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Evaluation of Xylazine HCl as a Potential Anesthetic for Laparogastrotomy Operation in Dogs

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Abstract

The present study aimed to evaluate intramuscular xylazine HCl 2% as an anesthetic for laparogastrotomy in dogs at different doses. Twenty-seven dogs were divided randomly and equally into three groups; group A received 4 mg/kg, group B, received 8 mg/kg, and group C received 14 mg/kg. Anesthetic indices, effect on physiological parameters, blood gases, and biochemical parameters were recorded. The onset was 4.00 ± 0.00, 3.50 ± 0.33, and 5.00 ± 0.33 min, and the duration was 18.00 ± 2.50, 21.00 ± 7.20, and 28.00 ± 4.30 min in the groups A, B, and C, respectively. Pedal reflex was absent in groups A and B from 5 - 30 min post-injection. Palpebral reflex was absent in all groups from 20 - 30 min post-injection. All dogs recorded a non-significant decrease in the rectal temperature, but a significant decrease in respiratory and heart rates. There was a significant increase in the $PvCO_2$ level and significant hyperglycemia in all dogs. Dogs in groups B and C exhibited a significant decrease in PvO_2. There was a significant decrease in the serum cortisol level in the group B. Creatinine level recorded non-significant decrease in the group A, while there was a non-significant increase in the group B. There was non-significant decrease in GGT levels in the groups A and C. Xylazine at dose of 14 mg/kg established a satisfactory stable anesthesia that was enough to conduct laparogastrotomy in dogs.

Keywords: Anesthesia, Biochemical parameters, Blood gases, Dogs, Xylazine.

Introduction

Several techniques and concepts have been developed during the last two decades for the utilization of safe and cheap analgesics for surgical procedures in small animals (Mathews, 2000; Mattos et al., 2009). The use of anesthetic drugs depends on species, breed, and age of the animal (Jean et al., 1990; Singh et al., 2006; Alsobayl et al., 2018; Zayed et al., 2020). These drugs should cause minimum stress, pain, and toxic side effects to the patients (Thurmon et al., 1996, William et al., 2007). Various sedatives or tranquilizing agents are used as pain killers and/or muscle relaxants in small animals, for these purposes, the commonest drugs used are ketamine and xylazine (Mahmud et al., 2014). Xylazine is a dose-dependent alpha-2 adrenergic agonist that causes bradycardia, hypertension followed by hypotension. It has sedative, analgesic, and muscle relaxant effects (Tranquilli et al., 2007). It has been used epidurally alone or in combination for minor surgical procedures (LeBlanc et al., 1988; LeBlanc and Eberhart, 1990; Jean et al., 1990; Zaugg and Nussbaum, 1990; Caulkett, 2003).

Pain is an unpleasant sensory or emotional experience commonly associated with many factors such as increased or decreased partial pressure of oxygen in blood and could be source of reactive oxygen (ROS) (Simeonova et al., 2004). Cortisol secretion increases in response to any stress in the body such as illness, trauma, or surgery (Brook and Marshal, 2011). Oxidative damage of the cellular structure and function is a result of uncontrolled increase of ROS concentration. The peroxidation of membrane phospholipids generates malondialdehyde (MDA)-an end product of lipid peroxidation and a bio-marker of oxidative stress (Alva et al., 2006). Tissue damage by lipid peroxides and toxic products, or surgical trauma from anesthesia indicated that something is wrong that may delay recovery (Tranquilli et al., 2007; Gaynor and Muir, 2008). Alsobayl et al. (2018) have preferred xylazine as a good muscle relaxant that increased sleep time and substantial analgesia. Pain must be managed during surgery to enhance recovery (Orskov, 2010).

Diagnosis of pain-reduction biomarkers as nitric oxide (NO) that normalize blood flow pathway and lessen nerves irritation also small amounts of transiently released NO decrease the pain with anti-inflammatory action (Abramson, 2008). Pain can also be evaluated by measuring serum cortisol levels to investigate the efficiency of the anesthesia (Naddaf et al., 2014).

There is a lack in studies regarding the possibility of the use of xylazine HCl as a potential anesthetic agent. This was the motivation to perform the current study. Therefore, the present study aimed to evaluate xylazine HCl as an anesthetic for laparogastrotomy operation in dogs at different doses with special regard to its anesthetic indices (onset, duration, recovery time, pedal, and palpebral reflexes), effect on physiological parameters (temperature, respiratory rate, and heart rate), blood gases, and biochemical parameters.

Materials and Methods

Ethical approval

The present study was approved by the National Ethical Committee of The Faculty of Veterinary Medicine, Assiut University, Assiut, Egypt, according to the OIE standards for the use of animals in research and teaching.

Experimental animals

The present study was conducted on 27 non-medicated, clinically healthy, adult mongrel dogs of both sexes (15 males and 12 non-pregnant, non-lactating females). Their body weight (BW) ranged from 11.0 to 17.5 Kg, and aged 2 - 3 years. Dogs were housed individually in standard cages with food and water ad libitum.

Animal groups

Dogs were divided randomly and equally into three groups (9 dogs in each) based on the administered dose of xylazine HCl 2% (Xyla-Ject, ADWIA Co., SAE, Egypt, injectable solution, xylazine hydrochloride 23.3 mg, Eq. to 20 mg xylazine base): group A administered 4 mg/kg, group B administered 8 mg/kg, and group C administered 14 mg/kg. Xylazine HCl was administered intramuscularly (IM) in all groups, in the quadriceps muscle, under complete aseptic conditions.

Anesthetic indices

Onset (min) (the time elapsed from the end of injection of xylazine HCl till disappearance of the pedal reflex), duration (min) (the time elapsed from the onset until the return of sensation), and recovery time (min) (the time elapsed from the return of sensation until the ability of the animal to stand) were recorded for each dog. Muscle relaxation was estimated manually by palpation.

Pedal reflex was recorded by clamping the toe web with a hemostat every minute from the end of injection until the onset of anesthesia, and then every ten minutes until the return of sensory sensation. It was graded on a scale of 0 to 3; grade 0: no limb withdrawal at the lock of the 3rd ratchet of a hemostat clamped on the toe web, grade 1: limb withdrawal at the lock of the 3rd ratchet, grade 2: limb withdrawal at the lock of the 2nd ratchet, and grade 3: limb withdrawal at the lock of the 1st ratchet (Njoku, 2015).

Palpebral reflexes were recorded every ten minutes from the end of injection until the return of sensation. It was graded on a scale of 1 to 4; grade 1: no change in reflex, grade 2: moderate reflex, grade 3: sluggish reflex, grade 4: absence of reflex (Jena et al., 2014).

Physiological parameters

Rectal temperature (ºC) (by the thermometer), respiratory rate (breath/min) (by counting the chest movements/min), and heart rate (beat/min) (by counting the heart beats using the stethoscope) were recorded before (0 time) injection, and then at 5, 15, 25, 45, and 60 min post-injection.

Blood gases

Blood samples were collected from the jugular vein in plastic syringes prior to xylazine injection at the time (0), 15 min post-injection, and then after the recovery. Samples were kept in test tubes containing heparin. The sample kept in icebox until the time of analysis. Blood gases were measured by the blood gases analyzer. The blood pH, PvCO2, PvO2, and Glucose

were measured for each case (Simeonova, 2004).

Biochemical parameters

Blood samples were collected from the cephalic veins in plastic syringes before xylazine injection at the time (0), 15 min post-injection, and after the recovery. Samples were kept in vacutainer tubes for the biochemical analysis. Blood samples centrifuged at 3000 RPM for 10 min. and then sera were collected and stored at -20 C° until analysis. Serum Cortisol Level was measured using Enzyme Linked immunosorbent assay (ELISA) method (Coetzee et al., 2008). Nitric Oxide (NO) and Malondialdehyde (MDA) were estimated colorimetrically by biodiognostic kits (Montgomercy and Dymock, 1961; Ohkawa et al., 1979). Creatinine and Gamma-Glutamyl-Transferase (GGT) were estimated calorometrically by spectrum Kits, (Tietz, 1986).

Laparogastrotomy in dogs

Dogs showed satisfactory anesthesia and appropriate duration (pedal reflex = 0 and palpebral reflex = 4) were subjected to midline laparogastrotomy according to Tobias (2010).

Statistical analysis

The values are expressed as mean ± SE. The data was analyzed by one way ANOVA using SPSS 16.00 Software (SPSS Inc., Chicago, IL, USA); significance was designated as P ≤ 0.05. Means were compared by Tukey post-hoc test when a significant difference was detected.

Results

Dogs in the groups A, B, and C tolerated the intramuscular (IM) xylazine HCl at doses of 4, 8, and 14 mg/kg, respectively. There were no deaths or severe complications throughout the whole study period.

Onset of anesthesia

There was a non-significant difference between the animal groups regarding the onset time of anesthesia ($P = 0.29$). The group B (8 mg/kg) achieved the shortest time (3.50 ± 0.33 min), followed by group A (4.00 ± 0.00 min) and group C (5.00 ± 0.33 min). The onset of anesthesia was evident by calming of the dog, loss of consciousness, and absence of pedal and palpebral reflexes (Fig. 1).
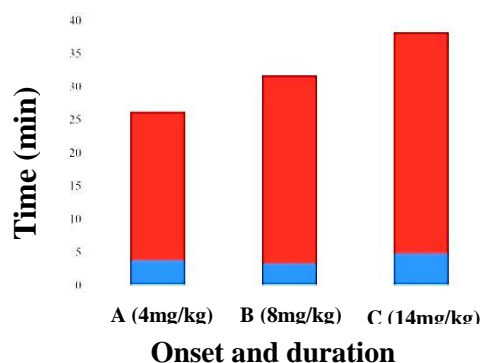
Fig. 1. The onset (blue) and duration (red) (min) of action following xylazine administration in groups A (4 mg/kg), B (8 mg/kg), and C (14 mg/kg).

Duration of anesthesia

The duration of anesthesia in the group C (28.0 ± 4.3 min) was longer than in both groups; B (21.0 ± 7.2 min) or A (18.0 ± 2.5 min). However, the difference between the three groups was a non-significant ($P = 0.27$), (Fig. 2). According to the recorded duration of the anesthesia, dogs in the group C were subjected to

midline laparogastrotomy operation in the next day.

Recovery time following xylazine administration

The recovery was smooth in all animals of the groups A, B, and C. Dogs in the group C had the longest recovery time, followed by those of the groups A and B in the order (Fig. 2).
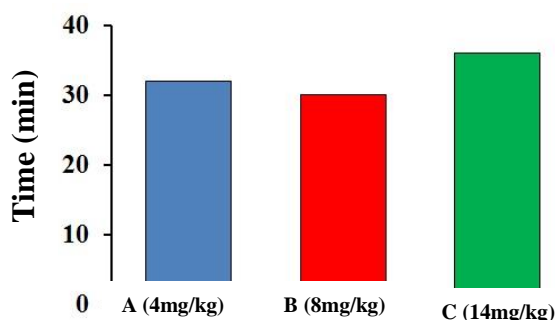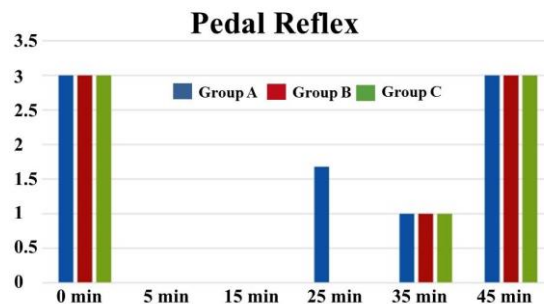

Recovery Time

Fig. 2. Recovery time (min) following xylazine administration in groups A (blue; 4 mg/kg), B (red; 8 mg/kg), and C (green; 14 mg/kg).
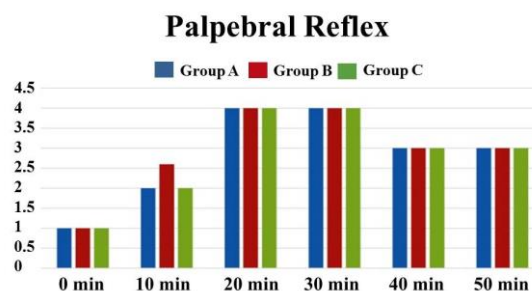
Pedal reflex following xylazine administration

The pedal reflex recorded grade 0 at 5 and 15 min post-injection of the xylazine in all dogs. Dogs of the group A recorded pedal reflex of grade 2 at 25min post-injection. However, in both groups B and C the pedal reflex was grade = 0. At 35 min post-injection, dogs in all groups exhibited pedal reflex of grade 1 (Fig. 3).

Fig. 3. Pedal reflex following xylazine administration in group A (blue; 4 mg/kg), B (red; 8 mg/kg), and C (green; 14 mg/kg).

Palpebral reflex following xylazine administration

The palpebral reflex was absent (grade 4) in all dogs from 20 to 30 min post-injection of xylazine. At 40 min post-injection, the palpebral reflex changed to record grade 3 (sluggish reflex) (Fig. 4).

Fig. 4. Palpebral reflex following xylazine administration in the in group A (blue; 4 mg/kg), B (red; 8 mg/kg), and C (green; 14 mg/kg).

Quality of anesthesia

Dogs in the different groups showed stable line of anesthesia with a good muscle relaxation but at different durations regarding to each group.
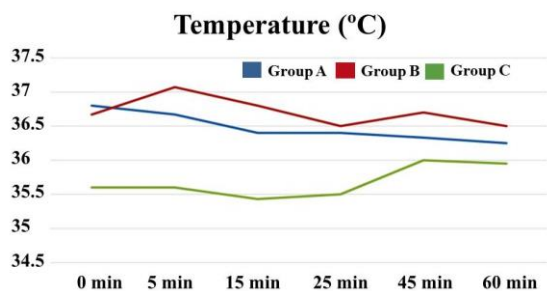
Adverse effects of xylazine administration

Dogs in different groups suffered vomiting following xylazine

administration, as well as, salivation during the period of anesthesia. This was overcome by lowering the head of the animal to avoid drenching into the respiratory system. Such adverse effects were not dose-dependent in its strength and repeatability in different animal groups.

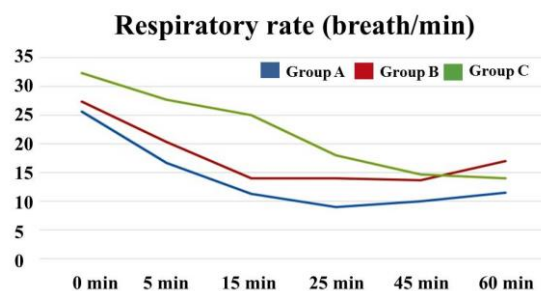### *Effect of xylazine administration on body temperature*

Dogs in the three groups; A, B, and C exhibited a non-significant decrease ($P>0.05$) in body temperature, throughout the maintenance period of anesthesia, at different intervals (Fig. 5).

Fig. 5. Effect of xylazine administration; A (blue; 4 mg/kg), B (red; 8 mg/kg), and C (green; 14 mg/kg) on body temperature (^{o}C) in dogs.

Effect of xylazine administration on respiratory rate

Dogs in the three groups recorded a significant ($P<0.05$) decrease in the respiratory rate throughout the maintenance period of anesthesia at the different intervals. The respiration was irregular, as well as, deep in all animals (Fig. 6).

Fig. 6. Effect of xylazine administration; A (blue; 4 mg/kg), B (red; 8 mg/kg), and C (green; 14 mg/kg) on respiratory rate (breath/min) in dogs.

Effect of xylazine administration on heart rate

Dogs in the groups; A, B, and C had a significant ($P<0.05$) decrease in the heart rate through the maintenance period of anesthesia. Heart rate was regular except for the animals in groups C, as it was irregular (Fig. 7).
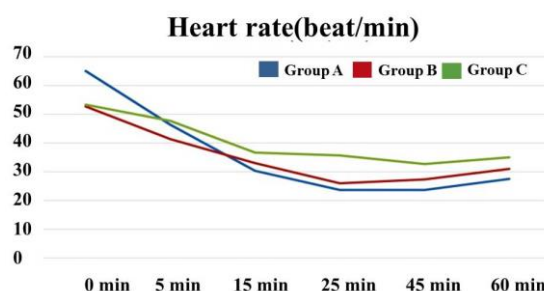
Fig. 7. Effect of xylazine administration; A (blue; 4 mg/kg), B (red; 8 mg/kg), and C (green; 14 mg/kg) on heart rate (beat/min) in dogs.

Effect of xylazine administration on blood gases

During the anesthetic period, dogs in all groups showed non-significant changes regarding the blood pH. There was a significant increase in all groups in the $PvCO_2$ level. The dogs in groups B and C

exhibited significant decrease in PvO_2. A significant hyperglycemia was manifested in the groups A, B, and C (Table 1).

Table 1: Effect of xylazine HCl administration on pH, blood gases; PvCO2 and PvO2, and glucose in group A (4 mg/kg), B (8 mg/kg), and C (14 mg/kg).

Group	A (4mg/kg)			B (8mg/kg)			C (14mg/kg)			P value
	before	during	after	before	during	after	before	during	after	
pH	7.2±0.01	7.2± 0.02	7.28±0.1	7.19±0.3	7.17±0.3	7.18±0.2	7.17±0.1	7.16±0.2	7.26±0.2	0.01
$PvCO_2$	48±2.00[a]	59.0±4.10[b]	54±3.8[b]	72±6.3[a]	86±1.91[b]	86±2.8[b]	48±4.7[a]	78.00±5.6[b]	90.00±4.6[b]	0.40
PvO_2	33.0±2.58	33.0±1.8	34.0±1.7	39±1.08[a]	30±2.70[b]	30±4.21[b]	54±0.98[a]	20.00±0.76[b]	32.00±1.76[ab]	0.30
Glucose	66±1.46[a]	73.0±6.8[b]	78±4.79[b]	60±1.76[a]	80±8.9[b]	85±3.08[b]	66±0.65[a]	88.00±7.50[b]	68.00±2.47[ab]	0.60

Effect of xylazine administration on biochemical parameters

During the anesthetic period, serum cortisol level decreased in the groups B and C, where the decrease was significant in the group B. The group A recorded a non-significant increase. Dogs in the group A recorded a significant increase in the NO level, while there was a non-significant change in the groups B and C. There was significant increase in MDA levels in the dogs of the group B, while there was non-significant decrease in the groups A and C. Creatinine level recorded non-significant decrease in the group A, while there was a non-significant increase in the group B. There was non-significant decrease in GGT levels in the groups A and C (Table 2).

Table 2: Effect of xylazine HCl administration on some biochemical parameters including in group A (4 mg/kg), B (8 mg/kg), and C (14 mg/kg).

	A (4mg/kg)			B (8mg/kg)			C (14mg/kg)		
	before	during	after	before	during	after	before	during	after
Cortisol	2.68 ±0.01[a]	3.32 ±0.01[ab]	3.43 ± 0.20[ab]	2.35 ±1.00[a]	1.60 ±0.80[b]	4.50 ±0.90[b]	4.86 ±0.54[a]	3.95 ±1.23[ab]	7.06 ±2.65[b]
NO	60.70 ±2.10[a]	80.00 ±1.76[b]	120.40 ±0.90[b]	150.20 ±0.10[a]	150.80 ±0.10[a]	115.20 ±0.86[b]	140.20 ±0.09[a]	140.30 ±0.87[a]	110.70 ±0.72[b]
MDA	8.94 ±0.57[a]	6.39 ±0.01[ab]	7.37 ±1.00[ab]	4.76 ±1.40[a]	9.04 ±0.46[b]	6.32 ±1.70[b]	3.86 ±0.74[a]	3.59 ±0.76[a]	4.00 ±0.0[a]
Creatinine	1.60 ±0.08[a]	1.50 ±0.01[a]	1.50 ±0.01[a]	0.90 ±0.01[a]	1.40 ±0.75[ab]	1.30 ±0.56[ab]	1.10 ±0.04[a]	1.10 ±0.23[ab]	1.20 ±0.65[ab]
GGT	3.00 ±0.00[a]	2.00 ±0.01[ab]	3.00 ±0.00[ab]	3.00 ±0.00[a]	3.00 ±0.00[a]	5.00 ±0.12[b]	4.00 ±0.65[a]	3.00 ±0.87[a]	9.00 ±1.86[ab]

Discussion

Previous studies have been carried out in various animal species to explore the sedative and analgesic role of xylazine HCl (Skarda and Muir, 1996). To the best of our knowledge, there is lack in studies regarding the evaluation of the xylazine HCl as an anesthetic for surgical operation in canine patients.

Owing to the characteristic potent analgesic, sedative, as well as, muscle relaxant effects of xylazine HCl (Mostachio

et al., 2008), we hypotheses that administration of xylazine at high doses may provide satisfactory duration of a good quality anesthesia for some surgical interventions in dogs.

The present study demonstrated that xylazine at dose 14mg/kg BW provided anesthesia of duration of 28 ± 4.3 min, which was satisfactory for conduction of the laparogastrotomy operations in the dogs. Also, xylazine at doses of 4 and 8 mg/kg BW provided duration of 18 ± 2.5 and 21 ± 7.2 min, in the order, which may be used for minor surgical interferences or diagnostic purposes, accordingly to the required time.

In the present study, xylazine was associated with a rapid onset, good anesthesia, as well as, a smooth recovery. The rapid onset of xylazine anesthesia may be attributed to its rapid absorption following intramuscular (IM) administration and its high bioavailability (52 - 90 %) in dogs (Mckelvey and Hollingshead, 2003).

Xylazine most likely acts by stimulation of alpha adrenoceptors at the spinal cord and brain there by inhibiting the release of neurotransmitters and norepinephrine (Kolahian, 2014). Muscle relaxation produced by xylazine may be related to decrease in intra-neural and synaptic transmission in the CNS (Mostachio et al., 2008; Kolahian, 2014).

The duration of xylazine anesthesia was proportional to the dosage of the drug. This was in agreement with Greene and Thurman (1998) who stated that the depressant effect of xylazine on CNS is dose dependent.

Dogs in the groups; A, B, and C exhibited a non-significant decrease in body temperature. This was similar to the results recorded by Sindak et al. (2010) and Mwangi et al. (2014). However, this was in disagreement with Ullah et al. (2017) who reported that xylazine HCl has no effect on body temperature.

The hypothermia after administration of xylazine may be due to depression of the thermoregulatory center (Pypendop and Verstegen 1998) and reduced muscular activity (Virtanen 1989).

In the present study, dogs exhibited a significant decrease in respiratory rate. This was in agreement with other studies (Lee et al., 2015; Restitutti et al., 2017), who reported that all α2-agonist decrease the rate of respiration. The reduction in respiratory rate may be due to depression of respiratory center (Hall et al., 2001).

The dogs in all groups A, B, and C had a significant decrease in heart rate after IM injection of xylazine HCl. Similar findings were reported in many studies (Tranquilli et al., 2007; Plumb, 2008). This might be due to inhibition of both sympathetic and parasympathetic systems due to dose dependent effect of xylazine (Hall et al., 2001). Selmi et al. (2003) have stated that xylazine administration associated with bradycardia, which may be due to decreased sympathetic activity and/or increased vagal tone.

In the present study, there were no significant changes regarding the pH level. However, there were a significant increase in the $PvCO_2$ in all animals and a significant decrease in PvO_2 in the B and C

groups. These findings were in agreement with Kurtdede et al. (1994).

The administration of xylazine developed significant hyperglycemia. The same result was observed by Fayed et al. (1989). Xylazine increased blood glucose concentration in the anesthetized dogs in a dose related manner (Ambrisko and Hikasa, 2002). The hyperglycemia might be due to the stress induced gluconeogenesis as a result of anesthesia and probable suppression of insulin and increased production of glucose in liver (Singh et al., 2006).

Serum cortisol level decreased in the B and C groups. Cortisol secretion increases in response to any stress in the body such as illness, trauma, or surgery (Hucklebridge, et al., 1999; Brook and Marshal, 2011). Cortisol secretion from the adrenal cortex increases rapidly following the start of surgery as a result of stimulation by ACTH. Anasthetic drugs may inhibit cortisol secretion and causing decrement of cortisol blood level (Desborough, 2000; Ko et al., 2000).

The main secondary cellular damage post-surgery is increase of lipid peroxides index MDA (Memduh et al., 2005). In this study, there was non-significant decrease in MDA level in groups (A) and (C), while there was significant increase in group (B). This was in disagreement with Alva et al. (2006) who reported no changes in serum MDA level after xylazine or xylazine-Ketamine anesthesia.

There was a significant increase in NO level in group A that may be due to imbalance between the PvO_2 and $PvCO_2$ or nerve injury during surgery (Liu et al., 2000). This was on the contrary to the findings of Monti et al. (1999) and Monti and Jantos (2004) who reported that nitric oxide (NO) decreases during sleep.

There were non-significant changes regarding the creatinine level in all groups. This was in agreement with the results of Simon et al. (1989) who recorded no changes in creatinine following administration of xylazine HCl. On the other hand, it has been reported that a high dose of xylazine was more effective in increasing the level of creatinine (Kinjavdekar et al., 2000). The increase in creatinine values might be related to the temporary inhibitory effect of xylazine on renal blood flow which, in turn, may have caused a rise in creatinine (Singh et al., 2006).

There was non-significant decrease in GGT level. This may be attributed to the anesthesia as it causes an initial reduction in hepatic arterial blood flow of 35 – 42 % in the first 30 min of induction of anesthesia (Pratt and Kaplan, 2000).

Conclusion

The present study explored that administration of xylazine at 14 mg/kg can produce a satisfactory stable anesthesia of duration time (28 ± 4.3 min) that was enough to conduct laparogastrotomy operation in dog. Further studies are required regarding the evaluation of the xylazine HCl anesthetic effect by constant IV infusion.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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