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Effects of Anaesthetic Protocol on Kidney and Liver Function of Female Dogs undergoing Ovariohysterectomy

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ABSTRACT

Background: Nearly all anaesthetic agent decreases renal and hepatic blood flow, so anaesthetic agents should be selected properly in patients particularly with pre-existing renal and hepatic impairment. The present study conducted to evaluate the effect of acepromazine, midazolam and dexmedetomidine as pre-anaesthetic agent followed by induction with propofol and maintenance with isoflurane on kidney and liver function of client-owned female dogs undergoing elective ovariohysterectomy.

Methods: Thirty-two clinically healthy female dogs were randomly divided into four groups with ten animals in the groups A and B and six animals in groups C and D for elective ovariohysterectomy. Animals were premedicated with acepromazine-butorphanol in group A, midazolam-butorphanol in group B, dexmedetomidine (I/M)- butorphanol in group C and dexmedetomidine (I/V)- butorphanol in group D. Animals in all four groups were induced (till effect) with propofol and maintained with isoflurane.

Result: All the groups showed non-significant marginal decline in BUN and serum creatinine at 5 minutes after pre-medication. Serum AST and ALT were non-significant decreased in groups A and B and non-significant increase in groups C and D during observations. Serum albumin and globulin gradually but non-significantly decrease in group A after premedication to T20 during anesthesia with isoflurane, then gradually increase upto extubation, but values remained lower in comparison to base values.

Key words: Aceprmozine, Alanine aminotransferase, Aspartate aminotransferase, BUN, Creatinine, Dexmedetomidine, Dog, Midazolam.

INTRODUCTION

Anaesthetic agent and their metabolites, underlying diseases, drug reaction and surgery adversely affect renal and hepatic function (O'Connor *et al.,* 2010). The kidneys receive nearly 25% and liver 20% of the body's cardiac output and are highly dependent for proper function on adequate blood flow. Nearly every anaesthetic agent decreases renal and hepatic blood flow, so anaesthetic agents should be selected properly in patients particularly with pre-existing renal and hepatic impairment. Due to intrinsic autoregulatory capacity of the kidney renal blood flow and glomerular filtration rate generally remain constant despite variations in systemic arterial blood pressure between 75 and 160 mm Hg. General anesthesia and surgery may adversely affect renal function by causing increased release of antidiuretic hormone (ADH), which results in vasoconstriction of the splanchnic and renal blood vessels while increasing water reabsorption from the renal tubules. Impairment in renal function secondary to anaesthesia and surgery is also due to decrease in effective circulating blood volume; after therefore blood volume should be maintained with the use of fluids (Monroe *et al.,* 1993). Maintenance of adequate blood flow and oxygen delivery during general anaesthesia is also important to prevent damage the hepatocytes (Weil *et al.,* 2010). The liver plays an important role in maintaining hemostasis and liver-associated hemostatic abnormalities. Liver is responsible for the metabolism and biotransformation of most of anaesthetic agent. It is important to maintain arterial carbon dioxide level, because hyperventilation and hypoventilation can result in a decrease in hepatic blood flow. Hypovolemia and dehydration should be avoided and corrected before anaesthesia. The routine intravenous administration of fluid to healthy dogs during anaesthesia is controversial. Intravenous fluids during surgery are administered to compensate the anaesthetic induced hypotension, haemorrhage and fluid losses from evaporation. Potential complications that may develop after fluid administration include circulatory overload, pulmonary edema and renal medullary wash out (Gayno *et al.,* 1996). Proper fluid therapy during anaesthesia prevents these complications. Serum concentrations of aspartate aminotransferase (AST), alanine amino-transferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), blood urea nitrogen (BUN), albumin and globulin are

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routinely measured in human and veterinary medicine as clinical indicators of hepatocellular and renal damage (Nishiyama *et al.,* 1998).

Pre anaesthetics and anaesthetic agents should be selected to support for maintain the blood flow in the vital organ. Premedication with sedatives and analgesic agents decrease the induction and maintenance dose of general anaesthesia. These general anaesthetic agents decrease cardiac output and reduce hepatic and renal blood flow. Acepromazine is a long-lasting (6 to 8 hours) phenothiazine tranquilizer and a dopamine antagonist (Baldessarini, 2001) and premedication with lower dose of acepromazine in renal patients may be advantageous because of the vasodilatory effect. Opioids also have many beneficial effects in patients with renal and hepatic impairments. They provide sedation and analgesia without reducing cardiac output (Lamont and Mathews *et al.,* 2007). Benzodiazepines used for tranquilization and muscle relaxation in patients with renal and hepatic disease. They may counteract the deleterious effects of anaesthetic agents like ketamine or decrease the dose of induction agents.

Propofol widely used as induction agent. It is an organ-protective agent by its efficient membrane-targeted and cytoprotective effects (Sellbrant *et al.,* 2016). Propofol has organ protective effects against reperfusion in many organs, such as the heart, kidney, liver and intestines (Li *et al.*, 2016; Motayagheni and Eghbali, 2016). Gaseous anaesthetic agent like halothane adversely affects liver and kidney function. New inhalational anaesthetic, isoflurane, sevoflurane commonly used as maintenance of anaesthesia has minimum effect on kidney and liver function. The objective of this study is to evaluate the effect of acepromazine, midazolam and dexmedetomidineas pre-anaesthetic agent followed by induction with propofol and maintenance with isoflurane on kidney and liver function of client-owned dogsundergoing elective ovariohysterectomy.

MATERIALS AND METHODS

The study was conducted in Referral Veterinary Polyclinic, IVRI, Izatnagar, (U.P.) India during period of 2018-2020. Thirty two clinically healthy client owned canines, irrespective of breed, weighing more than 5 kg and 16 weeks age to 6 years that were subjected for ovariohysterectomy in their physical status I according to the American Society of Anaesthesiologists Classification (Daabiss, 2011). The dogs were randomly divided into four groups with ten animals in the groups A and B and six animals in groups C and D.

The dogs were subjected to preoperative check up that included renal and hepatic function. The dogs were kept off fed for 12 hours prior to the trial of anaesthesia. After surgical preparation of the animal, atropine sulphate was given @ 0.04 mg/kg body weight intramuscularly in all the four groups. After 5 min animals were premedicated with acepromazine-butorphanol in group A, midazolam-butorphanol in group B, dexmedetomidine (I/M)-butorphanol in group C and dexmedetomidine (I/V)-butorphanol in group D. After 10 minutes premedication animal was induced (till effect) with propofol in all groups. Immediately just after induction animal was intubated and maintained with isoflurane till the last skin suture closed. The endotracheal tube was extubated once tracheal reflex regained. All the recordings were made before administration of drug, 5 minutes after administration pre-anaesthetic, immediately after induction and at 20, 40, 60 minutes during maintenance and after extubation. The blood samples were collected and centrifuged at 3000 revolutions per minutes for 15 minutes following which the serum was separated and stored at -20°C. Serum samples was used for estimation of the aspartate aminotransferase (AST), alanine amino-transferase (ALT), blood urea nitrogen (BUN), serum creatinine, albumin and globulin with the help of autoanaliser. The values of plasma creatinine were expressed in mg/dL whereas aspartate aminotransferase and alanine amino-transferase expressed in IU/L. Similarly albumin and globulin where expressed in gm/dl.

ANOVA (Analysis of variance) and Duncan's multiple range test (DMRT) were used to compare the means at different time intervals between different groups. Repeated measures ANOVA were used to compare the mean values at different intervals with their base values in each group (Snedecor and Cochran, 1994).

RESULTS AND DISCUSSION

Blood urea nitrogen changed non-significantly at various intervals from respective base values and in between groups at different interval of time during the observation period in all the four groups. BUN declined non-significantly (P>0.05) at 5 minutes after pre-medication in comparison to base values. Values of blood urea nitrogen were found nearly the same after pre-medication and just after induction with propofol in all the four groups (Table 1 and Fig 1). However, serum creatinine decreases non-significantly at all intervals during observation in comparison to base values in all groups (Table 1 and Fig 2). Groups A and B showed gradual non-significant decrease in serum creatinine at 5 minutes after pre-medication up to observation period. However, in groups C and D such gradual non-significantly decreased in serum creatinine were not observed.

Serum AST gradually decreases in group A after pre-medication during entire observations period except at extubation. However, group B showed a gradual reduction of serum AST up to T20 during maintenance with isoflurane after that serum AST gradually increase up to observation period, but remained lower in respect to base values. In groups C and D serum AST increased non-significantly after pre-anaesthetic administration. However, after pre-medication serum AST value did not showed a regular pattern of decrease or increase, but, the values of serum AST were lower at extubation with comparison to base values (Table 2 and Fig 3). Comparison between the groups showed that serum AST non-significantly (p>0.05) change at various intervals of time. Similarly, serum ALT differed non-significantly in all the four groups from the base values and in between groups at different interval of time during the

observation period (Table 2). Serum albumin and globulin gradually but non-significantly decrease ($p>0.05$) in group A after premedication to T20 during anesthesia with isoflurane, then gradually increase upto extubation, but values remained lower in comparison to base values (Table 2). Similarly, to group A, group B showed a similar pattern of decrease in serum album in upto induction and globulin up to T20 during anesthesia with isoflurane. Group C showed that serum albumin and globulin decreased non-significantly after pre-anaesthetic administration and then gradually increased at all intervals during observation period. In group D serum albumin and globulin reduced non-significantly more after pre-medication in comparisons too ther intervals (Fig 4).

In this study, the serum activities of BUN and creatinine lower after premedication in all protocol of anaesthesia, whereas serum AST, ALT decrease in acepromazine and midazolam groups and increase in both dexmedetomidine group (IM or IV) after pre-medication. In the present study,

Table 1: Mean ± SD values of serum blood urea nitrogen (BUN) (mg/dL) and serum creatinine (mg/dl) recorded in all the four groups at various intervals.

Parameters	Groups	Before pre-	After 5 min. pre-	At induction	T20	T40	At extubation
		Anaestheticanaesthetic					
BUN (mg/dL)	A	12.08±8.02	11.50±6.56	11.55±5.98	9.85±3.65	12.21±5.51	10.68±5.09
	B	15.29±7.54	12.17±3.63	13.51±2.74	13.33±3.57	12.78±3.43	12.35±1.97
	C	12.13±6.46	10.92±4.84	10.13±4.90	10.31±4.15	11.19±6.32	8.67±2.49
	D	14.56±4.416	14.15±6.66	14.28±4.27	15.57±5.82	14.73±6.80	13.67±7.39
Serum creatinine	A	1.15±0.29	1.12±0.29	1.00±0.24	0.97±0.23	0.83±0.18	0.97±0.14
(mg/dL)	B	1.17±0.31	1.07±0.36	1.13±0.34	1.01±0.31	0.99±0.49	0.86±0.36
	C	1.21±0.46	0.92±0.17	0.91±0.33	1.07±0.29	1.08±0.36	1.20±0.39
	D	1.16±0.40	1.10±0.39	1.05±0.37	1.07±0.52	0.86±0.44	0.95±0.30

The means with a different lower case superscript in a row differ significantly and the means with a different upper case superscript in a column differ significantly ($p<0.05$).

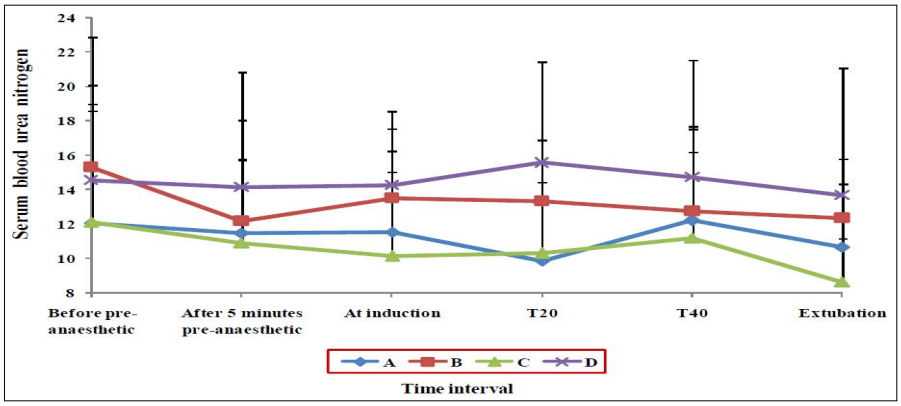

Fig 1: Mean±SD values of serum blood urea nitrogen (BUN) (mg/dL) recorded in all the four groups at various intervals.

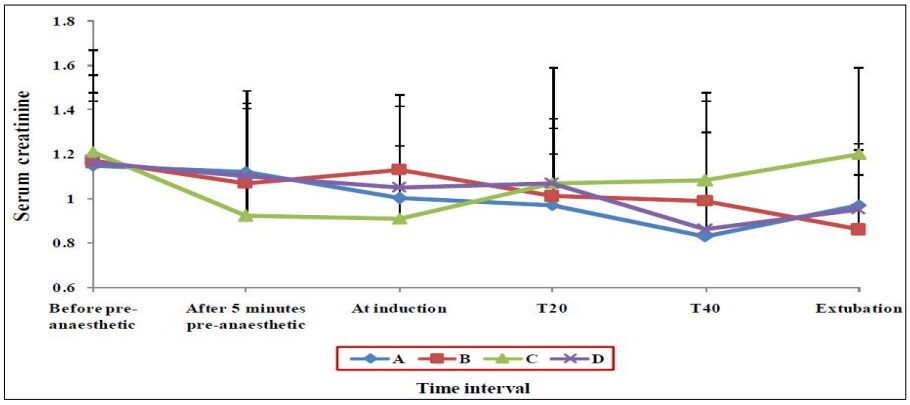

Fig 2: Mean ± SD values of serum creatinine (mg/dL) recorded in all the four groups at various intervals.

the decrease in blood urea nitrogen level might be due to continuous intravenous infusion of fluids, which maintained the normal kidney functions. In the present study, all the observed values of BUN were within the normal physiological limits.Similar non-significant decrease in blood urea nitrogen was reported by Kalaiselvan (2018) during pre-medication with DEX-BUT accompanied by induction and maintenance with propofol. Surbhi *et al.* (2010) was also reported that BUT along with xylazine, medetomidine and dexmedetomidine caused non-significant decline in BUN in canine undergoing orthopaedic surgery. However, Rafee (2013) reported pre-medication with DEX along with BUT or pentazocine accompanied by induction and maintenance with midazolam and ketamine caused non-significant rise in BUN in canines. Kinjavdekar *et al.* (2000) suggested that temporarily increase in urea nitrogen values might be due to decrease renal blood flow due to anaesthesia, but present study showed non-significant reductionin BUN, probably due to continuous administration of intravenous fluids, which maintained the normal circulatory fluid volume kidney functions.

Marginal changes in serum creatinine might be due to the intrinsic auto regulatory capacity of the kidney that kept glomerular filtration and renal blood flow rate generally constant in spite of variations in systemic arterial pressure between 75 and 160 mm Hg (Brown, 1993). Bostrom *et al.* (2003) observed a significant reduction in serum creatinine in dogs pre-medicated with acepromazine, however, the present study showed non-significant decrease in serum

Table 2: Mean ± SD values of serum AST (IU/L), serum ALT, serum albumin and serum globulin recorded in all the four groups at various intervals.

Parameters	Groups	Before pre-	After 5 min. pre-	At induction	T20	T40	At extubation
				Anaesthetic			
Serum AST	A	56.80±27.45	55.54±36.05	54.47±19.94	50.00±18.36	44.15±15.13	49.73±14.72
	B	47.33±12.87	43.29±12.82	44.18±12.18	39.48±17.15	40.67±7.93	46.94±14.65
	C	43.50±13.28	61.66±18.59	39.13±11.39	44.88±10.32	46.56±3.70	39.03±7.75
	D	56.71±18.80	59.67±26.74	53.00±15.34	70.46±32.00	61.83±10.14	54.48±7.69
Serum ALT	A	59.29±39.91	52.70±42.34	39.45±17.51	36.80±14.90	39.00±31.90	42.90±35.05
(IU/L)	B	40.50±18.63	38.50±19.17	35.30±13.11	44.12±21.52	36.50±17.32	22.50±8.15
	C	38.83±11.68	47.50±13.72	45.33±26.64	38.66±19.96	26.83±20.35	47.33±15.68
	D	35.66±15.38	37.01±19.76	39.33±20.45	43.83±13.61	52.66±22.46	42.66±25.34
Serum albumin	A	3.48±0.83	3.33±0.55	3.27±0.43	3.01±0.37	3.03±0.32	3.05±0.54
(gm/ dL)	B	3.58±0.50	3.37±0.43	3.31±0.42	3.47±0.80	3.31±0.46	3.47±0.88
	C	3.26±0.69	3.48±0.28	3.06±0.28	3.09±0.31	3.19±0.17	3.04±0.16
	D	4.00±0.66	3.47±0.60	3.66±0.31	3.67±0.53	3.51±0.10	4.10±2.01
Serum globulin	A	3.09±1.45	2.80±1.94	2.23±0.91	1.93±1.25	2.01±1.84	2.12±1.12
(gm/ dL)	B	2.64±1.11	2.58±0.97	2.46±0.97	2.41±1.61	2.58±1.58	2.29±0.88
	C	2.92±0.86	2.26±0.92	2.39±0.66	2.55±0.71	2.82±1.19	2.83±1.30
	D	2.94±1.24	1.86±0.74	2.37±0.91	2.27±1.28	2.75±1.90	2.64±1.58

The means with a different lower case superscript in a row differ significantly and the means with a different upper case superscript in a column differ significantly ($p<0.05$).

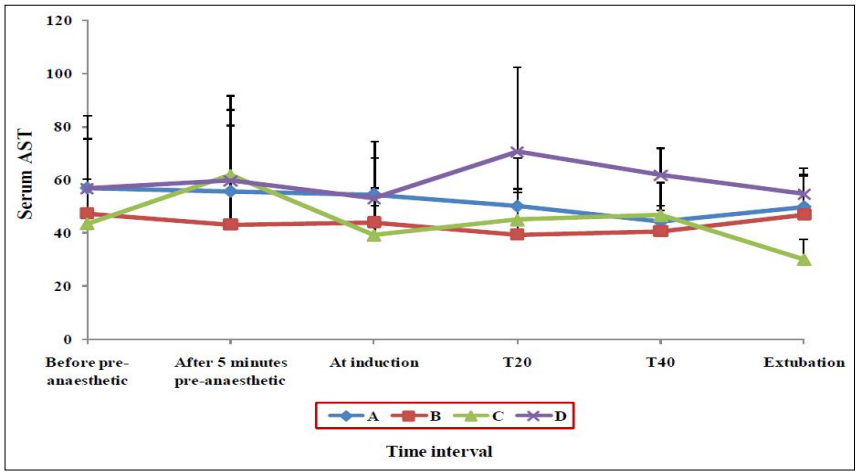

Fig 3: Mean±SD values of serum AST (IU/L) recorded in all the four groups at various intervals.

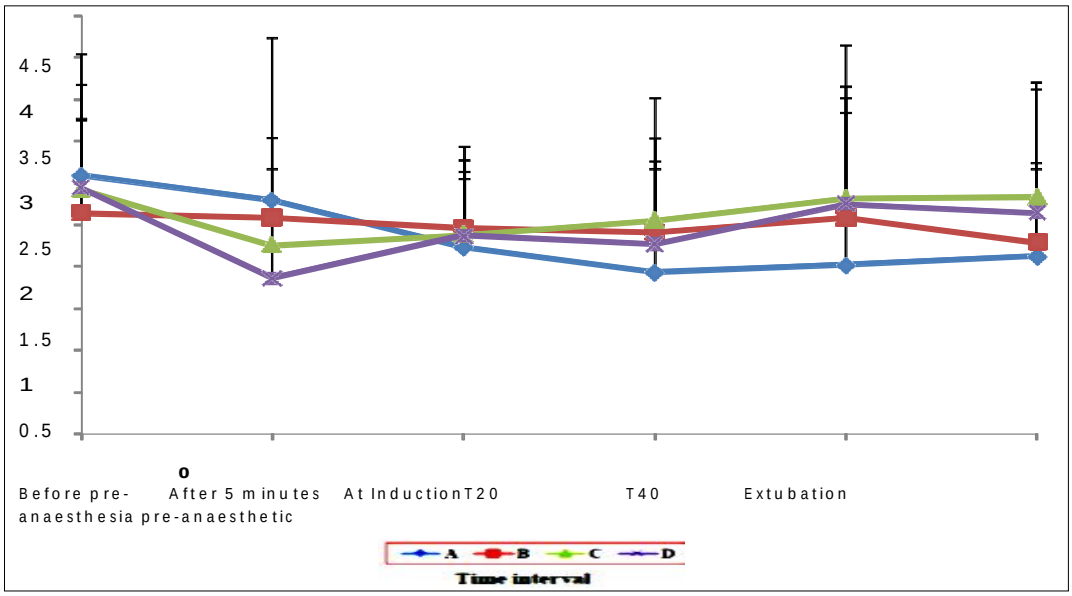

Fig 4: Mean±SD values of serum globul in recorded in the four groups at various intervals.

creatinine. Lobetti *et al.* (2000) suggested that sufficient renal function was maintained in healthy canines undergoing elective surgery under general anaesthesia even without concurrent intravenous fluid administration. They also reported that kidneys of dogs are generally resistant to ischemia-induced by hypotensive shock. Marginal non-significant decrease in serum creatinine in groups C and D might be due to dexmedetomidine role in preserving blood supply to most vital organs at the cost of non-vital organs and this redistribution does not depend upon type of anaesthesia used for maintenance (Lawrence *et al.,* 1996). Continuous fluid therapy and redistribution of blood supply by DEX might be responsible for adequate renal blood flow and normal glomerular filtration to maintain creatinine values near the base values. The present finding was in accordance with that of Kalaiselvan (2018).

Values of serum AST and serum ALT in the present study changed non-significantly at different intervals. Recorded values of serum AST showed non-significant decrease in groups A and B and non-significant increase in groups C and D during observations, whereas ALT showed non-significant decrease in groups A B and D and non-significant increase in groups C during observations. Alexandra (2003) and Stedile *et al.* (2009) did not find changes in serum ALT values with acepromazine, propofol and isoflurane anaesthesia in canines during laparoscopy surgery, however, the present study showed non-significant decrease in serum ALT in group A. Similar to present finding in group A, Chavhan (2014) reported a non-significant decrease in serum AST and ALT at different intervals within the group receiving butorphanol-acepromazine-propofol anaesthesia in canines. Increase in level of ALT and AST attributed hepatocytes damage resulting into the membranes becoming more permeable or wall may rupture, so that the enzyme diffuse into the blood stream and its level is increased in the blood circulation (Koichev *et al.,* 1988). However, in present study change in serum AST and ALT values was non-significant and within physiological limits. This is an indicative of least deleterious effects of dexmedetomidine and butorphanol combinations on liver (Bisht *et al.,* 2016). Sharma *et al.* (2014) also recorded a similar pattern of non-significant increase in serum ALT levels in the canines after systemic administration of dexmedetomidine. Singh *et al.* (2010) observed that medetomidine caused non-significant difference in serum AST and ALT in calves. In the present study, serum globulin and albumin in all four groups showed non-significant decrease at various intervals during an observation period in comparison to the respective baseline values. Potliya *et al.* (2015) also reported similar finding during premedication with glycopyrrolate and xylazine and induction with propofol. This decrease in serum globulin and serum albumin was might be attributable to haemodilution due to continuous fluid therapy during the entire period of observation and shifting of ECF to the intravascular compartment to maintain normal CO during anaesthesia. The similar findings were also reported by Dinesh (2017) during pre-medication with atropine- midazolam-pentazocine followed by induction and maintenance with propofol.

CONCLUSION

In present study, pre-medication with acepromazine, midazolam and dexmedetomidine with butorphanol and atropine sulphate followed by induction with propofol and maintenance with isoflurane did not affect kidney and liver function significantly. However, liver function decreases after pre-medication with dexmedetomidine either intravenous or intramuscular groups. So, pre-medication with acepromazine or midazolam with butorphanol and atropine sulphate followed by induction with propofol and maintenance with

isoflurane along with concurrent intravenous fluid can be used safely for balanced anaesthesia in surgery of canine with liver or kidney impairment.

Conflict of interest

All authors declare that they have no conflict of interest.

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