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Evaluation of Total Intra-Venous Anesthesia Using Ketamine HCl or Telazol in Mongrel Dogs

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Abstract

This study aimed to evaluate the anesthetic, hemato-biochemial and clinico-physiological effects of ketamine HCl and telazol on xylazine premedicated dogs. Sixteen apparently healthy dogs were used in this study. Total intravenous anesthesia (TIVA) was induced by ketamine HCl (5mg/kg Bwt) or telazol (6mg/kg Bwt) after premedication with xylazine HCl (1mg/kg Bwt). Blood samples were collected in both treatments five minutes before injection of the preanesthetic medication, then at (15, 30, 60 and 90) minutes after treatments for the hemato-biochemical evaluation, also clinico-physiological observations were recorded at the same previous times. Both ketamine HCl and telazol had no significant effect on the clinico-physiological parameters and also hemato-biochemical values of the dogs. Both drugs could be used as TIVA in dogs. However, telazol induced longer duration of anesthesia with complete muscle relaxation that suitable for most surgical operations.

1. INTRODUCTION

Surgical management of canine patients is considered to be painful & produce an inflammatory response. An Appropriate selection of anaesthetic and analgesic techniques is essential for the well-being of the surgical patient not only because of ethical reasons but also to decrease the risk of complications, facilitate the healing process, and avoid the development of chronic pain (Waterman-Pearson, 2000). General anesthesia should provide quick and pleasant induction, predictable loss of consciousness, stable operating conditions, minimal adverse effects, rapid and smooth recovery of protective reflexes and psychomotor functions. (Sukhminder et al., 2015). TIVA is a technique of general anesthesia in which induction and maintenance of anesthesia occurred with drugs given only by intravenous route, the characteristics of this technique are short duration of action and rapid clearance from the body so that the drugs have no cumulative effects (Campbell et al., 2001). Ketamine is a dissociative anesthetic, analgesic, and anti-inflammatory drug, and one of a limited number of noncompetitive of NMDAR antagonists (Mazar et al., 2005). It is related to a phenylcyclidine derivatives, works by depression of the thalamocortical system and stimulation of the reticular activating and limbic system (Gross, 2009). Furthermore, ketamine activates the monoaminergic descending inhibitory system, which may play a key role in ketamine's analgesic effect because blockade of inhibitory mechanisms (disinhibition) facilitates NMDA receptor and associated nociceptive processes (Costigan et al., 2009). Telazol is a 1:1 combination of the dissociative anesthetic, tiletamine and the benzodiazepine tranquilizer, zolazepam (Sulli et al., 2008). Tiletamine–zolazepam produces stable dissociative anesthesia in which the cranial nerves and spinal reflexes remain active. The swallowing reflex often is preserved in animals receiving a dissociative anesthetic like tiletamine (Dhanonjoy et al., 2007). Xylazine, an α2-adrenoreceptor agonist, has been combined with tiletamine/zolazepam to increase its anaesthetic and analgesic effects and to reduce the dose of tiletamine/zolazepam required to induce satisfactory anaesthesia in pigs (Kim et al. 2007).

2. MATERIALS AND METHODS

Sixteen apparently healthy adult dogs -of both sex, mean weights is (25±5) kg and mean ages are (15±5) months- were used in the study under investigation.

2.1. Study design

Two experiments were performed in this study.

Experiment I: included ten dogs which divided into two groups each of five animals. The animals in both groups were premedicated with slow intravenous (I\V) injection of xylazine HCl (Xyla-Ject, Adwia Co., S.A.E 10th Ramadan City, Egypt.), in a dose of 1 mg/kg Bwt **(Muir et al., 1977).** Then five minutes later dogs in first group were injected with 5mg/kg Bwt ketamine HCl (ketamine, Sigma-Tec pharmaceutical industries, Egypt-S.A.E.). While in the second group dogs were injected with 6 mg/kg Bwt telazol (Tiletamine HCl and Zolazepam HCl 100 mg/ml, Pfizer, NY 10017, Spain), in a dose of 6mg/kg Bwt. **(Dhanonjoy et al., 2007).**

Experiment II: included six animals undergo elective gastrotomy. Dogs also divided into two groups each of three animals. In this experiment after the dogs were prepared aseptically for surgery (immediately post xylazine I/V injection), the anesthesia was induced either by ketamine HCl or telazol with the same previously mentioned dose. The animals in this experiment were observed for pain reflex to surgery and muscle relaxation.

2.2. Animals preparation to anesthesia

The animals were fasted for 12 hours prior to anesthesia with free access to water in first experiment while in second experiment animals were fasted for 24 hours and water was withheld 12 hours prior to surgery. The area over the cephalic vein was clipped and shaved with manual shaver, then the process of degerming the skin was applied by betadine (Povidone-Iodine 10g, El-Nile Co. for pharmaceuticals and chemical industries, Cairo, Egypt – Mundipharma AG -Basel – Switzerland.) as antiseptic solution for aseptic injection, then Placement of an intravenous cannula (22 gauge and 33ml/min – Euromed medical industries, S.A.E., Cairo, Egypt.) was carried out for blood sampling and drug administration. Dose calculation was carried out according to the preliminary study on the drug concentration and animal weight as recorded before.

2.3. Assessment of anesthetic parameters

The anesthetic effect of both drugs were assessed through determining of onset of anesthesia (time from induction till loss of sensation and consciousness). Quality of induction was recorded based on pin prick test which induced by passing a hypodermic needle at three sites on every limb (digits, carpal/tarsal, proximal part of limb) and three sites on both sides of abdomen (neck, shoulder, posterior thorax) then the tail, perineum and thigh at 15, 30, 60 and 90 minutes' post injection. The induction quality was assessed using a zero to two scales where; 0=poor or no anesthetic effect / full response to pin prick, 1=fair or mild anesthetic effect / slight response to pin prick and 2=good or complete anesthetic effect / no response to pin prick. Evaluation of recovery depended on two methods; The first method is the Steward Scoring System according to ***Phua et al. (1991),*** which evaluates the recovery from anesthesia by physical evaluation (ventilation, movement, wakefulness). The second method of evaluation of recovery which was used in this study was by observing the return of protective airway reflexes like coughing and gagging and response to verbal commands like spontaneous opening of eyes, protrusion of tongue and lifting of head according to ***Sukhminder et al. (2015).*** Respiratory, hemodynamic parameters and the response to surgery were recorded during anaesthesia.

2.4. Blood sample collection

Venous blood samples were collected in vials containing EDTA, for hematological determination of RBCs, WBCs, Hemoglobin content (HB %), Hematocrit (HCT) and Platelets (PLT) before and 15, 30, 60 and 90 min after drug administration. Part of blood were collected in plain tubes, for detection of activities of Glucose, Cholesterol, ALT and AST (Fig., 1).

2.5. Clinico-physiological observation:

Clinical observation of pulse rate by sensing pulsation of the left femoral artery (medial aspect of thigh)/minute, respiratory rate by observing the thoraco-abdominal movement/minute and rectal temperature, was carried out before drug administration and continued with the same time of blood sampling 15, 30, 60 and 90 min after drug administration. Dogs were also examined for the behavioral changes like salivation, sweating, urination, defecation, penis or teat erection and other reflexes like palpebral, anal and pedal. Reaction to surgery (change in breathing pattern, vocalisation or motions) was continuously monitored. The reactions were graded as positive or negative.

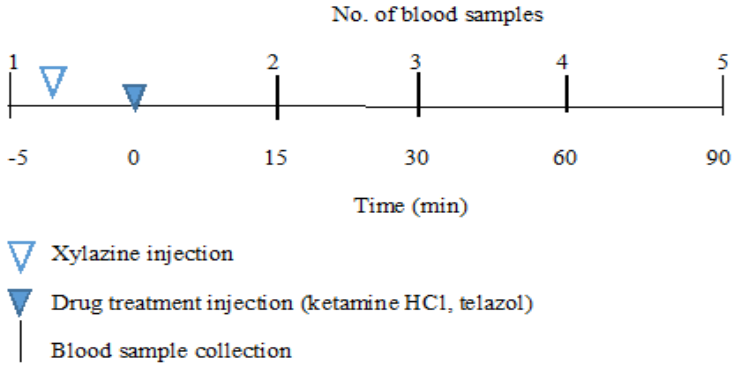

Figure (1): Illustrating time of drug administration (premedication and dissociative anesthetic drugs) and blood sampling.

2.6. Statistical analysis

The data for parametric observations such as heart rate, respiratory rate and rectal temperature were analyzed using one-way analysis of variance (ANOVA) for comparison of means between the groups at corresponding intervals. The data were presented as the mean ± SD. Significance was accepted at $p < 0.05$.

3. RESULTS

3.3. General anesthetic effects

The anesthetic effects depended on three parameters include (onset of anesthesia or quality of induction, duration of anesthesia and recovery) those three parameters were determined by inducing pin pricks (Fig., 2) and table (1).

3.3.1. Onset of anesthesia

After five minutes from I/V injection of ketamine, dogs showed a complete anesthetic effect and absence of sensation to pin prick test (good quality induction), but after I/V injection of telazol all dogs showed gradual signs of anesthesia like drowsing till ten minutes then the anesthetic effects appeared suddenly (mild quality induction), table (2).

3.3.2. Duration and depth of anesthesia

Dogs injected with ketamine showed mild depth of anesthesia (duration) scale 1, this grade regarded to the response to pinching, head elevation, ear erection, palpebral reflex, tongue appearance, teat/penis erection and anal straining. While with injection of telazol, it was found that some of body reflexes like straining of anal sphincter during measuring rectal temperature, palpebral reflexes and ear erection were presented during the course of anesthesia. The results meant that telazol had a good anesthetic depth, table (3). Also telazol induced longer anesthetic duration (80±12) than ketamine (25±5), table (1).

3.3.3. Response to elective gastrotomy

Dogs injected with ketamine showed hyper tonus spontaneous involuntary muscle movement during first twenty minutes. This problem appeared in two dogs from three of the ketamine group and had been overcome by poster dose of xylazine HCl to avoid muscle twitching and facilitating the wound closure. The other one was totally under the anesthetic effect of ketamine with no muscular tone or twitching. In contrast telazol injected dogs, showed a complete anesthetic effect with no muscle twitching, no straining and no difficulty in suturing. The result of response to surgery meant that ketamine had a poor anesthetic effect during elective gastrotomy while telazol had a good anesthetic effect, table (4).

3.3.4. Recovery

Recovery observing by the return of protective airway reflexes like coughing and gagging and response to verbal commands like spontaneous opening of eyes, protrusion of tongue and lifting of head according to Sukhminder et al. (2015**).** The group of dogs injected with ketamine intravenously characterized by rapid and smooth recovery period begin after 30 minutes at almost dogs and completed at 40 minutes reaching to the state of complete recovery. Telazol treated dogs were characterized by smooth prolonged recovery period in almost cases. There was a marked ataxia in the posterior part of hind limb in all dogs treated with telazol started from the beginning of recovery and continued till 30 minutes after the end of the experiment. All cases returned to normal activity after 120- 130 minutes after telazol injection, table (5).

3.4. Clinico-physiological findings (pulse rate, respiratory rate and rectal temperature)

Non-significant increase in the pulse rate and respiratory rate after I/V injection of telazol and decrease in pulse rate with non-significant increase in respiratory rate was observed in ketamine group, both groups gave non-significant change in rectal temperature, fig., (3) and table (6).

3.5. Hemato-biochemical findings (RBCs, WBCs, Hb%, PCV, platelets, Glucose, Cholesterol, ALT and AST)

Non-significant decrease in all blood and serum parameters at both treatments and this decrease was within physiological limit, except glucose level there was increase in the level around whole investigation, table (7)

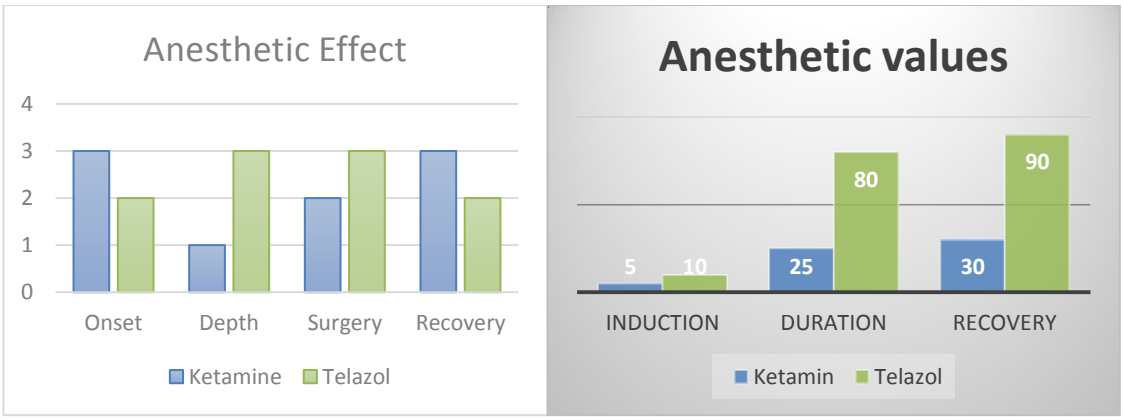

Fig. (2): Scales for grading the general anesthetic effect of I/V ketamine HCl and telazol.

Table (1): Values of induction, duration and recovery rate after intravenous injection of ketamine HCl and telazol premedicated by xylazine HCl.

Treatment		Time (minutes) for the anesthetic curve		
		Induction	Duration	Recovery
	Ket	5±0.5	25±5	30±5
Xyla	Tela	10±1.5	80±12	90±4

No. of dogs for each treatment = 5 dogs. Total no. of dogs / experiment = 10 dogs.

Table (2): Onset of general anesthesia in dogs treated with Ketamine HCl and Telazol treatment.

Parameter	No.	Time (minutes) before and after treatment									
		-5	↓	0	5		10		15	
		Poor			Fair	Good	Fair	Good	Fair	Good
Onset	5	5	Xyla	Ketamine	-	5	-	-	-	-
	5	5	Xyla	Telazol	-	-	-	5	-	-

Table (3): Duration and depth of general anesthesia in dogs treated with Ketamine HCl and Telazol at different times (minutes) before and after treatment.

Parameter	No.	Time (minutes) before and after treatment											
		-5	↓	0	15		30		60		90	
		Poor			Fair	Good	Fair	Good	Fair	Good	Fair	Poor
Depth	5	5	Xyla	Ketamine	-	5	3	2	3	2	-	5
	5	5	Xyla	Telazol	-	5	-	5	2	3	5	-

Table (4): Response to elective gastrotomy in dogs treated with ketamine HCl and Telazol at different times (minutes) before and after treatment.

Parameter	No.	Time (minutes) before and after treatment										
		-5	↓	0	15		30		60		90	
		Poor			Fair	Good	Fair	Good	Fair	Good	Fair	Poor
gastrotomy	3	5	Xyla	Ketamine	2	1	2	1	2	1	-	3
	3	5	Xyla	Telazol	-	3	-	3	-	3	-	3

Table (5): Recovery rate in dogs treated with Ketamine HCl and Telazol at different times (minutes) before and after treatment.

Parameter	No.	Time (minutes) before and after treatment								
					30		60		90	
		-5	↓	0	Poor	Fair	Fair	Good	Fair	Good
Recovery rate	5	-	Xyla	Ketamine	-	5	3	2	1	4
	5	-	Xyla	Telazol	4	1	3	-	-	5

↓: Time of preanesthetic medication (Xylazine HCl). 0: Time of induction general anesthesia (ketamine HCl or Telazol).
Poor: Rough recovery (Changes in respiration with marked head elevation).
Fair: Slightly rough recovery (Presence of tremors and slight convulsion).
Good: Smooth recovery (Complete return to normal body physiology).
No. of dogs for each treatment = 5 dogs. Total no. of dogs / experiment = 10 dogs.

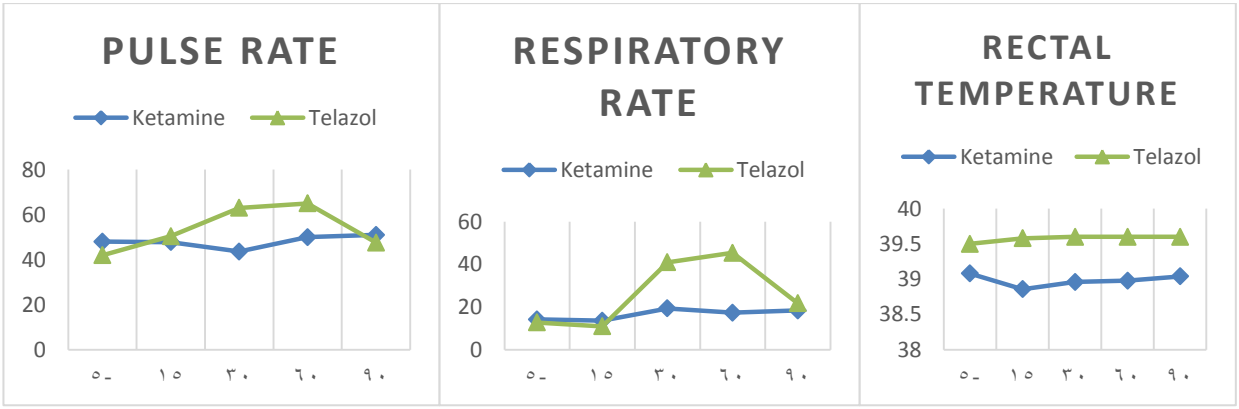

Fig. (3): showing the clinico-physiological changes after TIVA of ketamine HCl and telazol

Table (6): Clinico-Physiological findings in dogs treated with Ketamine and Telazol at different times (minutes) before and after treatment.

Parameters	Time (minutes) before and after treatment					
	-5	0	15	30	60	90
	Mean ± SD	↓	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Heart rate	48.00 ± 7.58	Xyla + Ket	47.80 ± 9.01	43.60 ± 9.86	50.00 ± 16.11	51.00 ± 16.73
	42.00 ± 2.74	Xyla + Telz	50.40 ± 7.13	63.00 ± 8.43	65.20 ± 11.30	47.60 ± 5.13
Respiratory rate	14.20 ± 6.22	Xyla + Ket	13.60 ± 5.32	19.40 ± 12.12	17.40 ± 7.33	18.40 ± 6.73
	12.80 ± 4.09	Xyla + Telz	11.00 ± 5.74	41.00 ± 20.66	45.40 ± 24.31	21.80 ± 10.69
Rectal temperature	39.08 ± 0.64	Xyla + Ket	38.86 ± 0.67	38.96 ± 0.46	38.98 ± 0.39	39.04 ± 0.52
	39.50 ± 0.50	Xyla + Telz	39.58 ± 0.40	39.60 ± 0.42	39.60 ± 0.42	39.60 ± 0.42

↓: Time of preanesthetic medication (Xylazine HCl) and general anesthetic (Ketamine or Telazol) injection.
Number of treated dogs in each treatment = 5

Table (7): Biochemical findings in dogs treated with Ketamine and Telazol at different times (minutes) before and after treatment.

Parameters	Time (minutes) before and after treatment					
	-5	0	15	30	60	90
	Mean ± SD	↓	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Cholesterol (mg/dl)	225.40 ± 40.30	Xyla + Ket	213.00 ± 26.32	205.80 ± 30.97	210.50 ± 36.70	216.33 ± 19.04
	208.60 ± 38.57	Xyla + Telz	186.80 ± 32.68	188.60 ± 47.60	192.20 ± 36.33	195.80 ± 25.96
Glucose (mg/dl)	71.72 ± 12.28	Xyla + Ket	77.88 ± 9.19	89.48 ± 17.14	101.05 ± 18.57	119.00 ± 15.87
	77.60 ± 12.03	Xyla + Telz	106.80 ± 21.22	135.04 ± 89.61	127.54 ± 50.08	142.80 ± 42.13
ALT (U/L)	30.82 ± 2.23	Xyla + Ket	32.84 ± 15.44	30.84 ± 10.72	31.75 ± 5.35	27.67 ± 8.89
	45.76 ± 2.87	Xyla + Telz	38.08 ± 2.26	46.54 ± 12.90	47.94 ± 17.93	48.54 ± 20.55
AST (U/L)	47.92 ± 12.94	Xyla + Ket	47.58 ± 21.13	41.20 ± 13.21	47.03 ± 9.76	41.40 ± 10.42
	77.36 ± 17.37	Xyla + Telz	54.68 ± 7.65	68.64 ± 24.29	78.50 ± 51.19	79.46 ± 59.94

↓: Time of preanesthetic medication (Xylazine HCl) and general anesthetic (Ketamine or Telazol) injection.
Number of treated dogs in each treatment = 5

4. DISCUSSION

Total intravenous anaesthesia (TIVA) is a technique of general anaesthesia that uses agents given solely by the intravenous route, and in the absence of all inhalation agents, TIVA always involves the delivery of a bolus dose or a fast loading infusion to achieve an adequate blood concentration of the anaesthetic drug, the ideal intravenous anaesthetic agent for TIVA should be painless and non-irritant on injection, while rapidly inducing sleep with a minimum of respiratory and cardiovascular side effects. In addition, the potential for anaphylactic and other allergic reactions should be very low *(Waelbers et al., 2009).* In this investigation ketamine HCl was compared with telazol as TIVA to evaluate their clinical anesthetic importance and the results showed that the combination of xylazine -as a preanesthetic medication- with either ketamine HCl or telazol -as total intravenous anesthesia- produce a comparable degrees of general anesthesia, while there were some differences between each other in the clinico-physiological, hemato-biochemical and anesthetic values. Ketamine HCl is considered a potent general anesthetic drug as the dogs in ketamine group exhibited the anesthetic signs such as; loss of conscious, absence of sensation to pin prick test and loss of major body reflexes except palpebral. This finding similar to the result of *Ferreira et al. (2015);* Ketamine was associated with better quality of induction and myoclonus scores. Also the smooth induction of telazol was observed. Telazol produces anesthesia within 5-12 minutes of administration and optimum muscle relaxation within 20-25 minutes. This result of good quality induction may be related to the dissociative anesthetic effect of both drugs as the expression of dissociative result from dissociation from the surroundings and this case accompanied by a state of superficial sleep with consciousness and unconsciousness alternatively *(Gross, 2009).* There was found that ketamine HCl is a poor muscle relaxant so the need of injectable muscle relaxant prior to TIVA with ketamine is important to avoid muscle twitching *Daabiss et al. (2009)* reported that ketamine possibly increases muscle tone and it induces spontaneous movement and, occasionally, convulsions. In contrast telazol is a good muscle relaxant and also can be used with or without muscle relaxant and the reasons behind that are; telazol is composed of 1:1 combination of the dissociative anesthetic, tiletamine and the benzodiazepine tranquilizer, zolazepam *(Sulli et al., 2008)* Tiletamine (hydrochloride) is an arylaminoalkalone, non-narcotic dissociative anesthetic agent; its pharmacologic action is characterized by rapid induction and cataleptoid anesthesia *(Wilson et al., 1993).* Zolazepam is a nonphenothiazine, benzodiazepine tranquilizer whose minor tranquilizing properties cause muscle relaxation *(Dhanonjoy et al., 2007).* Regarded to the depth of anesthesia, telazol was better than ketamine, as there were responses to pinching, head elevation,

ear erection, palpebral reflex, tongue appearance, teat/penis erection and anal straining with ketamine treated dogs. This also was similar to results of *Gross (2009)*. Telazol treated dogs were characterized by smooth prolonged recovery period in almost cases, the same results with *Lin (1996)*, in contrast recovery from ketamine was rapid and smooth, had a half-life of 4 hours or longer. That may be due to the poorly bound to plasma proteins, but some of its metabolites are still pharmacologically active that agreed with *Ghoneim and Korttila (1997).* Telazol also provided a gradual and predictable recovery, *Stirling et al. (1989)* supported our results, marked ataxia in the posterior part of hind limb and this regarded to; tiletamine produces a spectrum of central nervous system (CNS) effects ranging from excitement and ataxia at low doses to catalepsy and anesthesia at higher doses. These CNS effects are highly species specific, but catalepsy prevails in all species at moderate doses the same with *Wilson et al. (1993).* The present study revealed decrease in pulse rate and respiratory rate during first 30 minutes after I/V injection of ketamine then gradual increase till return to the baseline before ketamine induction, *Dhanonjoy et al., (2007)* have reported the same results, the reason may be regarded to the temporarily and partially bradycardic effect of xylazine *(Kim et al. 2007).* Other reason for the depressant action of ketamine TIVA is that ketamine is unique among anesthetics in that it maintains or increases cardiac output (CO) as a result of increased sympathetic efferent activity *(Wong & Jenkins, 1974)*, except under conditions of catecholamine depletion where ketamine may act as a direct myocardial depressant *(Pagel et al. 1992).* There was Increase in pulsation after induction of telazol *Dhanonjoy et al. (2007)* agreed with our result. The increased HR and respiratory rate of tiletamine–zolazepam is attributed to increased sympathetic tone and perhaps decreased vagal tone. There was a non-significant changes in rectal temperature, the decrease in RT may be due to generalized sedation, decrease in metabolic rate, muscle relaxation *(Zhang et al, 2012),* the curve was fluctuated toward increasing line the cause regarded to the season of the experiment was in summer. This study showed decrease in WBCs, RBCs and platelets count, also result revealed decrease in hematocrit and hemoglobin percent with reduction of each ALT, AST and cholesterol over whole the experiment of the two treatments. The decrease in these parameters during anaesthesia or sedation may be due to shifting of fluid from the extravascular compartment to the intravascular compartment, Zhang et al. (2012) agreed with this result.

5. CONCLUSION

Both ketamine HCl and telazol had no clinically significant effect on the clinico-physiological parameters and also hemato-biochemical values of the dog, but telazol is considered a good general anesthetic, muscle relaxant and analgesic. Both drugs can be used as TIVA in dogs. Telazol can be used only without muscle relaxant. Telazol has the longest duration of anesthesia, so it is recommended to use telazol as a total intravenous anesthetic in surgical purposes of long duration. Also the drug of choice for post-operative analgesia. This could be an option for induction and surgical procedures in dogs. Finally, telazol is better than ketamine HCl as a TIVA despite its high cost.

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