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Haemato-biochemical evaluation of glycopyrrolate, dexmedetomidine, butorphanol/buprenorphine as Preanesthetic with ketamine dissociative anesthetic in canines

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Abstract
The present study was conducted for evaluation of glycopyrrolate, dexmedetomidine, butorphanol and buprenorphine as preanesthetics with (dissociative anaesthetic) ketamine. The dogs of either sex were randomly divided into two groups havingsix dogs in each group. Animals of group I were premedicated with glycopyrrolate, dexmedetomidineand butorphanol intramuscularly and group II animals received glycopyrrolate, dexmedetomidineand buprenorphine intramuscularly. Animals of both the groups were anaesthetized by injecting Ketamine intravenously 5 mg/kg bwt. The haemato-biochemical parameters were recorded at 0, 0.5,1,6 and 24 hours. The haemato-biochemical parameters showed no adverse reaction on hepato-renal parameters.

Keywords: Glycopyrrolate, dexmedetomidine, butorphanol, buprenorphine, dogs, pre anesthetic

Introduction
An ideal anaesthetic should posses potent anaesthetic, adequate analgesic and sufficient muscle relaxant activities, produce sedation, amnesia and analgesia. Unfortunately there is no single anaesthetic available which posses all these qualities in adequate amount, therefore a combination of different drugs, such as anaesthetic, analgesic and muscle relaxant has been prepared. This type of combination is known as balanced anaesthetic and the condition produced after its administration is called the balanced anaesthesia. Preanaesthetic medication makes the patient easier to handle; provides amnesia, sedation, analgesic effects, decreases secretions and minimizes the total dose of anaesthetics to produce the desired level of anaesthesia (Tranquilli *et al.*, 2007) [20]. Preanesthetic agents are prefered over the use of a single agent to induce deep sedation. Moreover, synergistic interaction between these drugs reduces the dose requirements of the drugs thereby minimizes the unwanted side effects associated with each drug and helps in gaining the uneventful recovery.

Aim: The purpose of this study was to compare the hematological and biochemical effect of butorphanol and buprenorphine as pre-anesthetic protocols in dogs.

Material and Methods: The present experiment was conducted at department of Veterinary Surgery and Radiology, Veterinary Clinical Complex (V.C.C.), College of Veterinary Science & A.H. Mhow. The dogs came for routine surgery in the Department of Veterinary Surgery and Radiology were selected for the study purpose. Total 12 dogs were selected, and divided into two groups of six each. Group I animals were preanaesthetised with Glycopyrrolate (0.01 mg/kg bwt), Dexmedetomidine (5 µg/kg bwt) and Butorphanol (0.2 mg/kg bwt) loaded in a single syringe and administered intramuscularly followed by Induction of anaesthesia with Ketamine (5 mg/kg bwt) intravenously. Group II animal were preanaesthetised with Glycopyrrolate (0.01 mg/kg bwt), Dexmedetomidine (5 µg/kg bwt) and Buprenorphine (0.02 mg/kg bwt) loaded in a single syringe and administered intramuscularly followed by Induction of anaesthesia with Ketamine (5 mg/kg bwt) intravenously. Blood samples were taken initially before the administration of preanesthetic to serve as base value (control) at 0 hour. After administration of premedication, blood samples were collected at 0.5, 1, 6 and 24 hours from cephalic and sephenous veins into vacutainers for haematological and biochemical analysis. Blood smears for determination of differential leucocyte count (DLC) were prepared from

fresh blood at the time of blood collection (Schalm, 1967) [13]. Blood samples (2 ml) collected in vacutainers with K_3EDTA were utilized for haematological evaluation, whereas, blood samples (3 ml) collected in vacutainers without K_3EDTA were allowed to clot at room temperature. Serum were harvested by centrifugation at 4000 rpm for 10 minutes at 4 ^oC (Eppendorf 5804 R, Germany) and stored at -35 ^oC for biochemical parameters.

Results and Discussion

Hemoglobin (g/dl)

The mean value of haemoglobin decreased non-significantly from 0 to 1 hours in both groups. Increase in mean value was observed from 6 to 24 hours in group I and II. The values started approaching towards the base value at 24 hours. The mean ± SE values of haemoglobin (g/dl) of both the groups at various time intervals are shown in Table -1. A decrease in heamoglobin was observed due to pooling of circulatory erythrocytes in the spleen in order to maintain normal cardiac output (Wagner *et al.*, 1991) and also due to haemodilution in response to fluid therapy (Surbhi *et al.*, 2008 and Singh *et al*., 2013) [18, 9]. The findings of the present study was in accordance with Sika, 2013 [15] who used xylazine with butorphanol in dogs anaesthetized with Ketamine. During general anaesthesia the spleen usually expands, which cause erythrocyte sequestration and a lowering of haematocrit and hemoglobin concentration (Hawkey, 1985) [4].

Table 1: Mean±SE of heamoglobin (g/dL) at different time in group I and II in dogs

Time of observations (hours)	Groups	
	Group I	Group II
0	11.75 ± 0.40	12.28 ± 0.24
0.5	11.21 ±0.34	11.85 ±0.19
1	10.86 ± 0.38	11.21 ± 0.22
6	11.15 ± 0.35	11.56 ± 0.46
24	11.66 ± 0.34	12.11 ± 0.27

Packed cell volume (%)

A non-significant continuous decrease in mean values of PCV was observed in both the groups at 0 to 1 hour. Increase in mean value was observed from 6 to 24 hours in both the groups which started approaching to base value at 24 hours. The mean ± SE values of packed cell volume (%) in both the groups at various time intervals are shown in Table 2.

The values of PCV may be influenced by haemodilution in response to fluid therapy or vasodilation, resulting in decreased values and haemo-concentration due to dehydration and hypoxia results in higher values as opined by Malik and Singh (2007) [9]. Guedes *et al*., (2015) hypothesized that a reduction in the packed cell volume was due to either haemodilution or haemorrhage. Yadav *et al.*, 2015 reported a non significant decrease in PCV in Glyco-Dex-Butorphanol-propofol-Isoflurane group. Sethi *et al.*, (2017) [14] revealed non-significantly decreased pcv values in animals of group Atropine-dex-butor-ket

Table 2: Mean±SE of packed cell volume (percent) at different time in group I and II in dogs

Time of Observations (hours)	Groups	
	Group I	Group II
0	35.01 ± 0.79	34.98 ± 0.49
0.5	34.05 ± 0.69	34.75 ±0.73
1	33.26 ± 0.58	33.86 ± 0.75
6	34.13 ± 0.54	34.20 ± 0.85
24	34.96 ± 0.86	36.35 ± 0.51

Total erythrocyte count (millions/µl)

A non-significant continuous decrease was recorded in total erythrocyte count values from 0 to 1 hours in both groups. The values started increasing at 6 to 24 hours in both groups. The values started approaching towards the base value at 24 hours. The mean ± SE values of TEC (millions/µl) of both the groups at various time intervals are shown in Table -3

During general anaesthesia the spleen usually expands, which cause erythrocyte sequestration and a lowering of haematocrit and hemoglobin concentration (Hawkey, 1985) [4]. Biermann *et al*., (2012) [1] reported a significant decrease in total erythrocytic count owing to vasodilation and pooling of blood. Samsuddi *et al.*, (2014) [12] also reported non significant decrease followed by increase in Dexmedetomidine-Ketamine group and his finding is in aggrement with the present study.

Table 3: Mean±SE of total erythrocyte count (millions/µl) at different time in group I and II in dogs

Time of Observations (hours)	Groups	
	Group I	Group II
0	3.47 ± 0.12	3.67 ± 0.08
0.5	3.42 ± 0.14	3.61 ±0.11
1	3.36 ± 0.13	3.55 ± 0.09
6	3.48 ± 0.15	3.63 ± 0.13
24	3.59 ± 0.12	3.79 ± 0.09

Differential leukocyte count

Neutrophil. (Percent)

A continuous significant increase in mean value of neutrophil was observed in both the groups from 0 to 24 hours. Increase in neutrophil count might be due to painful surgeries along with the anaesthetic stress leading to stimulation of the adrenal cortex and subsequent production of glucocortoid that acts on the circulating neutrophils (Soliman *et al.*, 1965). The mean ± SE values of neutrophils of both the groups at various time intervals are shown in Table -4

Table 4: Mean±SE of neutrophil (percent) at different time in group I and II in dogs

Time of observations (hours)	Groups	
	Group I	Group II
0	67.66 ± 0.95^{c}	65.00 ± 1.15^{C}
0.5	68.83 ± 0.30^{bc}	67.50 ± 0.76^{BC}
1	69.16 ± 0.54^{bc}	68.16 ± 0.70^{B}
6	70.66 ± 1.25^{ab}	69.5 ± 0.76^{AB}
24	71.66 ± 1.02^{a}	71.33 ± 0.84^{A}

Lymphocyte (percent)

A non-significant continuous decrease was recorded in lymphocyte count from 0 to 1 hours in group I and 0 to 6 hours in group II. The values started increasing from 6 to 24 hours in group I, however in group II values started increasing at 24 hours. The mean ± SE values of lymphocytes of both the groups at various time intervals are shown in Table -5.

Present finding was found in correlation with Dar *et al.*, (2018) [2] who also reported a non significant decrease in lymphocyte throughout the observation period in group ButDK. In the present study values for lymphocyte count of remain within normal range throughout the observation period for the groups. lymphocytopenia in the animals of all group might be attributed to the stimulation of adrenal gland and restoration of ACTH levels (Yadav *et al*., 2015)

Table 5: Mean±SE of lymphocyte (percent) at different time in group I and II in dogs

Time of observations (hours)	Groups	
	Group I	Group II
0	29.16 ± 0.87	31.83 ± 1.07
0.5	28.16 ± 0.65	30.50 ± 1.20
1	27.83 ± 0.98	29.16 ± 1.16
6	28.00 ± 0.89	28.5 ± 0.84
24	28.83 ± 0.87	29.83 ± 0.70

Monocyte (percent)

The present study revealed that no significant difference was observed in the values of monocytes when compared with their base line values in both the groups, however values decreased till 1 hour in both the groups and thereafter increased till 24 hours. Jena *et al*., (2014) [5] also observed no significant change in monocyte count at any time interval with xylazine or dexmedetomidine- propofol anaesthesia in dogs. Similarly Dar *et al.,* (2018) [2] also revealed that monocyte count decreased non significantly but remained within normal range in the group ButDK during the observation period. The mean ± SE values of monocytes of both the groups at various time intervals are shown in Table 6.

Table 6: Mean±SE of monocyte (percent) at different time in group I and II in dogs

Time of observations (hours)	Groups	
	Group I	Group II
0	1.33 ± 0.21	1.16 ± 0.40
0.5	1.16 ± 0.30	1.00 ± 0.25
1	0.86 ± 0.16	0.83 ± 0.30
6	1.16 ± 0.16	1.50 ± 0.22
24	1.50 ± 0.22	1.83 ± 0.30

Eosinophils (percent)

Although count decresed non significantly till 1 hour in both the groups, however no significant difference was recorded in the values of eosinophils in comparison to their base line values in both the group. Jena *et al.,* (2014) [5] reported that eosinophil count showed a non-significant decrease in group Dexmedetomidine. Dar *et al*., (2018) [2] also revealed the eosinophil count remained within normal range in the group ButDK during the observation period. The mean ± SE values of eosinophils of both the groups at various time intervals are shown in Table -7

Table 7: Mean±SE of eosinophil (percent) at different time in group I and II in dogs

Time of Observations (hours)	Groups	
	Group I	Group II
0	1.16 ± 0.40	0.83 ± 0.16
0.5	0.83 ± 0.16	0.66 ± 0.21
1	0.66 ± 0.21	0.50 ± 0.22
6	1.00 ± 0.36	0.83 ± 0.16
24	1.33 ± 0.21	1.16 ± 0.30

Biochemical parameters

Transaminases (IU/L)

Serum aspartate transaminase

A non significant continuous increase was recorded in serum aspartate transaminase from 0 to 6 hours and from 0 to 1 hours in group I and II respectively. The values started decreasing from 24 and 6 hours in group I and II respectively and approaching towards the base value at 24 hours. The mean ± SE values of transaminases (IU/L) of both the groups at various time intervals are shown in Table -8

Table 8: Mean±SE of serum aspartate transaminase (IU/L) at different time in group I and II in dogs

Time of observations (hours)	Groups	
	Group I	Group II
0	38.43 ± 2.53	41.07 ± 3.66
0.5	39.90 ± 2.45	42.50 ± 3.31
1	40.86 ± 2.29	43.90 ± 3.47
6	41.00 ± 1.82	42.58 ± 3.36
24	39.21 ± 2.13	43.54 ± 3.26

Serum alanin transaminase

In both the groups a non-significant increase in the levels of AST and ALT was seen. The mean ± SE values of transaminases (IU/L) of both the groups at various time intervals are shown in Table -9. All the changes observed within the groups were non-significant. General anaesthetics reduces blood circulation to the liver which may damage liver cells and alter their permeability resulting in leakage of the enzyme into the blood and causing an increase in level of enzymes (Vikers *et al.,* 1984; Pandey and Sharma, 1994; Tiwari *et al.,* 1999) [21, 10, 19]. Many factors lead to alteration of AST such as hypoxia, stress due to anaesthesia and surgery (Kumar *et al.* 1978 and Davies,1991) [3]. Similarly Dar *et al*., (2018) [2] also observed a non significant increase in the level of ALT initially, later on returned to base value and a non significant increase in AST value. Biermann *et al.,* (2012) [1] also reported non-significant changes in ALT and AST values following dexmedetomidine-ketamine anaesthesia.

Table 9: Mean±SE of serum alanin transaminase (IU/L) at different time in group I and II in dogs

Time of Observations (hours)	Groups	
	Group I	Group II
0	34.53 ± 2.71	39.58 ± 3.50
0.5	35.43 ± 2.94	40.86 ± 3.43
1	37.31 ± 2.99	42.98 ± 3.46
6	36.04 ± 3.66	42.25 ± 3.15
24	35.66 ± 2.98	41.71 ± 3.66

Serum creatinine Values (mg/dl)

A non significant continuous increase was revealed in serum creatinine from 0 to 1 hour in both the groups. The mean ± SE values of transaminases (mg/dl) of both the groups at various time intervals are shown in Table -10. The values started decreasing from 6 to 24 hours in both the groups. The values started approaching towards the base value at 24 hours.

Due to continuous intravenous fluid therapy sustained amount of blood was flowing through the renal system resulting in good glomerular filtration rate which helps in maintaining the plasma creatinine value within the acceptable limits. The fluctuations in creatinine values were attributed to the inhibitory effect of drugs on the renal blood flow, increased creatinine production from muscle damage and amino acid degeneration (Restitutti *et al*., 2012 and Singh *et al.,* 2013) [11, 16].

Table 10: Mean±SE of serum creatinine (mg/dl) at different time in group I and II in dogs

Time of observations (hours)	Groups	
	Group I	Group II
0	0.92 ± 0.08	1.10 ± 0.21
0.5	1.05 ± 0.09	1.20 ± 0.20
1	1.18 ± 0.08	1.29 ± 0.21
6	1.09 ± 0.05	1.20 ± 0.19
24	0.98 ± 0.06	1.17 ± 0.16

Blood Urea Nitrogen Values (mg/dl)

In the present study non significant continuous increase was observed in blood urea nitrogen level which came down to normal base values at 24 hours. The mean ± SE values of BUN (mg/dl) of both the groups at various time intervals are shown in Table -11. The increase in urea nitrogen values might be attributed to the temporary inhibitory effects of anaesthetic drugs on the renal blood flow, which in turn might have caused a rise in plasma urea nitrogen level as suggested by Kinjavdekar *et al.,* (2013) [6]. The non-significant marginal increase in the value of BUN may be due to the fact that dexmedetomidine continuously supply blood to vital organs like brain, heart, liver and kidney at the expense of organs like skin and pancreas and this distribution is not affected by type of anaesthesia (Lawrence *et al*, 1996) [8]. This effect of dexmedetomidine might have been responsible for maintaining plasma urea nitrogen and creatinine values near the baseline. Present study was found in agreement with Dar *et al.,* (2018) [2] who stated that blood urea nitrogen concentration increased non-significantly but remained within normal range throughout the observation period and did not differ significantly in the group Butorphanol-Dexmedetomidine-Ketamine.

Table 11: Mean±SE of blood urea nitrogen (mg/dl) at different time in group I and II in dogs

Time of observations (hours)	Groups	
	Group I	Group II
0	22.95 ± 1.80	24.51 ± 2.24
0.5	24.90 ± 1.78	26.90 ± 2.16
1	27.70 ± 1.80	28.89 ± 2.15
6	25.41 ± 1.50	25.37 ± 2.04
24	23.41 ± 1.55	25.29 ± 2.03

Serum Glucose values (mg/dl)

There was a significant difference observed in the values of plasma glucose in both the groups. In group I and II values started increasing significantly from 0 to 1 hr. thereafter a significant fall was observed in the values on 6 to 24 hours. The mean ± SE values of glucose (mg/dl) of both the groups at various time intervals are shown in Table -12. Restitutti*et al.,* (2012) [11] stated that increase in blood glucose concentration may be due to decreased membrane transport of glucose, decreased glucose utilization, impaired insulin activity and increased blood concentration of adrenocortical hormones. Ketamine has been reported to cause sympathetic stimulation leading to release of catecholamines and increased glucose concentration in plasma (Ylitalo *et al*., 1976) [23]. Dar *et al.,* (2018) [2] also reported that there was a non-significant increase in the glucose concentration in the group after administration of the Butorphanol-Dexmedetomidine-Ketamine.

Table 12: Mean±SE of serum glucose (mg/dl) at different time in group I and II in dogs

Time of observations (hours)	Groups	
	Group I	Group II
0	70.58 ± 1.33^{d}	69.88 ± 0.64^{D}
0.5	88.43 ± 1.38^{b}	91.22 ± 0.96^{B}
1	99.11 ± 1.82^{a}	100.56 ± 0.6^{A}
6	91.51 ± 1.16^{b}	90.03 ± 1.60^{B}
24	77.14 ± 1.57^{c}	74.62 ± 0.75^{C}

Mean values shows significant difference at $p< 0.05$ and $p< 0.01$ from the base value

Conclusion

Based on the present study it has been concluded that both the pre- anesthetic combination are safer to user for their clinical use in diagnostic, an imaging and short surgical procedures. The haemato-biochemical parameters showed no adverse reaction on hepato-renal parameters.

Competing Interests

The authors declare that they have no competinginterests.

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