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EFFECT OF USING KETOPROFEN AND PHENOBARBITAL SODIUM AS PREEMETIVE AGENTS WITH TOTAL INTRAVENOUS ANESTHESIA (TIVA) INFUSION ON SOME BLOOD PARAMETERS AND LIVER ENZYMES IN DONKEYS: PART I

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ABSTRACT
The purpose of this study was to compare experimentally the effect of using Ketoprofen or Phenobarbital sodium injection as a preemetive agents with total intravenous anesthesia (TIVA) infusion of Xylazine- ketamine mixture as a general anesthetic protocol in donkeys. The study was designed using 10 clinically healthy male donkeys weighing (81.20 ± 6.36) kg. and aged (9.40 ±1.12) months; they were divided randomly into two groups: First group (n=5): was given 2.2 mg/kg B. Wt. Ketoprofen (Isofenal®) IM as preemptive agent followed by I.M injection of 0.5 mg/kg B. Wt. Xylazine and after 10 minutes induction done by I.V injection of 2.2 mg/kg B. Wt. Ketamine then maintenance done by TIVA infusion of 0.8 ml Xylazine:100ml Normal saline pluse1ml ketamine : 100 ml normal saline (as a mixture)for one hour . Second group (n=5): was given 20 mg/kg B. Wt. Phenobarbital IV as preanesthetic (Smith, 2008) followed by I.M injection of 0.5 mg/kg B. Wt. Xylazine and after 10 minutes induction was done by I.V injection of 2.2 mg/kg B. Wt. Ketamine then maintenance done by TIVA infusion of 0.8 ml Xylazine:100ml Normal saline pluse1ml ketamine: 100 ml normal saline (as a mixture) for one hour. Results concerning hematological parameters showed significant changes within each group and between groups in (R.B.Cs; P.C.V; Hb, and W.B.Cs). In both protocols they tend to decrease mostly after time 20 minutes and the decrease in P2 was most obvious. While liver function tests (livers enzyme) showed a significant increase within each group but among these two protocols the changes were non-significant.

KEYWORDS: Ketoprofen, Phenobarbiton sodium, blood parameters, liver enzymes.

INTRODUCTION

Equine is one of the most challenging species to anesthetize because of its anatomical difficulties with predispose to major complications before, during and after anesthesia in addition to that it is well known risk of death comes with any equine anesthesia[1,2]. Pre-emptive analgesia is an antinociceptive treatment that starts before surgery and prevents establishment of altered processing of afferent input following incisional and inflammatory injuries, which amplifies postoperative pain[3, 4]**.** Generally, veterinary clinical hematology is a useful diagnostic tool in the practice of veterinary medicine[5] for determination of the main hematological and serum biochemical parameters of animals which helps veterinarians to confirm clinical diagnosis, estimate the severity of cases, administer appropriate treatment, and evaluate treatment outcomes[6-8]**.** In anesthesiology hematological values play a vital role to ensure optimum patient safety, certain core standards of monitoring which should be used before, during anaesthesia and recovery. These parameters provide information that facilitates early recognition and management of critical incidents[9]**.** So the aim of this study was to know if these preemptive agents affect or not on some blood parameters before, during and after general anesthesia.

MATERIALS & METHODS

This study took-place at the teaching and Research farm of the Veterinary medicine Collage- (Abu-Ghareb), Baghdad University by using ten clinically healthy male donkeys weighing (81.20 ±6.36) kg and aged (9.40 ±1.12) months. They were divided randomly into two groups: First group (n=5) (P1): was given 2.2 mg/kg B. Wt. Ketoprofen (Isofenal®) IM as preanesthetic followed by I.M injection of 0.5mg/kg B.Wt. Xylazine and after 10minutes induction done by I.V injection of 2.2 mg/kg B. Wt. Ketamine then maintenance done by TIVA infusion of 0.8 ml Xylazine: 100ml Normal saline pluse1ml ketamine: 100 ml normal saline (as a mixture) for one hour. While Second group (n=5) (P2**)**: was given 20 mg/kg B. Wt. Phenobarbital IV as pre-anesthetic followed by I.M injection of 0.5 mg/kg B. Wt. Xylazine and after 10 minutes induction was done by I.V injection of 2.2 mg/kg B. Wt. Ketamine then maintenance done by TIVA infusion of 0.8ml Xylazine: 100ml Normal saline pluse1ml ketamine:100 ml normal saline (as a mixture)for one hour.

Donkeys were housed in the animal's barn belongs to animal's farm of Veterinary Medicine College/ Baghdad University. Throughout the study they were maintained in individual cages under controlled normal environment including climate, management and feeding for at least 15 days before initiation of the study for the observation and

adaptation. Donkeys were dewormed with ivermectin in a dose of 0.2 mg/ kg.B.w. in the lateral mid- line of the neck at least 14days before starting experiment[10] Prior to initiate the experiment (application any one of anesthetic protocols or surgical operation) the administration of any medication was stopped; donkeys were fasted and water withdrawn for 12 hours[1].The donkeys were examined before administration of anesthetic agents which have been used in this experiment. Under aseptic condition an IV injection using 23–gauge mm needle syringe in the jagular vein for administration of preanesthetic and anesthetic regime; and for collection of blood samples to measure some main blood parameters and liver function enzymes. Which include: R.BCs; Hb; PCV and W.BCs (as main blood parameters) these parameters were estimated prior to anesthesia (0 time) till TIVA infusion stopped (after 1 hour) in the following intervals (20, 40 and 60) minutes. In addition to GOT and GPT (as liver function enzymes) which were done according to RANDOX laboratories leaflet by Veterinary medicine department laboratory specialist in Veterinary medicine college–Baghdad University. Two ml of blood were drawn from the jugular vein into a glass tube containing ethylene diamine tetraacetic acid (EDTA) as anticoagulant. These samples were used for hematological examination. Three ml of blood were collected in a dry clean tube without anticoagulant for separation of serum into plastic vials for biochemical study. Serum samples were stored at room temperature and analyzed within 3 hours. However the hematological tests were done within 6 hr after collection. PCV was determined by Microhaematocrit and W.B.Cs. count was done by hematocytometric method [11].

Statistical analysis was performed using SPSS-21 (Statistical Packages for Social Sciences- version 21)[12]. Data were analyzed using Two way ANOVA and Least significant differences (LSD) post hoc test (multiple comparisons), to assess significant difference among means. Also independent t test was used to assess the significant difference between two groups. $P < 0.05$ was considered statistically significant.

RESULTS & DISCUSSION

Results of Red Blood Cells count (R.BCs)/106/µl R.B.Cs count record a significant decrease at time 20 minutes in both groups P1 and P2 and this decrease continuous till the end of experiment. In P1 group there was a significant increase in R.B.Cs count at time 20 minutes which start to decrease gradually till the end of experiment while in P2 a significant decrease were noticed at time 20 minutes which continuo till the end of experiment (Table 1, Fig. 1).

TABLE 1: Mean time of R.B.C under different anesthetic protocols

Time/minutes / Groups	0	20	40	60
P1	C5.41±0.03a	A6.35±0.007a	B5.75±0.008a	B5.67±0.007a
P2	A5.41±0.02a	B4.72±0.17b	C4.30±0.09b	C4.20±0.02b
LSD	0.2069			

Means with different small letter in the same column significantly different (P<0.05).
Means with different capital letter in the same column significantly different (P<0.05).
P1: ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine.
P2: Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine.

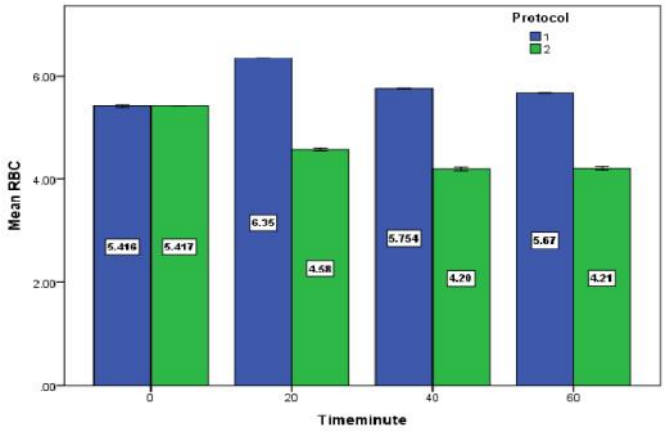

FIGURE 1: The effect of different anesthetic protocols on R.B.C
Green column: PI (Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine)
Blue column: P2 (ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine)

From table (2) we can notice the significant decrease in Hb /g/dL count between P1 and P2 at time 40 minutes which last tills the end of experiment. While within P1 the decrease was significantly recorded at time 20 minutes which last till end of experiment this decreased could be noticed also in P2 start from time 20 minutes also[2].

TABLE 2: Mean time ± SE of Hb under different anesthetic protocols

Time/minutes / Groups	0	20	40	60
P1	A11.18±0.03a	B9.20±0.08a	B8.60±0.16a	B8.48±0.16a
P2	A11.17±0.01a	B8.68±0.61a	C7.50±0.20b	C7.43±0.12b
LSD	0.7294			

Means with different small letter in the same column significantly different (P<0.05).
Means with different capital letter in the same column significantly different (P<0.05).
P1: ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine.
P2: Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine.

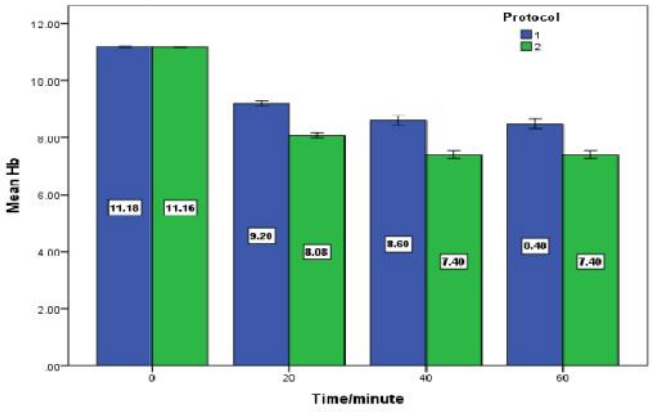

FIGURE 2: Effect of different anesthetic protocols on Hb
Green column: PI (Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine)
Blue column: P2 (ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine)

Packed Cell Volume (PCV) % showed no significant changes between P1 and P2 while within each group either P1 or P2 the significant decrease were notice at time 20 minutes (Table 3 ; Fig. 3).

TABLE 3: Mean time ± SE of P.C.V under different anesthetic protocols

Time/minutes / Groups	0	20	40	60
P1	A43.60±0.66a	B27.00±0.70a	B27.20±1.59a	B26.60±0.21a
P2	A43.07±0.18a	B29.12±3.52a	C24.34±0.58a	C23.71±0.25a
LSD	4.1483			

Means with different small letter in the same column significantly different (P<0.05).
Means with different capital letter in the same column significantly different (P<0.05).
P1: ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine.
P2: Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine.

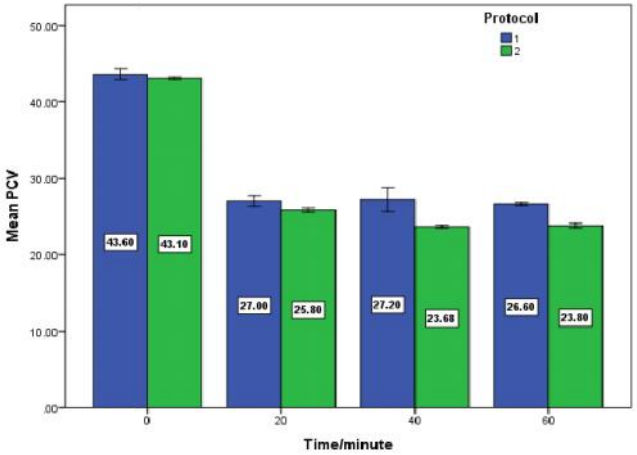

FIGURE 3: Effect of different anesthetic protocols on PCV
Green column: PI (Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine)
Blue column: P2 (ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine)

From table (4) White Blood Cells count (W.BCs) /10^3/µl showed a significant decrease in P2 comparison with P1 at time 20 minutes, this decrease continuous significantly till the end of experiment. In P1 we can seen a significant decrease in W.B.Cs count start from time 20 minutes and last till the end of experiment the same think could be seen in P2 (4).

TABLE 4: Mean time ± SE of W.B.C under different anesthetic protocols

Time/minutes / Groups	0	20	40	60
P1	A11.83±0.15a	B8.30±0.15a	C7.60±0.16a	C7.10±0.10a
P2	A11.81±0.08a	B5.92±1.45b	C4.02±0.54b	C3.83±0.14b
LSD	1.6286			

Means with different small letter in the same column significantly different (P<0.05)
Means with different capital letter in the same column significantly different (P<0.05)
P1: ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine
P2: Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine

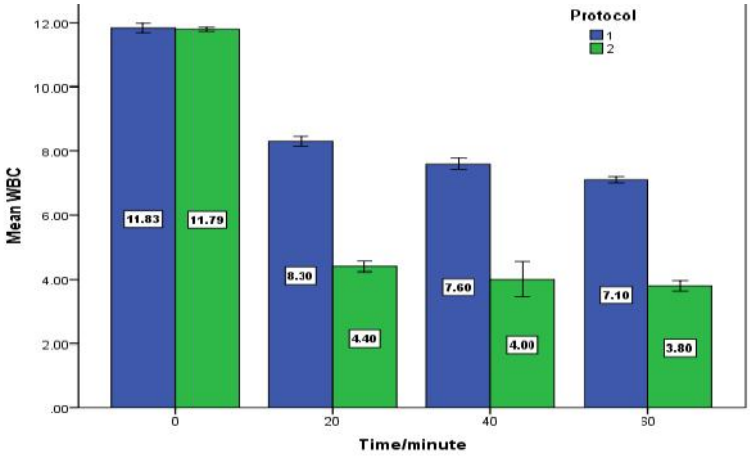

FIGURE 4: Effect of different anesthetic protocols on W.B.C
Green column: PI (Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine).
Blue column: P2 (ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine).

Generally Blood sampling is necessary for measuring circulating hormone and metabolite levels in biomedical research and clinical diagnostics. Even repetitive blood sampling is usually unproblematic in humans and larger animals [13] since Haematological parameters play a crucial role in clinical diagnosis of infectious and parasitic diseases, in assessing the responses of donkeys to treatment and in prevention of diseases. The changes in blood values are important in evaluating the responses of the animals to various physiologic conditions. In conclusion, haematological values of donkeys are largely influenced by age, sex, physical factors of the environment and physical activity, and consideration of the factors will aid accurate diagnosis and therapeutic evaluation of equine diseases[14].

R.B.Cs count record significant decrease at time 20 minutes in both groups P1 and P2 and this decrease continuous till the end of experiment. Normally, production and destruction of red cells are kept in balance. The hormone responsible for the regulation of the rate of erythropoiesis is a glycoprotein, called erythropoietin (EP)[15]. The fundamental stimulus to EP production is tissue hypoxia, and so the concentration in plasma is related to the ratio of oxygen supply to oxygen demand. Erythropoietin affects red cell production in four ways which include: (a) More stem cells differentiate to red cell precursors, (b) Stages of red cell development are speeded up; (c) Transit time out of bone marrow is reduced and (d) immature red cells are released [16].

In our study there was significant decrease in Hb count between P1 and P2 at time 40 minutes which last tills the end of experiment. In Packed Cell Volume (PCV), the significant decrease were notice at time 20 minutes, there was no significant changes between P1 (27.00 ±0.70) and P2 (29.12 ±3.52).The hemoglobin from a defunct red cell is also broken down. The (protein) globin fraction is lysed into its component amino acids which join the general body amino acid pool, either being restructured into new proteins as needed, or being deaminated with the amino residue excreted as urea and the carbohydrate residue entering the fuel metabolism pathways. The hem fraction loses its iron atom, which is not excreted but is recycled into a new hemoglobin molecule. The remaining part of the hem complex becomes bilirubin[16].

Our result showed significant decrease in P2 (5.92 ±1.45) comparison with P1 (8.30 ±0.15) at time 20 minutes, this decrease continuous significantly till the end of experiment. Although it is well known that surgical stress causes changes in the composition of white blood cells in peripheral blood, but also anesthesia itself has been

suggested to have an immunosuppressive effect[17]. The decrease of white blood cells in P2 could be to the effect of Phenobarbital.

Aspartate Amino Transferase (AST or GOT)/ IU/L levels showed no significant changes noticed between P1 and P2 but there was a significant increase in GOT level start at time 20 minutes continuous till the end of experiment within P1 and the same notice recorded in P2. (Table 5; Fig. 5).

TABLE 5: Mean value of liver enzyme AST (GOT) different anesthetic protocols

Time/minutes / Groups	0	20	40	60
P1	B89.00±0.00a	A163.00±7.00a	A163.00±7.07a	A149.00±4.25a
P2	B88.75±1.70a	A163.60±18.58a	A174.40±5.70a	A159.33±3.56a
LSD	23.251			

Means with different small letter in the same column significantly different (P<0.05)
Means with different capital letter in the same column significantly different (P<0.05)
P1: ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine
P2: Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine

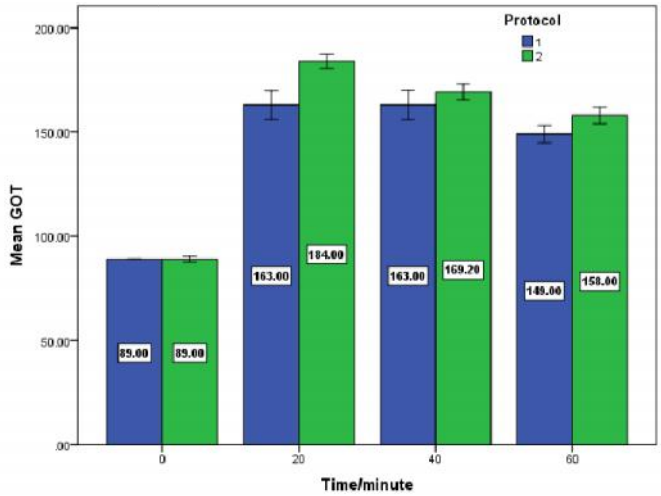

FIGURE 5: Effect of different anesthetic protocols on liver enzyme (AST GOT)
Green column: PI (Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine)
Blue column: P2 (ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine)

Alanine Amino Transferase (ALT or GPT)/ IU/L levels showed no significant changes noticed between P1 and P2 but there was a significant increase in GPT level start at time 20 minutes continuous till the end of experiment within P1 and the same notice recorded in P2. (Table 6; Fig. 6)

TABLE 6: Mean value of liver enzyme ALT (GPT) different anesthetic protocols

Time/minutes / Groups	0	20	40	60
P1	B6.40±0.79a	A10.00±1.41a	A10.00±1.41a	A10.00±1.41a
P2	B6.00±1.77a	AB9.20±0.80a	A10.60±0.74a	A9.50±0.42a
LSD	3.2392			

Means with different small letter in the same column significantly different (P<0.05)
Means with different capital letter in the same column significantly different (P<0.05)
P1: ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine
P2: Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine

Liver is one of the most essential organs involved in the regulation of energy homeostasis; it has a variety of transaminases to synthesize and break down amino acids and to interconvert energy storage molecules. The concentrations of these enzymes in the serum (the non-cellular portion of blood) are normally low. However, if the liver is damaged, the hepatocytes become more permeable and some of the enzymes leak out into the blood stream. So Liver Function Tests (LFTs) are one of the most commonly requested screening blood tests. Whether for the investigation of suspected liver disease, monitoring of disease activity, or simply as 'routine' blood analysis[18].The two amino transaminase commonly measured are ALT and AST. Elevated levels are quite sensitive for liver injury, meaning that they are likely to be present if there is injury. However, they may also be elevated in other conditions *e.g.* (Cirrhosis). ALT is not commonly found outside the liver. AST too is most commonly found in the liver, but also in significant amounts in heart and skeletal muscle. In fact, AST is another liver enzyme that aids in producing proteins. It's used as a part of diagnosing heart attacks[19]. ALT plays an

important role in amino acid metabolism and gluco neogenesis [20]. Both Transaminases (ALT and AST) are two closely related enzymes of clinical significance, particularly in the assessment of liver function[21]. The liver produce a large amount of ALT, AST, and LD which are secreted to the circulation with injury or death, where leakage enzymes escape from the cystol causing elevation in the serum level of these enzymes[22], in additioin, release of liver enzyme from cystol can occur secondary to cellular necrosis with membrane damage[23]. On the other hand, Serum alanine aminotransferase and aspartate aminotransferase are widely used as markers for acute and chronic hepatocellular damage due to various causes [24].

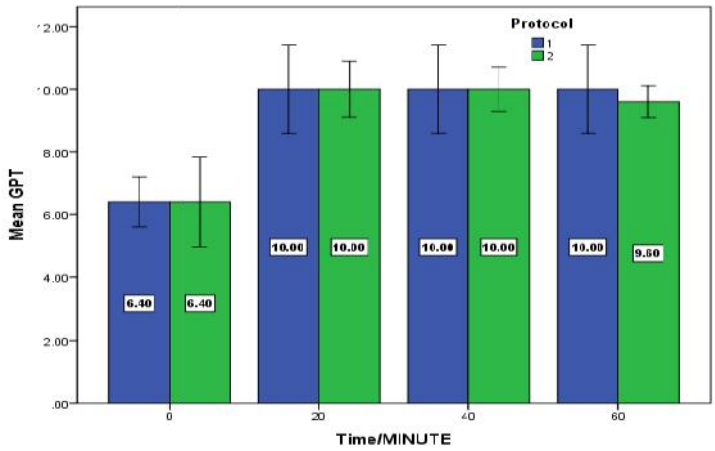

FIGURE 6: Effect of different anesthetic protocols on liver enzyme ALT (GPT)
Green column: PI (Phenobarbital – Xylazine –Ketamine + Xylazine – Ketamine)
Blue column: P2 (ketoprofen – Xylazine – Ketamine + Xylazine-Ketamine)

Our results showed a significant increase in GOT level in both protocols start at time 20 minutes, P1 (163.00 ±7.00) and (163.60 ±18.58) for P2.that increase continuous till the time 60 which became (149.00 ±4.25) in P1 and (159.33 ±3.56) in P2 respectively**.** It is well known that drugs are an important cause of liver injury in which the initial steps of injury are triggered by the offending drug, or more commonly, drug metabolites. The hepatotoxic metabolites are often the result of phase I drug metabolism and the polymorphic cytochrome P450 (CYP450) family of proteins[25].The increase of GOT level may be due to mild liver damage because of administration of ketoprofen or phenoparabital and continuous infusion of xylazine–ketamine mixture during 1hr and the metabolism of this drug via liver all these facts could be the reason for this increase. It is well known that any defect affect liver causes a noticeable increase in the liver enzymes level [18].
In both protocols there was a significant increase in GPT level start at time 20 minutes continuous till the end of experiment in which P1 recorded (10.00 ±1.41IU/L) and P2 (9.20 ±0.80IU/L). Normally, ALT is found inside liver cells. But if the liver is inflamed or injured, ALT is released into the bloodstream. Measuring blood levels of ALT can give doctors important information about the liver and whether a disease, inflammation, drug, or other problem is affecting it.
Our results agree with [26] in which they noticed increase in AST, GGT, and ALP levels in normal miniature donkeys treated intravenously with ketoprofen.

CONCLUSION

The present study indicated that both protocols were safe with non obvious complications concerning blood parameters.

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