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Effect on hemato-biochemical parameters following administration of glycopyrrolate-butorphanol, glycopyrrolate-dexmedetomidine and glycopyrrolate-acepromazine as pre-anaesthetics with propofol anaesthesia in dogs

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Abstract
The present study was conducted to evaluate the effect on various haematological and biochemical parameters following administration of glycopyrrolate-butorphanol, glycopyrrolate-dexmedetomidine and glycopyrrolate-acepromazine as preanaesthetics to propofol anaesthesia in dog. Eighteen adult dogs of either sex were randomly divided into three groups (BP, DP and AP) with six animals in each group. Ten minutes prior to the anaesthetic administration, dogs were administered with glycopyrrolate @ 0.02 mg/kg b.wt. intramuscularly and animals of group BP, DP and AP were premedicated intramuscularly with butorphanol @ 0.3 mg/kg b.wt., dexmedetomidine @ 10 µg/kg b.wt. and acepromazine @ 0.4 mg/kg b.wt. respectively. General anaesthesia was induced with propofol @ 7 mg/kg b.wt. intravenously. Haematological parameters viz. Hb, PCV, TEC, TLC and DLC and biochemical parameters viz. serum glucose, serum total protein, serum urea nitrogen, serum creatinine, ALT and AST were estimated before sedation (0) and at 30, 60,120 min. and 6 hrs post propofol anaesthesia. Haematological studies revealed a non-significant decrease in Hb, PCV, TEC TLC and DLC following propofol anaesthesia in all the groups. Hyperglycemia was noted in animals of all the groups after propofol anaesthesia. Other biochemical parameters like serum total protein, serum urea nitrogen, serum creatinine and serum enzyme viz, AST and ALT values showed non-significant changes at various time intervals but remained within normal physiological range. Therefore, it can be concluded that glycopyrrolate-butorphanol, glycopyrrolate-dexmedetomidine and glycopyrrolate-acepromazine with propofol combination does not produce any deleterious effect on vital organs and changes remained within physiological limits, thus propofol can be safely used as induction agent in dogs.

Keywords: Acepromazine, biochemical, butorphanol, dexmedetomidine, dogs, glycopyrrolate, hamatological, preanaesthetic, propofol

Introduction
Canines are subjected to a wide range of affections requiring surgical interventions which necessitate the use of a safe and effective anaesthetic that can produce sleep, amnesia and muscle relaxation. There is no single anaesthetic agent available till date that can provide these desirable effects by itself. Therefore, combination of sedatives and other anaesthetics have been widely used in animal practice to attain desirable effects of general anaesthesia. Today in an era of balanced anaesthesia, this is achieved by use of multiple drugs and characterized by muscle relaxation, unconsciousness and analgesia. The combination of complementary drugs permits use of decreased dose of each drug to achieve anaesthesia with reduction in their commensurate side effects (Grimm *et al*., 2001) [16]. For this purpose, commonest drugs used are propofol, dexmedetomidine, butorphanol, acepromazine and glycopyrrolate or atropine sulphate.

Propofol (2-6 di-isopropylphenol) is a nonbarbiturate, nonsteroid, short acting general anaesthetic that is associated with a rapid induction and recovery, but may cause hypotension and apnoea. Propofol is an intravenous hypnotic agent commonly administered intravenously for induction and maintenance of anaesthesia by bolus or continuous infusion in dogs and produces unconsciousness in a rapid, smooth and safe fashion in healthy animals (Lerche *et al*., 2000) [26]. The mechanism of action of propofol is exactly unknown but it induces depression by enchancing the effects of the inhibitory neurotransmitter GABA and decreasing

the metabolic activity of the brain (Concas *et al*., 1999). The fast redistribution from the brain to other tissues and effective clearance from plasma by metabolism accounts for the brief action and smooth emergence. Because of its lipophilic nature, propofol has a high volume of distribution (Lumb and Jones, 2007) [28]. However, propofol is a general anaesthetic with minimal analgesic property. Consequently, it is necessary to supplement propofol with analgesic drugs such as butorphanol, detomidine, xylazine, dexmedetomidine, acepromazine, etc.

Premedication of animals before induction of anaesthesia provide significant advantages in terms of cardiovascular stability, analgesia and quality of recovery (Lemke, 2007) [25]. A good preanaesthetic is needed before induction of anaesthesia with propofol to produce desired surgical anaesthesia. Glycopyrrolate inhibits cholinergic transmission by blocking peripheral muscarinic receptors and is a synthetic quaternary ammonium compound, anticholinergic with no central effects and chemically {(1,1-dimethyl-2,3,4,5-tetrahydropyrrol-3yl) 2-cyclopenty l-2 hydroxy-2-phenyl-acetate}. It is about five times as effective as atropine and has a powerful and long-lasting antisialagogue effect. Opioids are the most commonly used analgesics to supplement anaesthesia for tolerance of surgical procedures due to their efficacy, rapid onset of action and safety. Butorphanol tartrate is a centrally acting agonist antagonist type of opioid that provides sedation, short duration analgesia and reduces the dose of intravenous anaesthetics for induction (Koc *et al*., 2006) [23]. The potency of butorphanol on a weight basis as an analgesic, compared to morphine, pentazocine, and meperidine is 4-7, 15-30, and 30-50 times, respectively.

The alpha 2 adrenergic agonists are useful adjuncts to anaesthesia because of their sedative, anxiolytic and analgesic effects. Dexmedetomidine is the dextro-rotary and active enantiomer of the racemic mixture medetomidine and is the most potent and selective alpha 2 agonist commercially available today. Selective steroisomers are used in anaesthesia because of more predictable pharmacokinetics and pharmacodynamics, compared to their racemic mixture (Uilenreef *et al*., 2008) [51]. Acepromazine is a phenothiazine tranquilizer that depresses the reticular activating system and inhibits dopamine receptors in the CNS, resulting in drowsiness. It has a longer half-life in young animals because it is processed by the liver and removed by the kidney. In infants and juveniles, it produces a 4-8-hour effect. It induces mild to moderate traquilisation, muscle relaxation and a decrease in spontaneous activity attributable principally to central dopaminergic antagonism. Because of the dopamine inhibition in the chemoreceptor trigger zone, it also possesses antiemetic, antihistaminic, antiarrhythmic and antishock characteristics (Turi and Muir, 2011) [50].

Since review reveals very scanty literature on the use of propofol with glycopyrrolate, butorphanol, dexmedetomidine and acepromazine in dogs, therefore, the aim of present anaesthetic study was to assess the effect on various heamatological and biochemical parameters following administration of glycopyrrolate-butorphanol, glycopyrrolate-dexmedetomidine and glycopyrrolate-acepromazine as preanaesthetics with propofol anaesthesia in dog.

Materials and Methods

Place of work

The present work was carried out in confinement of Department of Veterinary Surgery and Radiology and Teaching Veterinary Clinical Complex (T.V.C.C.) in College of Veterinary Science & A.H. Anjora, Durg (C.G.).

Study design

Eighteen healthy dogs of either sex weighing between 10 to 20 kg body weights were randomly divided into three groups viz., group BP, group DP and group AP, comprising of 6 animals in each. All dogs were dewormed with Praziplus (Albendazole 300mg with Praziquental 25 mg) Tab. @ 1 Tab. /10 kg body weight orally fifteen days before the start of anaesthestic study. The animals were fasted overnight and the drinking water was withheld for 4 hours before the administration of anaesthesia. The animals were kept under uniform feeding and managemental practices throughout the experiment. Ten minutes prior to the anaesthetic administration, all dogs were administered with glycopyrrolate @ 0.02 mg/kg b.wt. intramuscularly. The animals of group BP, DP and AP were premedicated intramuscularly with butorphanol @ 0.3 mg/kg b.wt., dexmedetomidine @ 10 µg/kg b.wt. and acepromazine @ 0.4 mg/kg b.wt. respectively. General anaesthesia was induced with propofol @ 7 mg/kg b.wt. intravenously in animals of all the groups and dogs were intubated with suitable endotracheal tubeof (4.5 to 8.5 OD mm) with guidance of laryngoscope.

Evaluation of haematological parameters

The haeamotological parameters estimated were haemoglobin (Hb), packed cell volume (PCV), total erythrocyte count (TEC), total leucocyte count (TLC), differential leucocyte count (DLC) for which 1 ml blood sample was collected from the cephalic/saphenous/recurrent tarsal vein of each animal in vacutainer containing EDTA before premedication (0) and at 30, 60, 120 minutes and 6 hour after induction of propofol anaesthesia. These parameters were estimated by standard procedures using automatic haematological analyzer (HDC 5-Part MS4S2).

Evaluation of biochemical parameters

For estimation of biochemical parameters, 2 ml blood was collected from cephalic/saphenous/recurrent tarsal vein of each animal in vacutainers containing clot activator. Blood samples were collected from the animals before premedication (0) and at 30, 60, 120 minutes and 6 hr. post induction with propofol anaesthesia. The vials were kept in tilted position for one hour and serum was separated and collected in Eppendorf tubes for estimation of biochemical parameters. The biochemical parameters estimated were Serum Glucose, Serum Total Protein, Serum Urea Nitrogen (SUN), Serum Creatinine, Alanine Amino Transferase (ALT) and Aspartate Amino Transferase (AST) by standard procedures using semi-automated biochemical analyzer (ERBA Chem 7).

Statistical analysis

The data collected was statistically analysed using analysis of variance (ANOVA) and Duncan's multiple range tests (DMRT). The mean and standard error of the recorded values were calculated. Comparison within group and between groups was made using SPSS v25 statistics software program and data was presented as Mean±S.E. Statistically significant differences were considered at 5 percent level (5%).

Results

Haematological Parameters

Haemoglobin (gm/dL)

Animals of group BP and AP recorded non-significant decrease in the value of haemoglobin up to 60 min. post induction from 13.06±0.30 to 11.33±0.44 gm/dL and 13.04±0.15 to 11.68±1.17 gm/dL respectively whereas in group DP, haemogloblin showed non-significant decrease up to 120 min post induction from 13.02±0.35 to 11.08±1.45 gm/dL (fig.1). However, values gradually increased non-significantly and returned to preadministration level at 6 hr of the study period.

Packed Cell Volume (%)

Dogs anaesthetized with butorphanol-propofol (BP group), dexmedetomidine-propofol (DP) and acepromazine-propofol (AP) showed a non-significant decrease in the PCV at 60 min. post induction from 41.40±1.59 to 36.08±0.91%, 41.37±1.50 to 39.17±1.73% and 41.77±1.22 to 38.93±1.08% respectively as compared to base value (fig. 2). In all the three groups, PCV values then gradually increased non- significantly at 120 min. interval post induction and returned to near baseline by 6 hr of the observation periods. However, the PCV values remained within normal physiological range in all the three groups.

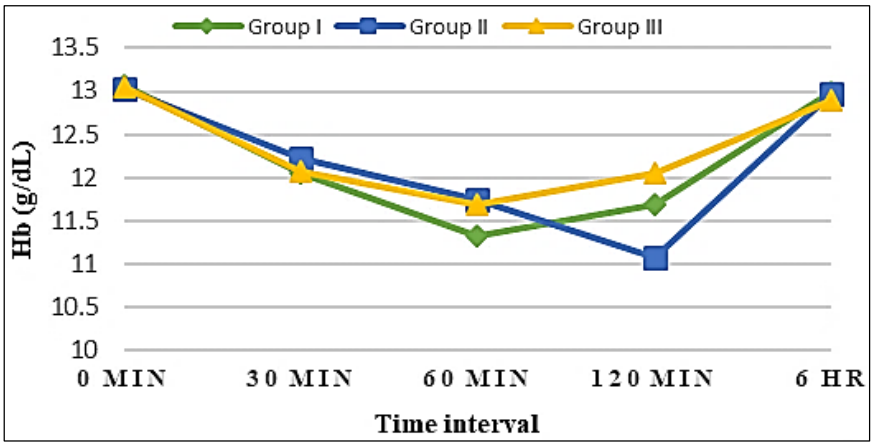

Fig 1: Effect on Haemoglobin (g/dL) after induction with propofol in different groups

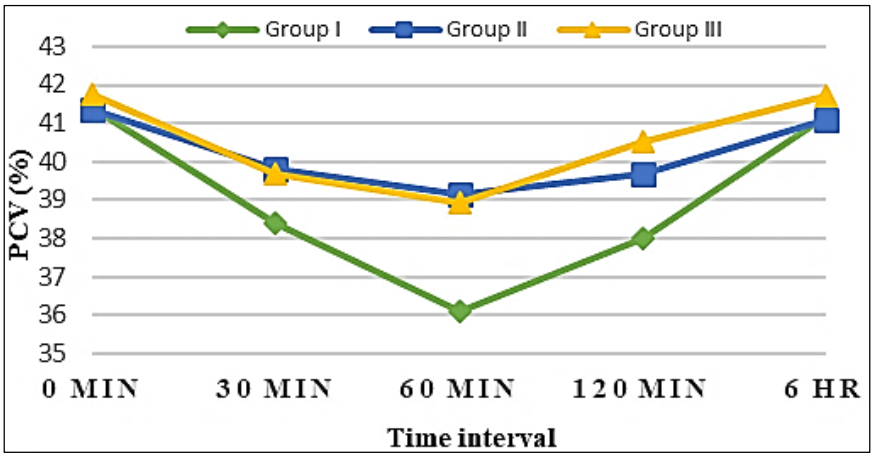

Fig 2: Effect on Packed cell Volume (%) after induction with propofol in different groups

Total Erythrocyte Count (×10^6 / µL)

Mean TEC level in group BP (butorphanol-propofol) and group AP (acepromazine-propofol) recorded non-significant decrease at 60 min. post induction from 6.15±0.28 to 5.54±0.24 (× 10^6/µL), and 6.22±0.20 to 5.65±0.28 (×10^6 /µL) respectively as compared to base value (fig.3.). On the other hand, animals of group DP (dexmedetomidine-propofol) showed a non-significant decrease up to 120 min. post induction from 6.16±0.21 to 5.36±0.20 (× 10^6/µL). Mean TEC values which further increased non-significantly and returned to near baseline at 6 hr of the observation period in all the three groups. However, the TEC values remained within normal physiological range in all the groups. Total erythrocyte count (TEC) values showed non-significant difference between groups at various time interval of the observation period.

Total Leucocyte Count (× 10^3/µL)

The trend in TLC in animals premedicated with butorphanol, dexmedetomidine and acepromazine and anaesthetized with propofol showed decline following induction of anaesthesia. A non-significant decrease in TLC was recorded at 60 min. post induction in group BP from 8.40±0.63 to 7.75±0.57 × 10^3/µL whereas the animals of group DP and group AP showed non-significant decrease up to 120 min. post induction from 8.41±0.59 to 8.04±0.61 (× 10^3/µL) and 8.70±0.36 to 8.16±0.33 (× 10^3/µL) respectively (fig.4.). TLC values then further increased non-significantly and returned to near baseline at 6 hr of the observation periods in all the three groups. However, the TLC values remained within normal physiological range in all the groups. Total leucocyte count (TLC) values showed non-significant difference between groups at various time interval of the observation period.

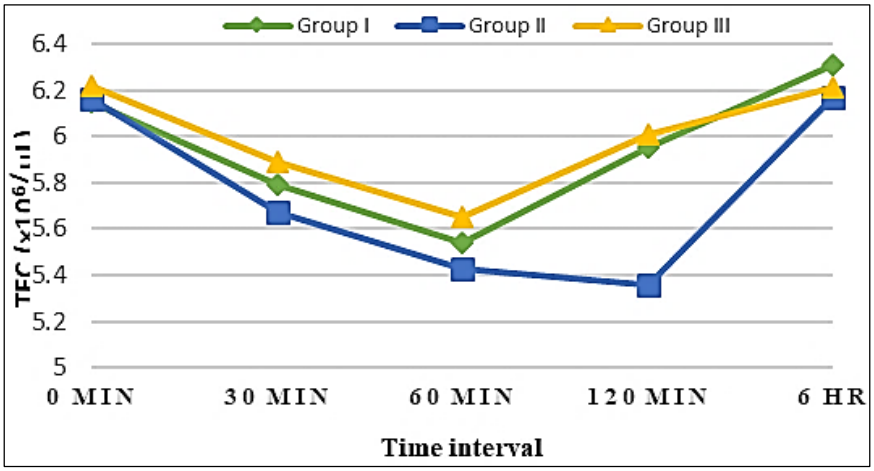

Fig 3: Effect on TEC ($\times 10^6/\mu L$) after induction with propofol in different groups

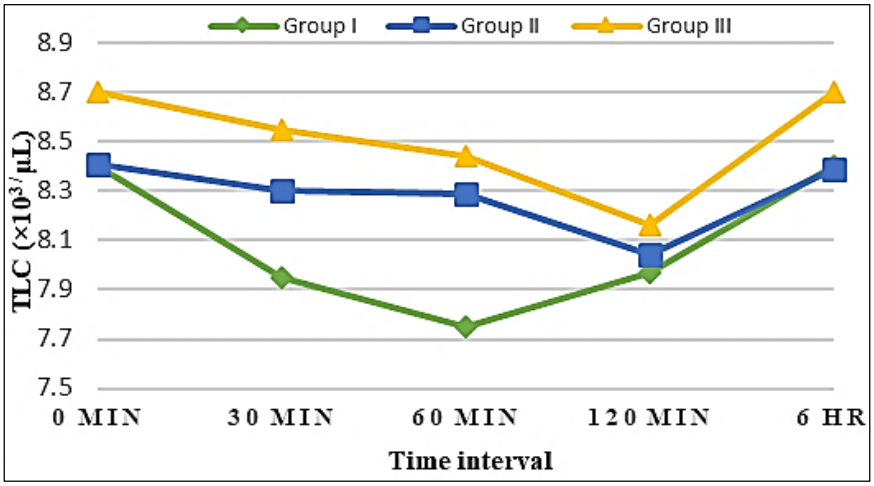

Fig 4: Effect on TLC ($\times 10^{3}/\mu L$) after induction with propofol in different groups

Neutrophils (%)

There was an increase in neutrophil count in animals anaesthetized with butorphanol-propofol, dexmedetomidine-propofol and acepromazine-propofol following induction with propofol anaesthesia. Group BP recorded a non-significant increase of neutrophil count up to 60 min. post induction from 71.63±2.54 to 72.52±2.53% which further showed deceasing trend to reach the baseline at 6 hr of observation period. On other hand, animals of group DP and AP showed a non-significant increase up to 120 min. post induction from 72.5±1.56 to 74.96±2.41% and 72.45±0.53 to 74.58±2.51% respectively (fig.5.). These values returned to near base value at 6 hr of the study period. Neutrophil count showed non-significant difference between groups at various time interval of the observation period. However, neutrophil count remained within normal physiological range in all the three groups. There was a corresponding neutrophilia in response to lymphopenia as observed in animals of the three groups.

Lymphocytes (%)

There was lymphocytopenia in animals anaesthetized with butorphanol-propofol, dexmedetomidine-propofol and acepromazine-propofol following induction with propofol anaesthesia. Animals of group BP showed a non-significant decrease in lymphocyte count up to 60 min. post induction from 23.43±1.17 to 22.53±0.42% as compared to base value. On other hand, animals of groups DP and AP recorded a non-significant decrease up to 120 min. post induction from 23.85±0.84 to 22.28±0.88 % and 23.45±1.29 to 22.22±1.08% respectively (fig.6.). However, these values returned to near normalcy within 6 hrs of observation period in all the three groups and lymphocyte count remained within normal physiological range. Lymphocyte count showed a non-significant difference between groups at various time interval of the observation period. Lymphopenia was observed in animals in all the three groups in response to neutrophilia following induction of propofol anaesthesia

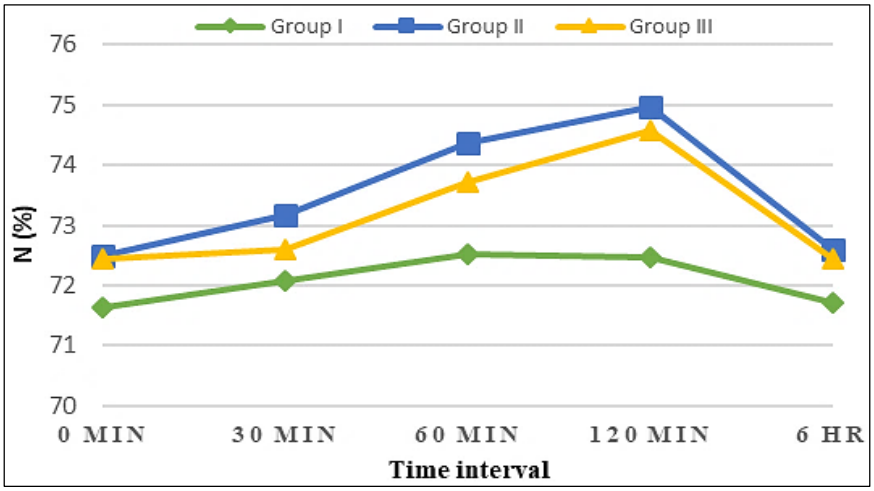

Fig 5: Effect on Neutrophil (%) after induction with propofol in different groups

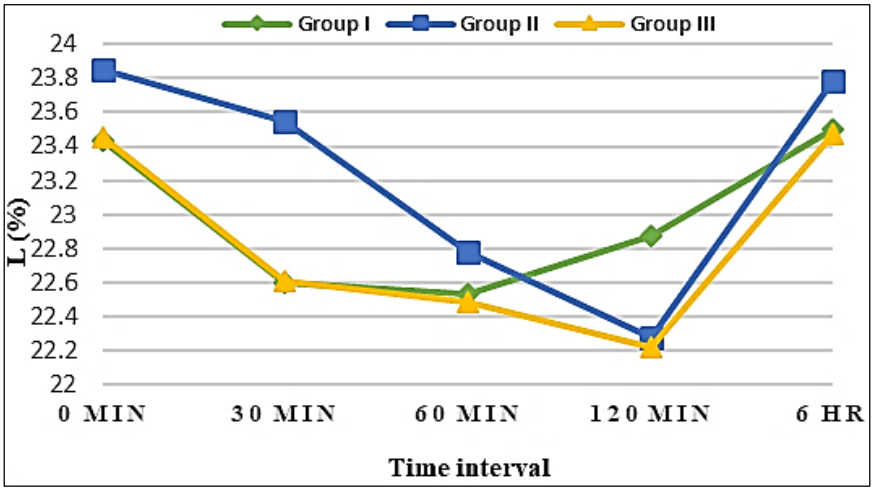

Fig 6: Effect on Lymphocyte (%) after induction with propofol in different groups

Eosinophils (%)

Eosinophil count showed a non-significant decrease in animals anaesthetized with butorphanol-propofol, dexmedetomidine-propofol and acepromazine-propofol following induction with propofol anaesthesia which fluctuated and returned to normalcy. Animals of group BP and AP showed a non-significant decrease in eosinophil count (%) up to 60 min. post induction from 1.99±0.15 to 1.65±0.10% and 1.98±0.11 to 1.62±0.11% respectively (fig.7.) On other hand, animals of group DP recorded a non-significant decrease up to 120 min. post induction from 2.01±0.16 to 1.58±0.19%. However, eosinophil count increased non-significantly and returned to near normalcy within 6 hrs of the study period. In all the three groups, eosinophil count remained within normal physiological range. The eosinophil count showed non-significant difference between groups at various time interval of the observation period.

Monocytes (%)

Monocyte count showed non-significant decrease in animals anaesthetized with butorphanol-propofol, dexmedetomidine-propofol and acepromazine-propofol following induction with propofol anaesthesia which fluctuated and returned to normalcy. Group BP and DP showed a non-significant drop in monocytes count upto 120 min. post induction from 2.88±0.30% to 2.50±0.27% and 2.60±0.15% to 2.17±0.12% after administration of butorphanol-propofol and dexmedetomidine-propofol respectively (fig.8.). On the other hand, group AP recorded a non-significant decrease at 60 min. post induction from 2.82±0.24% to 2.58±0.27% after administration of acepromazine-propofol. Thereafter, the monocytes count increased gradually and returned to base value at 6 hrs of the study period in all the groups.

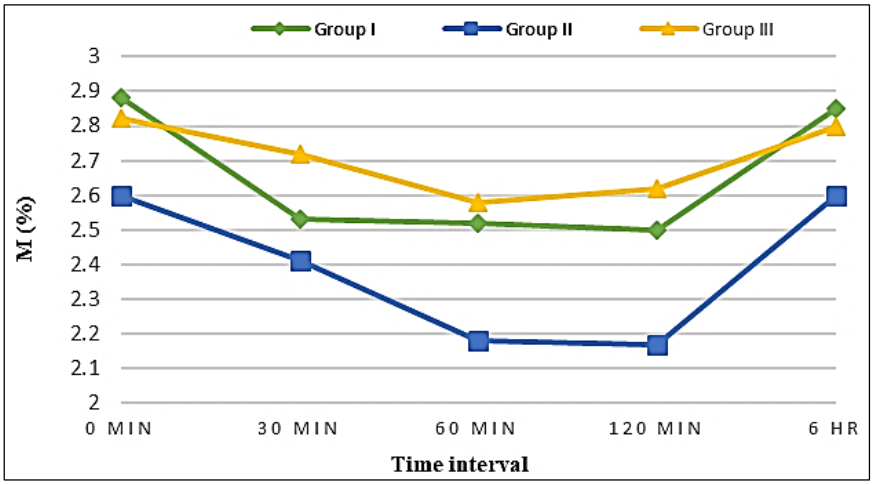

Fig 7: Effect on Monocyte (%) after induction with propofol in different groups

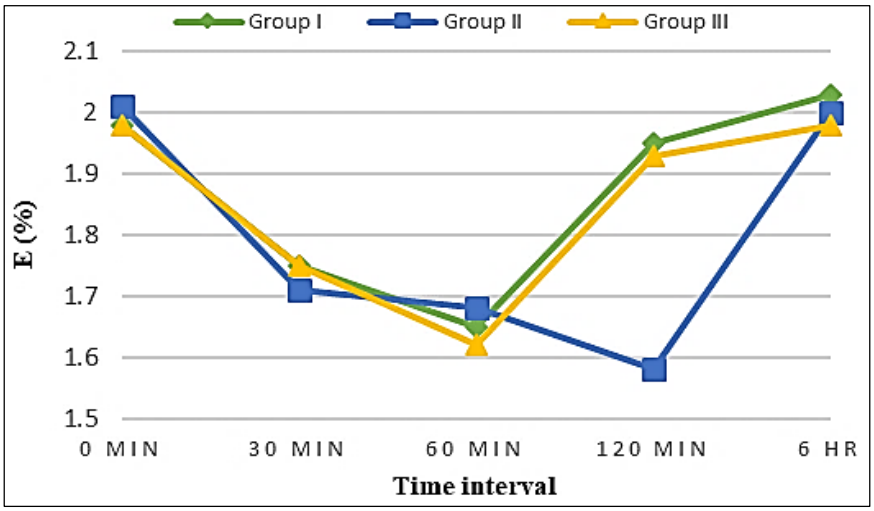

Fig 8: Effect on Eosinophil (%) after induction with propofol in different groups

Biochemical parameters

Serum Glucose (mg/dL)

Hyperglycemia was noted in all the three groups following induction with propofol anaesthesia. In group BP and AP, a significant (P<0.05) increase in serum glucose was recorded up to 60 min. post anaesthesia from 87.24±1.20 to 104.27±2.03 mg/dL and 89.10±1.53 to 102.66±1.35 mg/dL after administration of butorphanol-propofol and acepromazine-propofol respectively (fig.9.). On other hand, animals of group DP showed a significant (P<0.05) increase in serum glucose was recorded up to 120 min. post induction from 87.89±1.45 to 108.37±1.70 mg/dL after administration of dexmedetomidine-propofol. Thereafter, the serum glucose level decreased significantly (P<0.05) and returned to normalcy by 6 hrs. In all the three groups, serum glucose level remained within normal physiological range. The serum glucose level showed significant (P<0.05) difference between groups at 120 min. and remained non-significant at other time intervals between groups.

Serum total protein (g/dL)

Serum total protein (g/dL) showed a non-significant decrease in group BP up to 60 min. post anaesthesia from 6.19±0.20 to 5.65±0.21 g/dl whereas animals of groups DP and AP recorded a non-significant decrease up to 120 min. post induction from 6.54±0.35 to 5.79±0.32 g/dl and from 6.43±0.13 to 5.94±0.25 g/dl following administration of dexmedetomidine-propofol and acepromazine-propofol anaesthesia respectively (fig.10.). Later on, this value non-significantly increased and returned to baseline within 6 hrs of study period. Serum total protein showed a non-significant difference between groups at the various time interval of the observation period. However, serum total protein remained within the normal physiological range in all three groups.

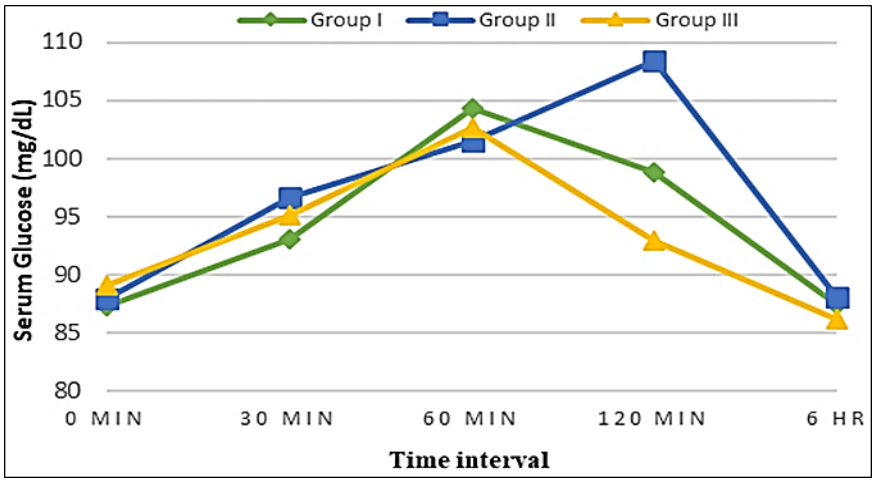

Fig 9: Effect on Serum Glucose (mg/dL) after induction with propofol in different groups

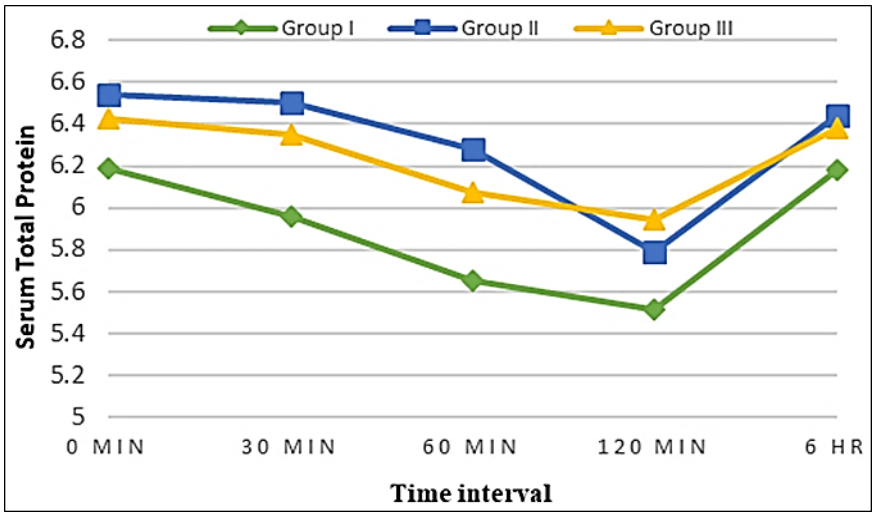

Fig 10: Effect on Total Serum Protein (g/dL) after induction with propofol in different groups

Serum urea nitrogen (mg/dL) and serum creatinine (mg/dL)

A non-significant increase in serum urea nitrogen was recorded in group BP, DP and AP up to 120 min. post induction from 16.04±2.04 to 20.88±1.84 mg/dL, 16.92±1.50 to 19.22±1.39 mg/dL and 17.04±1.46 to 19.27±1.36 mg/dL respectively following induction with propofol anaesthesia (fig.11.). There was also a non-significant increase in serum creatinine in group BP, DP and AP up to 120 min. post anaesthesia from 1.14±0.13 to 1.44±0.16 mg/dL, 1.11±0.18 to 1.47±0.32 mg/dL and 1.09±0.20 to 1.49±0.37 mg/dL respectively following administration of propofol anaesthesia (fig.12.). Later on, these values decreased non-significantly and returned to baseline within 6 hrs of the study period. Serum urea nitrogen and serum creatinine didn't show any significant difference between groups at the various time interval of the observation period. However, the values remained within the normal physiological range in all three groups.

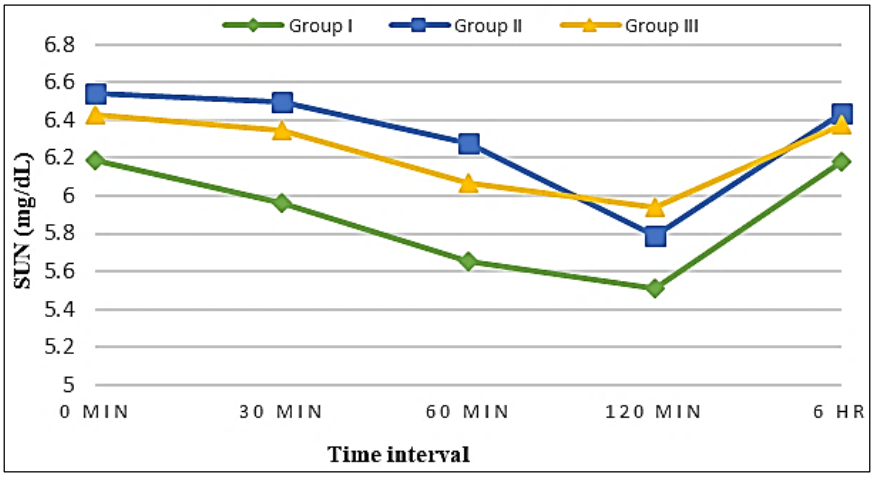

Fig 11: Effect on Serum Urea Nitrogen (mg/dL) after induction with propofol in different groups

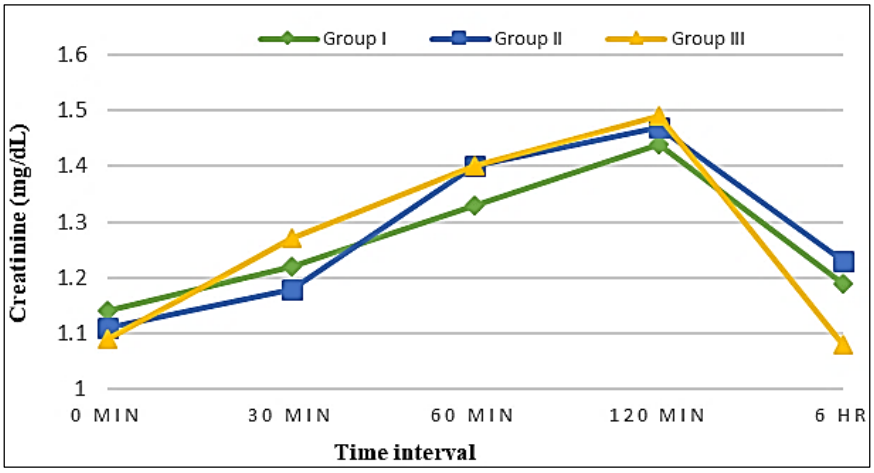

Fig 12: Effect on Serum Creatinine (gm/dL) after induction with propofol in different groups

Alanine Amino Transferase (ALT) and Aspartate Amino Transferase (AST) (IU/L)

Animals of group BP, DP and AP recorded a non-significant increase in ALT up to 120 min. post induction from 31.89±1.77 to 35.19±1.50 IU/L, 30.80±1.22 to 32.78±1.40 IU/L and 30.01±2.68 to 35.27±2.73 IU/L respectively (fig.13) after administration of propofol anaesthesia. There was a non-significant increase in AST in animals of groups BP, DP and AP up to 120 min. from 29.03±1.91 to 35.81±1.97, 29.17±1.52 to 33.17±1.74 and 29.93±1.60 to 34.55±1.60 IU/L respectively after propofol anaesthesia (fig.14). Later on, these values decreased non-significantly and returned to baseline within 6 hrs of study period. ALT and AST showed a non-significant difference between groups at various time intervals of the observation period. However, ALT and AST remained within normal physiological range in all the three groups.

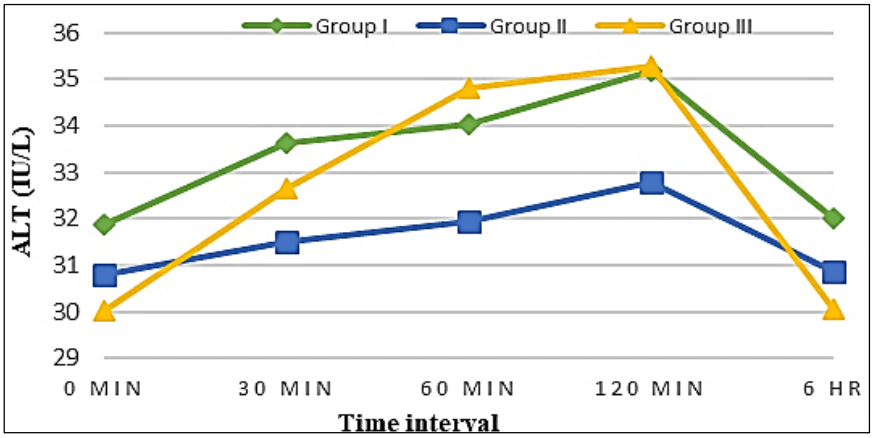

Fig 13: Effect on ALT (IU/L) after induction with propofol in different groups

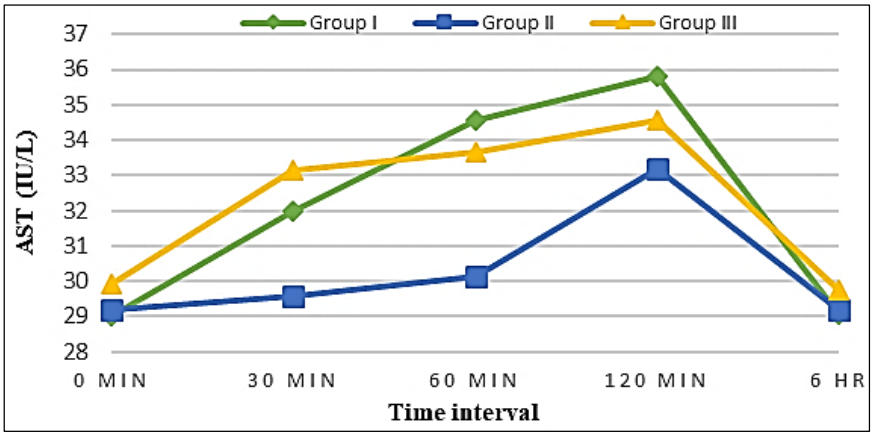

Fig 14: Effect on AST (IU/L) after induction with propofol in different groups

Discussion

Haematological parameters

The decrease in haemoglobin, PCV, TEC and TLC levels was observed in all the three groups following induction with propofol anaesthesia which might be due to splenic pooling of erythrocytes that occurs with most of the anaesthetics or due to haemodilution in response to fluid therapy as present research was carried out in summer season. During general anaesthesia, the spleen usually expands, which cause erythrocyte sequestration and lowering of haematocrit and haemoglobin concentration (Hawkey, 1985) [18]. The findings of above study are in accordance with those recorded by Surbhi *et al.* (2010) [47]; Jena *et al.* (2014) [20]; Anandmay *et al.* (2016); Dewangan *et al.* (2016) [14]; Mate and Aher, (2018) [33] in dogs and Maravi (2016) [31] in goats. Naghibi *et al.* (2002) [36] also reasoned decrease in haemoglobin observations due to vasodilation at the level of microcirculation and passage of many RBCs from circulation in peripheral veins which was also called as plasma skimming. Kappa mediated diuretic effect of butorphanol also causes decrease in packed cell volume. Rankin (2015) [38] reported that acepromazine causes a decrease in PCV and reduction of platelet aggregation. Similary, Wamaitha *et al.* (2018) [54] also mentioned a significant ($P<0.05$) reduction in PCV up to 30 min. after administration of acepromazine-ketofol in dogs whereas, animals anaesthetized with medetomidine-ketofol showed comparatively less decrease in PCV as compared to above drug. Lerche *et al.* (2000) [26] also reported significant ($P<0.05$) decrease in PCV during continuous infusion of propofol in dogs. The TEC changes could be due to the sequestration of blood cells in spleen and lungs during anaesthesia (Lumb and Jones, 1996) [29]. The fall in TEC levels after propofol administration in dogs has also been reported by various workers (Bayan *et al.,* 2007; Biermann *et al.,* 2012; Suresha *et al.,* 2012) [5, 7, 48]. TLC decline was caused by increased peripheral blood levels of adrenaline or nor-adrenaline, which inhibits the proliferative response of peripheral blood leucocytes (Felsner *et al.,* 1995) [15]. The administration of α2-agonist has been shown to suppress the circulating catecholamines therefore exerting a modulating effect on leukocyte subpopulations. In earlier studies with α-2 agonist, a decrease in TLC was noticed in dogs (Amarpal *et al.* 1996) [2]. Contrary to our study, there was transient increase in TLC after propofol anaesthesia as also reported by various workers in dogs (Sharma and Bhardwaj, 2010; Dewangan *et al.,* 2016) [43, 14]. This could be attributed to stress and release of ACTH on account of anaesthetic administration.

Neutrophilia and lymphopenia observed were also in concurrent with the findings of Maravi (2016) [31] in goats and Vijay *et al.* (2018) [52] in dogs. There was non-significant increase in neutrophils and decrease in lymphocyte count in all the groups after propofol anaestthesia which might be due to anaesthetic stress that led to stimulation of adrenal cortex resulting in glucocorticosteroid stimulation and action on the circulating neutrophils (Soliman *et al.,* 1965) [45]. The transient increase in the neutrophil count might be associated with systemic stress associated with endogenous release of corticosteroids after administration of anaesthetics (Benjamin, 1985) [6]. Canpolate *et al.* (2016) [9] recorded a substantial drop in the number of lymphocytes, which might be attributed to the animal's stress throughout the study. The rise in neutrophil count in each group varied conversely to decrease in lymphocyte count as recorded by Surbhi *et al.* (2010) [47]; Jena *et al.* (2014) [20] and Chandrakala *et al.* (2017) [10] in dogs after propofol anaesthesia. In contrast to our study, Amarpal *et al.* (1996) [2] has reported decreased neutrophil count after administration of aplha-2 agonist in dogs. Eosinophil count and monocyte count showed a non-significant decrease in all the three groups of animals after propofol anaesthesia which fluctuated marginally and returned to normalcy. The minor changes in eosinophil and monocyte count level could be attributed to the suppressive effects of butorphanol, dexmedetomidine, acepromazine and propofol on the immune systems of the animal as well as adreno-cortical stimulation and subsequent effect of glucocorticoids after anaesthetic administration (Soliman *et al.,* 1965) [45]. The findings of the present study are concurred with Jena *et al*. (2014) [20] in dogs following propofol anaesthesia. Non-significant change in monocyte count at any time interval after propofol anaesthesia in dogs was recorded because propofol promotes the stability in the number of cells. On the other hand, Maravi (2016) [31] recorded non-significant increase in eosinophil count and decrease in monocyte count after propofol anaesthesia in combination with detomidine and buprenorphine in goats which further increased gradually and returned to near base value at 6 hr. Contrary to our study, Chandrakala *et al.* (2017) [10] noticed transient increase in monocyte count after propofol anaesthesia in dogs.

Biochemical parameters

Hyperglycaemia observed in the present study might be attributed to increased hepatic glucose production, decreased glucose utilization, decreased membrane transport and reduced plasma concentration which are mediated by activation of α2-adrenoceptors present in the β-cells of pancreatic islets exerting a negative control of basal insulin release (Burton *et al.* 1997) [8]. Jena *et al.* (2014) [20] observed that practically every anaesthetic stimulates the secretion from adrenal cortex, responsible for gluconeogenesis during anaesthesia and Maeda *et al*. (2018) [30] opined that propofol have an indirect effect on glucose by inhibiting glucose metabolism, resulting in hyperglycemia. In the present study, hyperglycemia was noted at 60 min. in group BP and AP respectively whereas, in group DP at 120 min. after administration of propofol. The increase in serum glucose level is probably an indication of the stress of anaesthesia. Moreover, during the period of anaesthesia, there is decrease in basal metabolic rate of the animal and muscular activity is negligible, so utilization of glucose by the muscle is also decreased probably causing a slight increase in glucose concentration. However, hyperglycemia produced was transient in nature and within the normal physiological limit, therefore, a clinical significance cannot be fixed. This collaborates with the findings of Anandmay *et al.* (2012) [3] and Costa *et al.* (2013) [13] after propofol anaesthesia in dogs. Significant ($P<0.05$) hyperglycemia has also been reported during propofol administration in dog by Dewangan *et al.* (2016) [14]; Chandrakala *et al.* (2017) [10] and Mate and Aher (2018) [33]. The rise in glucose level in group DP was up to 120 min after administration of dexmedetomidine-propofol that might be due to decreased insulin release by the inhibitory effects of dexmedetomidine (Restitutti *et al.* 2012) [39]. Hyperglycaemic effects of dexmedetomidine was recorded by McSweeney *et al.* (2012) [34], that has been investigated in earlier studies and could be due to the suppression of insulin release, stimulation of glucagon release or both in alpha and beta cells of the pancreas. A similar

finding has also been documented by Maravi *et al.* (2018) [32] following propofol administration in atropinized goats. A significant increase in plasma glucose level in dogs was reported by Chandrashekharappa and Ananda (2009) [11] after pentazocine and propofol administration which are in support to the present findings. The rise in glucose level might be due to an increase in circulatory catecholamines after premedication (Hall *et al.*, 1994) [17] and also the effect of the anaesthetic agent on a subcortical pathway, which was responsible for the regulation of adrenocorticotropic hormone (ACTH) and produces stress like conditions with increased release of glucocorticoids (Jena *et al*. 2014) [20].

Serum total protein showed a non-significant decrease in all the three groups of animals after propofol administration which fluctuated and returned to normalcy within 6 hr. The alteration in serum total protein in our study could be attributed due to the splenic pooling of erythrocytes resulting in overloading of water in the blood. The non-significant decrease in serum total protein might have resulted due to increased levels of glucocorticoids, adrenal activity and protein turnover resulting in decreased plasma protein and albumin. The decrease in insulin levels might modify the general metabolism and impair protein synthesis (Schumann, 1990) [41]. A reduction in total protein values might be due to haemodilution or secondary elevation of globulins since colloidal osmotic pressure is maintained by an osmotic mechanism. Similar findings have also been reported by Parikh *et al.* (1995) [37]; Anandmay *et al.* (2012) [3] and Dewangan *et al.* (2016) [14] after propofol anaesthesia in dogs. On the contrary to our study, Kim *et al.* (1999) [22] and Chandrakala *et al*. (2017) [10] reported a significant (P<0.05) increase in total serum protein values after propofol anaesthesia in dogs. The resulted stress-causing rise in glucocorticoids might have led to slight rise in the total protein level (Benjamin, 1985) [6].

There was a non-significant increase in serum urea nitrogen and serum creatinine level up to 120 min. following induction with propofol anaesthesia with butorphanol, dexmedetomidine and acepromazine in all the animals. The transient increase in the level of SUN and serum creatinine in the present investigation might be due to the temporary inhibitory effect of anaesthetic drugs on renal blood flow leading to hypotension and retention of nitrogenous substances in the blood. A consequent decrease in glomerular filtration rate along with an increased hepatic urea production from amino acid degradation during anaesthesia might have also accounted for the observed increase in SUN levels in the present study. However, it is difficult to describe about the possible renal damage because all the recorded values were within the normal physiological limits. Surbhi *et al.* (2010) [47] recorded increased BUN and serum creatinine during propofol anaesthesia in dogs premedicated with medetomidine. Jain *et al.* (2007) [19] reported that an increase in BUN and serum creatinine level might also be due to induced alterations in glomerular filtration rate only for a short period causing an increase in the level of creatinine during propofol anaesthesia in dogs. The non-significant alteration in serum urea nitrogen and serum creatinine values might be due to increased level of anti-diuretic hormone (ADH) which in turn caused decreased glomerular filtration as emphasized by Suresha *et al.* (2012) [48] during propofol anaesthesia in dogs. Similar findings were also observed by Chandrashekharappa and Ananda (2009) [11]; Anandmay *et al.* (2016); Chandrakala *et al.* (2017) [10] and Shinde *et al.* (2018) [44] in dogs while Dewangan *et al.* (2016) [14] and Vijay *et al.* (2018) [52] recorded significant (P<0.05) increase in SUN and serum creatinine after propofol anaesthesia in dogs. To its contrary, Jena *et al.* (2014) [20] recorded a non-significant decrease in the value of BUN and serum creatinine followed by a non-significant increase during propofol anaesthesia in dogs which might be due to continuous infusion of IV fluids thus maintaining the normal kidney function. Anaesthetics may indirectly alter the renal function via the change in cardiovascular and neuroendocrine activity (Stephen, 1996) [46], but this did not happen in the present study as suggested by a non-significant alteration in the serum urea nitrogen. A non-significant increase in blood urea nitrogen and serum creatinine has been reported following the use of medetomidine along with butorphanol in dogs (Ahmad, 2010; Santosh, 2011) [1, 40]. A non-significant increase in serum urea nitrogen and serum creatinine values has been reported following dexmedetomidine-propofol anaesthesia in dogs (Meshram, 2015) [35]. The above findings are in accordance with Mate and Aher (2018) [33] in dogs and Maravi (2016) [31] in goats.

The serum ALT and AST showed a non-significant increase up to 120 min. post induction followed by non-significant decrease to base value at 6 hrs after propofol anaesthesia in all the three groups. The transient increase in ALT and AST level might be associated with increased cell membrane permeability in response to haemodynamic changes induced by anaesthetic agent as a result of an oxidative transformation of these drugs in the liver during the process of elimination resulting in leakage of the enzyme into the blood and causing an increase in their level of enzymes (Vikers *et al.*, 1984) [53]. The changes in the AST levels observed in the present study might be associated with immediate response to cardiac insufficiency (Lehninger, 1990) [24] by anaesthetic agent and also due to the hypoxia created as a consequence of respiratory centre depression caused by propofol. ALT is a cytoplasmic enzyme found mainly in hepatocytes. ALT is the liver-specific enzyme in dogs and the pathology involving the hepatic parenchyma allows the leakage of a large amount of this enzyme in the blood. AST is a cytoplasmic and mitochondrial enzyme found in hepatocytes and other cells. Reversible or irreversible damage to the liver causes release of the cytoplasmic AST; however, only irreversible damage to the cell will cause release of mitochondrial AST. An increase in AST activity is generally parallel to that of ALT however; AST is less specific for liver injury than ALT because increases in activity of AST may also be due to cardiac or skeleton muscle injury or *ex vivo* haemolysis. Hepatic metabolism is first and foremost, a mechanism that converts drugs and other compounds into products that are easily excreted and that usually have a lower pharmacological activity than the potent compound. Most ALT activity in the opioid groups might be attributed to the fact that the opioids are exclusively metabolized in the liver hence causing no more changes at the cellular level (Scott and Perry, 2000) [42]. Propofol was rapidly cleared by hepatic and perhaps, extrahepatic metabolism and was mainly metabolized by glucuronide conjugation in the liver (Kanto and Gepts, 1989) [21]. Butorphanol was cleared in hepatic by hydroxylation, dealkylation and conjugation. Metabolism of acepromazine occurs in the liver and eliminated by the kidneys. Chandrashekharappa and Ananda (2009) [11] and Suresha *et al*. (2012) [48] reported ALT levels did not differ significantly after propofol anaesthesia in dogs. Sharma and Bhardwaj

(2010) [43] reported a non-significant increase and decrease in AST values after administration of midazolam-propofol in dogs. The transient increase in ALT and AST level might be due to hepatic metabolism of drugs (butorphanol, dexmedetomidine, acepromazine and propofol) used in the present study and values remained within the normal physiological range indicating no deleterious effect on the liver but the possibility of pathological changes could not be ruled out. It collaborates with the finding of Meshram (2015) [35]; Chandrakala *et al.* (2017) [10]; Mate and Aher (2018) [33] and Thejasree *et al.* (2018) [49] following induction of propofol anaesthesia in dogs. On other hand, Anandmay *et al.* (2012) [3] and Dewangan *et al.* (2016) [14] have reported significant ($P<0.05$) increase in ALT and AST after propofol anaesthesia in dogs and in goats (Maravi, 2016) [31]. However, Shinde *et al.* (2018) [44] showed slight fluctuation in ALT and AST after propofol anaesthesia in dogs. Similarly, Lim and Jang (2000) [27]; Apaydin *et al*. (2006) [4] and Jain *et al.* (2007) [19] also reported an increase in ALT and AST level after administration of propofol along with various preanaesthetic agents in the dogs.

Conclusion

All the haematological and biochemical parameters showed a transient change which were compensated within 6 hours and remained within physiological limits. However, these changes did not show any deleterious effect on vital organs under these combinations. The results of the present study suggested that propofol can be used safely as an induction agent in glycopyrrolate-butorphanol, glycoprrolate-dexmedetomidine, glycopyrrolate-acepromazine premedicated dogs in surgical cases and healthy dogs.

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