lumeij, J. T. and Vries, H. W. (1988). Four methods for general anaesthesia in the rabbit: a comparative study. Lab Anim. 22: 355-360.

3- Short, C.E.(1987). Anticholinergics. In: Short CE, ed. Veterinary Anesthesia. Baltimore: Williams & Wilkins: 8-15.

4- Lumb, W.V. and Jones, E.W.(1984). Veterinary Anesthesia. Philadelphia: Lea & Febiger.

5- Wixson, S.K.; White, W.J.; Hughes, H.C.; Lang, C.M. and Marshall, W.K. A.(1987). Comparison of pentobarbital, fentanyl, ketaminexylazine and ketamine-diazepam anesthesia in adult male rats. Lab Anim Sci. 37: 726-735.

6- Green, C.J.; Knight, J.; Precious, S. and Simpkin, S.(1981). Ketamine alone and combined with diazepam or xylazine in laboratory animals: a 10 year experience. Lab Anim . 15:163-170.

7- Harvey, R.C. and Walberg, J.(1987). Special considerations for anesthesia and analgesia in research animals. In: Short CE, ed. Principles and Practice of Veterinary Anesthesia. Baltimore: Williams & Wilkins. 380-392.

8- Eisele, P.H.(1990). Anesthesia for laboratory animals: practical considerations and techniques. In: Rollin BE, Kesel ML, eds. The Experimental Animal in Biomedical Research. Boca Raton: CRC Press. 275-317.

9- SAS (2001). The SAS system for windows v6.12.

10- Omar R A (2009). Efficiency of some analgesics mixed with general anaesthesia and their influence on bone healing in rabbits. Ph.D. Thesis- Pharma Veterinary Med coll Uni Bagh .1-191.

11- Holdcroft MB and HallG M (1978). Heat loss during anaesthesia. British J Anaesthesia. 50(2): 157-164.

12- Eesa,M.J.; Omar,R.A. and Mohammed Nazhat,H.H. (2010). Evaluation of general anesthesia by using Propionylpromazine, Xylazine and Ketamine in rabbits. Iraqi J. Vet. Med. 34(1): 208-217.

13- Olson,M.E.; Vizzutti,D.W. and Cox,A.K.(1993). The Parasympatholytic Effects of Atropine Sulfate and Glycopyrrolate in Rats and Rabbits. Can. J. Vet. Res. 57: 254-258.

14- Quesenberry KE (1995). Rabbits. Section 12. In: Saunders manual of Small animal practice. Edited by: Birchard S J and Sberding RG . WB Saunders Company.Pp:1345-1348.

15- Tabaru H Ogawa H Otsuka H and Ito K (1987). Effect of xylazine on arterial blood pressure, heart rate and electrodi agram in spinal dogs. Jpn J Vet Sci . 49(2):391-394.

16 -Oda S Tsuda T and Sasaki Y (1994). Adrenergic effects on pancreatic glucagonsand insulin secretion in rabbits. Tohoku J Agricu \ Rese: 45(1-2):29-35.

17-Linn, J. M. (2000). Rabbits: Biology. In: Laboratory Animal Medicine and Science - Series II. produced by the Health Sciences Center for Educational Resources, Universityof Washington. USA: 1-12.

18- Hedenqvist, P. (2008). Anaesthesia and analgesia for surgery in rabbits and rats:A comparison of the effects of different compounds. PhD thesis from the department of physiology and pharmacology, Karolinska institute, Stockholm, Sweden. P12.

19- Borkowski, G. L.; Danneman, P. J.; Russel, G. B. and Lang, C. M. (1990). An evaluation of three intravenousanesthetic regimens in New Zealand rabbits. Lab Anim Sci.; 40(3):270-6 (Medline).

20- Akindele, A. J. and Adeyemi, O. O. (2007). Antipyretic activity by Byrsocarpus coccineusschum and thonn. (Connaraceae). Intern .ournal of pharm; 3(4): 357-361.

21- Khan, A.; Rahman, M., and Islam, S. (2008). Antipyretic Activity of Peperomia pellucida Leaves in Rabbit. Turk. J. Biol., 32: 37-41.

22- Fahim, I.; Ismail, M., and Osman, O. H. (1973).Role of 5 hydroxy tryptamine in ketamine-induced hypothermia in the rat. Br. J .Pharmac., 48: 570-576.

23- Kramer, J. W. and Hoffman, W. E. (1997). Clinical Enzymology. In: Clinical Biochemistry of Domestic Animals. (Kaneko, J. J., J. W. Harvey, M. L. Bruss, Eds.). Academic Press. San Diego, London, Boston, New York, Sydney, Tokyo, Toronto, Pp: 303-325.

24- Dufour, D. R.; Lott, J. A.; Nolte, F. S.; Gretch, D. R.; Koff, R. S. and Seeff, L. B.(2000). Diagnosis and monitoring of hepatic injury recommendations for use of laboratory tests in screening, diagnosis, and monitoring.Clin. Chem., 46: P:2050-2068.

25- Tiwari, S. K.; Kumar, A. and Parikh, P. V. (1999)."Clinico-surgical effects of epidural xylazine and detomidine with or without local anaesthesia in buffaloes," Indian J. of Vet. Surg., 76(2):108–111.

26- Hamel, (2003).Clinical Chemistry. In: Tighe, M. M. and Brown, M. (eds.). Mosby's Comprehensive Review for Veterinary Technicians. 2nd ed., Mosby, Pp:98-99.

27- Weiss, D. J. (2004).Tests for evaluation of liver disease, Section VI, Liver and Muscle. In: (Ed.) Cowell, R. L., Clinical pathology secrets, Elsevier Mosby, Pp:168-172.

28- Nyblom, H.; Björnsson, E.; Simren, M.; Aldenborg, F.; Almer, S. and Olsson, R. (2006).The AST/ALT ratio as an indicator of cirrhosis in patients with PBC. Liver Int., 26(7): 840-845.