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Physiological and haemodynamic alternations following thiopentone sodium anaesthesia premedicated with butorphanol, dexmedetomidine and acepromazine in dogs

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Abstract
The present study was conducted to evaluate the physiological and haemodynamic alternations following thiopentone sodium anaesthesia premedicated with butorphanol, dexmedetomidine and acepromazine in dogs. Eighteen adult dogs of either sex were randomly divided into three groups (A, B and C) with six animals in each. Ten minutes prior to the anaesthetic administration, all the dogs were premedicated with glycopyrrolate @ 0.02 mg/kg I/M. The animals of group A, B and C 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 thiopentone sodium @ 18 mg/kg b.wt. Physiological and haemodynamic parameters *viz*. rectal temperature, heart rate, respiration rate, systolic, diastolic, mean blood pressure, SpO_2 and CRT were recorded before (0), 5 min. following sedation, after induction and at 10, 20, 40, 60 and 120 min. post thiopentone anaesthesia. The physiological and haemodynamic parameters displayed transient changes that were compensated and remained within normal range during the study period. Therefore, it can be concluded that thiopentone sodium can be administered safely as an induction agent in dogs premedicated with butorphanol or dexmedetomidine or acepromazine.

Keywords: Acepromazine, butorphanol, dexmedetomidine, dogs, glycopyrrolate, haemodynamic, physiological, thiopentone sodium

Introduction
An optimal anesthetic should induce analgesia, sleep, amnesia, and muscular relaxation. Since a single drug cannot produce all of these effects, a mixture of drugs known as balanced anesthesia is utilized (Thurmon and Short, 2007) [28]. Therefore, combination of sedatives, tranquilizers, analgesics and general anaesthetics has been widely used in animal practice to attain desirable effect of general anaesthesia. When preanaesthetics are administered prior to inducing anesthesia, the quality of anesthesia is enhanced and the side effects of each individual anesthetic drug are minimized. Glycopyrrolate is a synthetic quaternary ammonium compound which is anticholinergic and has no central effects. It is approximately five times more potent than atropine and has a strong, long-lasting antisialagogue action (Hall *et al*., 2001) [10] and by blocking peripheral muscarinic receptors, it prevents the transmission of cholinergic signals.
Butorphanol is synthetic opioid with agonist-antagonist activity at specific opioid receptors. Dexmedetomidine is highly effective alpha-2 agonist with sedative, analgesic, muscle relaxant with anaesthetic reducing qualities (Gertler *et al*., 2001) [6]. The most common side effects of dexmedetomidine are bradycardia, decreased respiration and hypothermia. Acepromazine is a phenothiazine derivative that blocks dopamine receptors in the CNS and depresses the reticular activating system resulting in sedation. It also possesses antiemetic, antihistaminic, antiarrhythmic and antishock properties because of its dopamine inhibition in the chemoreceptor trigger zone (Turi and Muir, 2011) [30]. Thiopentone sodium is an ultra-short acting barbiturate that has been used in variety of animal species to produce a short term surgical anaeshesia. A potent hypnotic, thiopental sodium causes dose-dependent central nervous system depression (Jadon *et al.*, 1998) [11]. Because a rapid intravenous infusion directly depresses the myocardium as result blood pressure drops. The therapeutic dose of barbiturate depresses respiration.

Therefore, the present study was aimed to evaluate the physiological and haemodynamic alternations following thiopentone sodium anaesthesia premedicated with butorphanol, dexmedetomidine and acepromazine in dogs.

Materials and Methods

The present study was conducted on 18 healthy dogs of either sex weighing between 10 to 20 kg body weight and were randomly divided into three groups *viz*., group I, II and III, comprising of 6 animals in each. The animals were fasted overnight and drinking water was withheld for 4 hours before the administration of anaesthesia. Ten minutes prior to the anaesthetic administration, all dogs were administered glycopyrrolate @ 0.02 mg/kg b.wt. intramuscularly. The animals of group A, B and C 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. After premedication, general anaesthesia was induced by thiopentone @ 18 mg/kg b.wt. intravenously in all the groups and dogs were intubated by suitable endotracheal tube of (4.5 to 8.5 OD mm) with guidance of laryngoscope. The physiological parameters *viz*., heart rate, respiratory rate and rectal temperature were recorded at before (0), 5 min. after premedication, following induction and at 10, 20, 40, 60 and 120 minutes after administration of thiopentone anaesthesia. Various heamodynamic parameters included blood pressure, SpO_2 and capillary refill time were recorded at before (0), 5 min. after premedication, following induction and at 10, 20, 40, 60 and 120 minutes after propofol anaesthesia. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were determined using a non-invasive system with the cuff placed on the fore leg over the metacarpal artery and recorded by the veterinary patient monitor (New Gen Medical Systems) Mean arterial pressure (MAP) was calculated using the formula MAP = DP + 1/3(SP-DP). Haemoglobin oxygen saturation (SpO2) was monitored by the pulse oximeter using multiparameter veterinary patient monitor and recorded with the sensor probe placed on the lateral surface of the tongue or ear pinna of each dog. Capillary refill time (seconds) was monitored by pressing the gingival mucosa digitally. Analysis of variance (ANOVA) and Duncan's multiple range tests (DMRT) were applied to compare mean within group and between groups 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 and Discussion

(A) Physiological parameters

1. Heart Rate

In group A, a non significant decrease in heart rate (90.50±1.17 to 89.16±1.13 beats/min.) was observed after sedation with butorphanol which further decreased significantly ($p<0.05$) after induction with thiopentone sodium up to 20 min. interval (89.16±1.13 to 82.50±2.34 beats/min.) post anaesthesia. Later on, the values increased and returned to near normalcy by 120 min. In group B, a non-significant decrease in heart rate (92.33±3.57 to 89.00±3.27 beats/min.) was observed after sedation with dexmedetomidine which further decreased significantly ($p<0.05$) after induction with thiopentone sodium up to 40 min. (89.00±3.27 to 78.00±2.48 beats/min.) post anaesthesia. Later on, the values increased and returned to near normalcy by 120 min. Where as in group C, a non significant decrease in heart rate (90.66±3.41 to 87.50±3.11 beats/min.) was observed after sedation with acepromazine which further decreased significantly ($p<0.05$) after induction with thiopentone sodium up to 10 min. (87.50±3.11 to 80.66±3.20 beats/min.) post anaesthesia. Later on, the values increased and returned to near normalcy by 120 min. interval (fig.1).

The reduction in heart rate with butorphanol and thiopentone sodium anaesthesia was comparatively for longer period as compared to acepromazine and thiopentone sodium. However, the decrease in heart rate with dexmedetomidine and thiopentone anaesthesia was for maximum period upto 40 min. interval. Additionally, butorphanol has been reported to cause considerable reductions in heart rate due to enhanced vagal tone, decreased diastolic pressure, and increased peripheral vascular tone (Paddleford, 1988) [22]. The decrease in heart rate could be attributed to depression of vasomotor reflexes mediated by hypothalamus or brain stem and due to alpha-1-adrenergic blockade, peripheral anti-adrenergic direct vasodilatory action and direct cardiac depression by acepromazine (Paddleford, 1988; Hall and Clarke, 1991) [22, 9]. After stimulating alpha-2 adrenergic receptors in arteries and veins, dexmedetomidine causes peripheral vasoconstriction, which leads to initial hypertension. This is followed by hypertension resulting from bradycardia, which is caused by vasomotor depression through central and peripheral action, increased vagal tone, decreased sympathetic activity, and heart rate through stimulation of pre synaptic alpha adrenergic receptors (Lemke, 2007) [17]. Barbiturates are also known to directly reduce the heart and brain's vasomotor drive, which lowers cardiac output and arterial pressure (Bodh *et al*., 2013) [2]. Contrary to our study, Likiw *et al*. (1991) [18], Kumar *et al*. (1995) [15] and Muhammad *et al*. (2009) [20] reported elevated heart rates during thiopental sodium anaethesia in dogs as arterial baroreflex is unaltered after thiopental administration which caused the dogs' heart rates to rise above baseline (Manat, 2001) [19].

2. Respiration Rate

In group A, a non-significant decrease in respiration rate (20.16±0.75 to 19.66±0.33 breaths per min.) was observed after sedation with butorphanol which further decreased significantly ($p<0.05$) after induction with thiopentone sodium up to 10 min. (19.66±0.33 to 14.00±0.68 breaths per min.) post anaesthesia. Later on, the values increased and returned to near normalcy by 120 min. In group B (dexmedetomidine + thiopentone sodium) there was significant ($p<0.05$) decrease in respiration rate (26.00±0.44 to 11.16±0.83 breaths per min.) up to 40 min. and later on, the values increased and returned to near normalcy by 120 min. In group C, a non significant decrease in respiration rate (24.33±0.49 to 23.00±0.51 breaths per min.) was observed after sedation with acepromazine which further significantly ($p<0.05$) decreased after induction with thiopentone sodium up to 10 min. (23.00±0.51 to 14.66±0.61 breaths per min.) post anaesthesia. Later on, the values increased and returned to near normalcy by 120 min (fig 2). Respiratory depression after thiopentone anaesthesia in animals of all the three groups was observed in nearby upto 60 min. from the base value could be due to direct action of this drug on central inspiratory drive and ventilator response to $PaCO_2$. Similarly,

the present study is in accordance with finding of Likiw *et al.* (1991) [18]; Muhammad *et al.* (2009) [20] and Kassem *et al.* (2019) [12] who reported decreased respiration rate during thiopental sodium anaesthesia in dogs. Acepromazine has been shown to decrease the respiration rate either directly by depressing the brain stem or by reducing the activation of aortic and carotid pressoreceptors (Booth, 1982) [3]. It has been observed that butorphanol significantly lowers respiration rate by directly depressing the medullary respiratory center (Booth, 1982; Paddleford, 1988 and Bufalari *et al*., 1997) [3, 22, 5]. Reduction in respiration rate after thiopentone administration might be due to depression of brain's respiratory center (Paddleford, 1988) [22]. The reduction in respiratory rate could potentially be attributed to the combined effects of systemic dexmedetomidine and barbiturate anaesthetic (Sabbe *et al*., 1994) [24]. Clarke and England (1989) [32] found respiratory depression under dexmedetomidine anaesthesia. It might be due to alpha 2-agonists, such as dexmedetomidine, directly depress the respiratory system by activating the α-2 adrenergic pathway, which in turn inhibits the locus coeruleus neurons (Oyamada *et. al.*, 1998) [21]. The respiratory depression effects of the alpha-2 agonist are likely to enhanced when combined with other analgesic or anesthetic agents i.e. opioids, barbiturates. The drop in respiration rate following thiopentone anaesthesia may be due to depression of the respiratory center of the brain (Bodh *et al*., 2013) [2]. The decrease in respiration rate observed in present study confirms the finding of Grimm *et al*. (1998) [8]; Kojima *et al*. (2002) [14] and Saini *et al*. (2017) [25] following alpha-2 agonist and barbiturate anaesthesia in dogs.

3. Rectal Temperature

In animals of group A, a non significant decrease in the rectal temperature was observed after administration of thiopentone sodium in combination with butorphanol which persisted upto 20 min (101.43±0.09 to 99.88±0.25°F) and in group B, a non significant decrease in the rectal temperature was observed after administration of thiopentone sodium in combination with dexmedetomidine which persisted upto 40 min (101.61±0.10 to 99.23±0.3°F). In animals group C, there was a significant decrease ($p<0.05$) in the rectal temperature upto 20 min (101.36±0.06 to 99.83±0.20°F). However, the values returned to baseline by 120 min. in all the groups (fig.3.)

In the present study, rectal temperature falls following thiopentone anaesthesia in animals of all groups might be due to peripheral vasoldilation, muscle relaxation, basal metabolic rate, depression of the thermoregulatory center, and decreased shivering (Manat, 2001) [19]. Similarly, Short (1987) [26] and Muhammad *et al.* (2009) [20] also reported decreased temperature during thiopental sodium anaesthesia in dogs. Medetomidine administration in dog slightly reduces body temperature. Dexmedetomidine have action on alpha-2 adrenoceptors which might have caused hypothermia thereby decrease in rectal temperature (Lemke, 2007; Saini *et al*., 2017) [17, 25]. On the contrary to our study, Ahmad *et al.* (2013) [1] reported a non-significant elevation in rectal temperature in dogs after administration of dexmedetomidine alone at 20 µg/kg I/M and Kassem *et al*. (2019) [12] also found significant ($p<0.05$) rise in rectal temperature after administration of thipentone in dogs which continued until the end of the experiment. However, the drop in rectal temperature after the onset of anaesthesia as drugs have direct effect on hypothalamus and muscular activity reduction results in decrease heat production (Virtanen, 1989) [31]. In accordance to our finding, decrease in rectal temperature was also recorded following acepromazine thiopentone anaesthesia in dogs (Bostrom *et al*., 2003) [4].

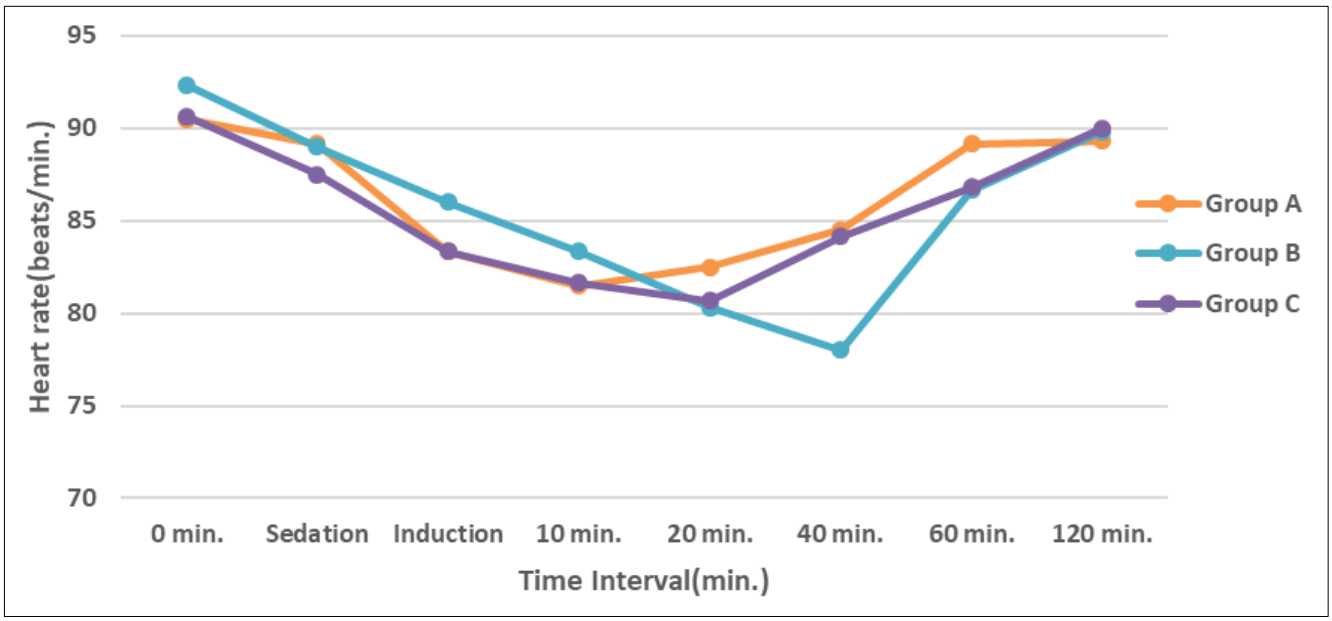

Fig 1: Showing heart rate (beats/min.) after various anaesthetic protocol in different groups

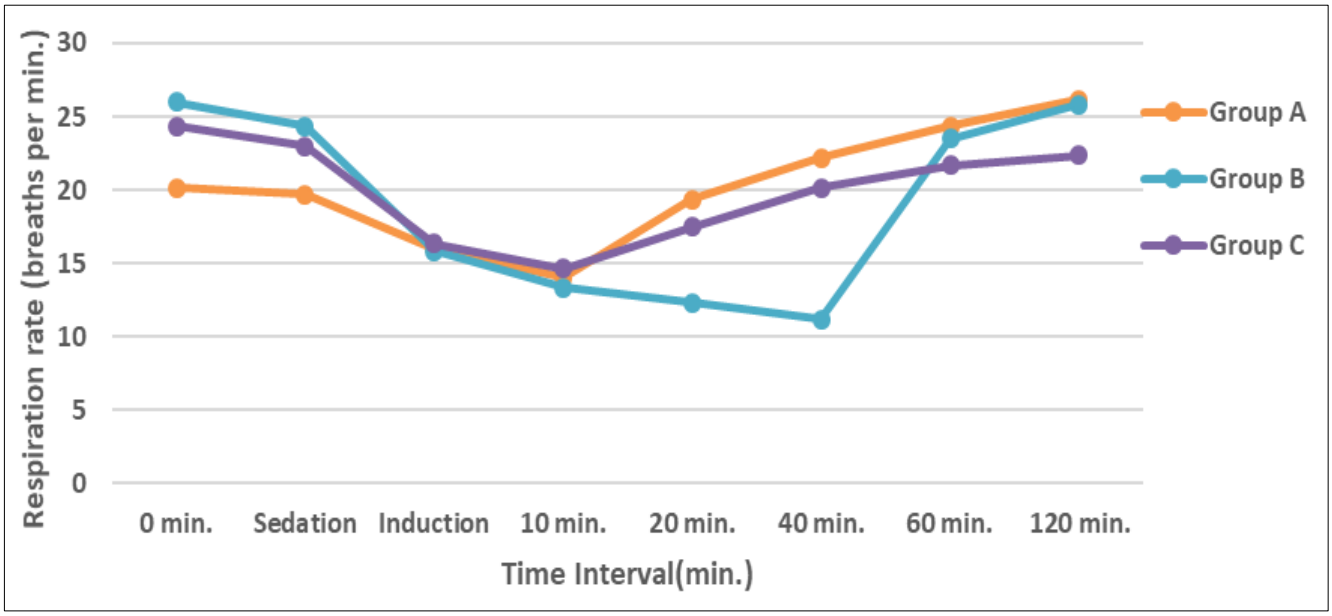

Fig 2: Showing Respiration rate (per min.) after various anaesthetic protocol in different groups

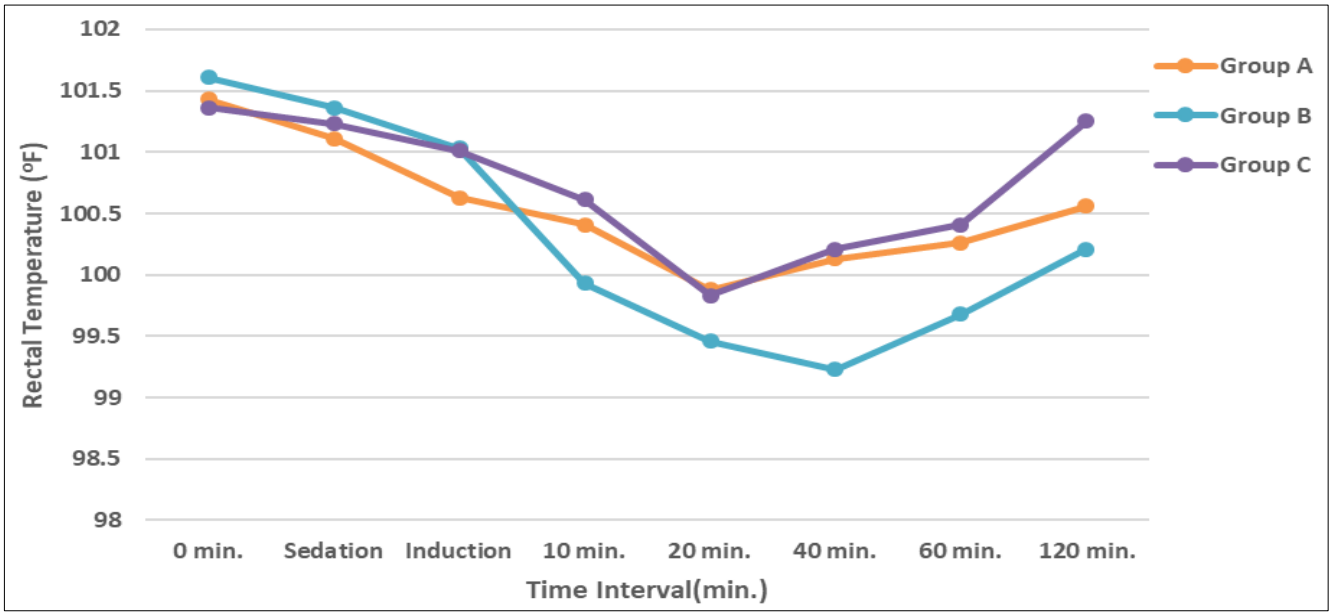

Fig 3: Showing Rectal Temperature (ºF) after various anaesthetic protocol in different groups

(B) Haemodynamic Parameters

1. Systolic Blood Pressure

In group A, non significant decrease in systolic blood pressure (128.33±3.77 to 123.33±3.44 mmHg) was observed after sedation with butorphanol which further significantly (p<0.05) decreased after induction with thiopentone sodium up to 20 min interval (123.33±3.44 to 100.83±3.77 mmHg) post anaesthesia. Later on, the values increased and returned to near normalcy by 120 min. In group B, non significant decrease in systolic blood pressure (126.16±1.40 to 123.50±0.92 mmHg) was observed after sedation with dexmedetomidine which further decreased significantly (p<0.05) after induction with thiopentone sodium up to 40 min. (123.50±0.92 to 103.50±1.80 mmHg) post anaesthesia (fig.4). Later on, the values increased and returned to near normalcy by 120 min. In group C, non significant decrease in systolic blood pressure (128.83±3.14 to 123.83±3.26 mmHg) was observed after sedation with acepromazine which further decreased significantly (p<0.05) after induction with thiopentone sodium up to 20 min. (123.83±3.26 to 108.66±2.07 mmHg) post anaesthesia. However, the values approached the pre administration data by 120 minutes interval. The blood pressure decreased gradually with non significant difference among the groups after induction of anaesthesia in all the three groups (fig.4.). Similarly, Suthar *et al.* (2018) [27] also noted a drop in blood pressure following the anaesthesia of barbiturates and propofol. He explained the reason that these anaesthetics cause a drop in peripheral vascular resistance, myocardial depression, which lowers the heart's contractibility, and a decrease in sympathetic outflow, which results in hypotension. It is well known that the barbiturates cause a dose-dependent drop in blood pressure.The primary cause of the effect is vasodilation, particularly veinodilation, with a direct decrease in cardiac contractibility having a less significant effect (Goodman and Gillman, 2005) [7].

2. Diastolic blood pressure

In group A, a non significant decrease in diastolic blood pressure (82.16±4.09 to 77.33±4.27mmHg) was observed after sedation with butorphanol which further decreased significantly ($p<0.05$) after induction with thiopentone sodium up to 20 min. (77.33±4.27 to 66.16±2.84 mmHg) post anaesthesia. Later on, the values increased and returned to near normalcy by 120 min. In group B, a non significant decrease in diastolic blood pressure (79.50±1.40±1.40 to 78.00±1.69 mmHg) was observed after sedation with dexmedetomidine which further decreased significantly ($p<0.05$) after induction with thiopentone sodium up to 40 min. (78.00±1.69 to 67.16±1.62 mmHg) post anaesthesia. Later on, the values increased and returned to near normalcy by 120 min. In group C, a non significant decrease in diastolic blood pressure (82.33±3.49 to 78.83±3.09 mmHg) was observed after sedation with acepromazine which further decreased significantly ($p<0.05$) after induction with thiopentone sodium up to 10 min. (78.83±3.09 to 71.83±3.39 mmHg) post anaesthesia (fig.5). Later on, the values increased and returned to near normalcy by 120 min. interval. Within the group, there was a modest, non-significant drop in diastolic blood pressure. However, the reduction lasted longer in animals who received dexmedetomidine and thiopentone sodium for anesthesia. Barbiturates and alpha-2 agonists are known to reduce peripheral vascular resistance, causing venous and arterial vasodilation, myocardial depression, which lowers the heart's contractibility, and sympathetic outflow, which results in hypotension (Suthar *et al*., 2018) [27].

3. Mean arterial pressure (MAP)

In group A, a non significant decrease in mean arterial pressure (97.55±2.33 to 91.33±2.65 mmHg) was observed after sedation with butorphanol which further decreased significantly ($p<0.05$) after induction with thiopentone sodium by 20 min interval (91.33±2.65 to 78.43±1.87 mmHg) post anaesthesia. Later on, the values increased and returned to near normalcy by 120 min. In group B, a non significant decrease in mean arterial pressure (97.11±1.30 to 92.00±1.37 mmHg) was observed after sedation with dexmedetomidine which further decreased significantly ($p<0.05$) after induction with thiopentone sodium up to 40 min. interval (92.00±1.37 to 78.00±3.07 mmHg) post anaesthesia. In animals of group C, a non significant decrease in mean arterial pressure (96.94±2.4 to 90.66±1.90 mmHg) was observed after sedation with acepromazine which further decreased significantly ($p<0.05$) after induction with thiopentone sodium up to 20 min. (90.66±1.90 to 77.33±1.99 mmHg) post anaesthesia (fig.6). However, the values increased and returned to preadministration level by 120 min. of observation period. The animals in all three groups experienced a non-significant decrease in mean arterial pressure following induction of barbiturate anaesthesia. Barbiturates immediately lower blood pressure, cardiac output, brain vasomotor drive, and myocardium (Redondo *et al*., 2000; Bodh *et al*., 2013) [23, 2]. It has also been observed that acepromazine, when administered prior to surgery to animals under halothane anaesthesia, causes a little reduction in mean arterial pressure (Tranquilli *et al*., 2007) [29]. Similarly, the depressive effects of thiopentone sodium and dexmedetomidine on the cardiovascular and respiratory system led to a drop in mean arterial pressure (Kinjavdekar *et al*., 2010) [13].

4. Haemoglobin oxygen saturation (SpO_2)

In group A, a non significant decrease in haemoglobin oxygen saturation (97.83±0.65 to 94.16±1.01%) was observed after sedation with butorphanol which further non-significantly decreased after induction with thiopentone sodium up to 20 min. (94.16±1.01 to 89.50±1.25%) post anaesthesia. Later on, the values increased and returned to near normalcy by 120 min. In group B, a non-significant decrease in haemoglobin oxygen saturation (97.00±0.57 to 95.66±0.55%) was observed after sedation with dexmedetomidine which further decreased significantly ($P<0.05$) after induction with thiopentone sodium up to 40 min. interval (95.66±0.55 to 85.53±0.72%) post anaesthesia. Later on, the values increased and returned to near normalcy by 120 min. In group C, a non significant decrease in haemoglobin oxygen saturation (98.66±0.21 to 97.50±0.22%) was observed after sedation with acepromazine which further decreased non-significantly after induction with thiopentone sodium up to 20 min. (97.50±0.22 to 92.66±2.95%) post anaesthesia (fig.7). Later on, the values increased gradually and returned to preadministration level by 120 min of observation. In the present study, all three groups showed lower SpO2 following sedation, which could be due to varying degrees of respiratory depression in each group. There were notable significant differences in the SpO2 levels at 20 minutes in dogs under dexmedetomidine + thiopentone anesthesia. However, in other two groups the decrease was non-significant. The lower level of SpO2 in acepromzine group may be caused by its predominant effect which is to blocks alpha-1 adrenergic receptor and causes vasodilation and hypotension (Lemke, 2007) [17]. Analogous observations were also made with dexmedetomidine anesthesia in dogs, which could be ascribed to vasoconstriction caused by the combined effect of α-2 agonist like dexmedetomidine (Kuusela *et al.*, 2000) [16]. During the present study, SpO2 reduction was just temporary and compensated during observation period.

5. Capillary Refill time (seconds)

The capillary refill time in all the animals at 0 (base value), sedation, after induction and at 10, 20, 40, 60 and 120 min. post thiopentone sodium anaesthesia was recorded less than 2 seconds. Over the course of the study period, there was no noticeable change in the capillary refill time. Capillary refill time is the time taken for a capillary bed to refill with blood following digital pressure on the gum which normally takes less than two seconds for the colour to return but any circulatory failure increase the capillary refill time. In the current investigation, only surgical anaesthesia was induced and dosage of thiopentone sodium was appropriate, thus cyanosis or pallor mucous membranes were not observed at any time interval in animals belonging to various groups.

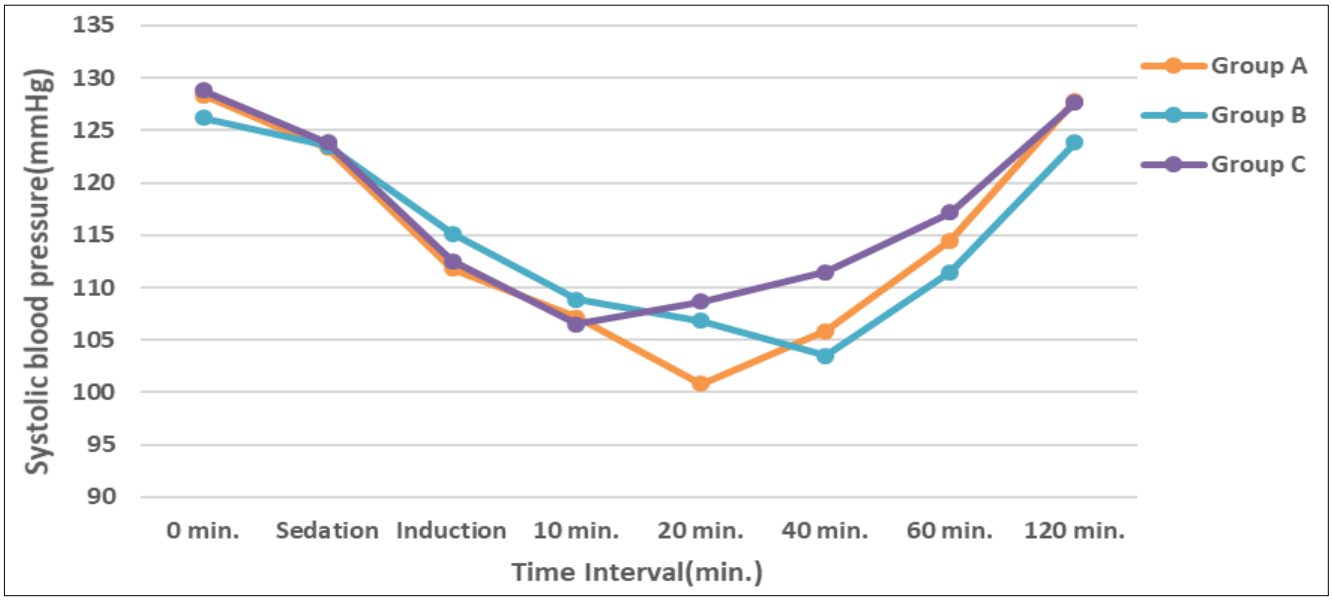

Fig 4: Showing Systolic blood pressure (mmHg) after various anaesthetic protocol in different groups

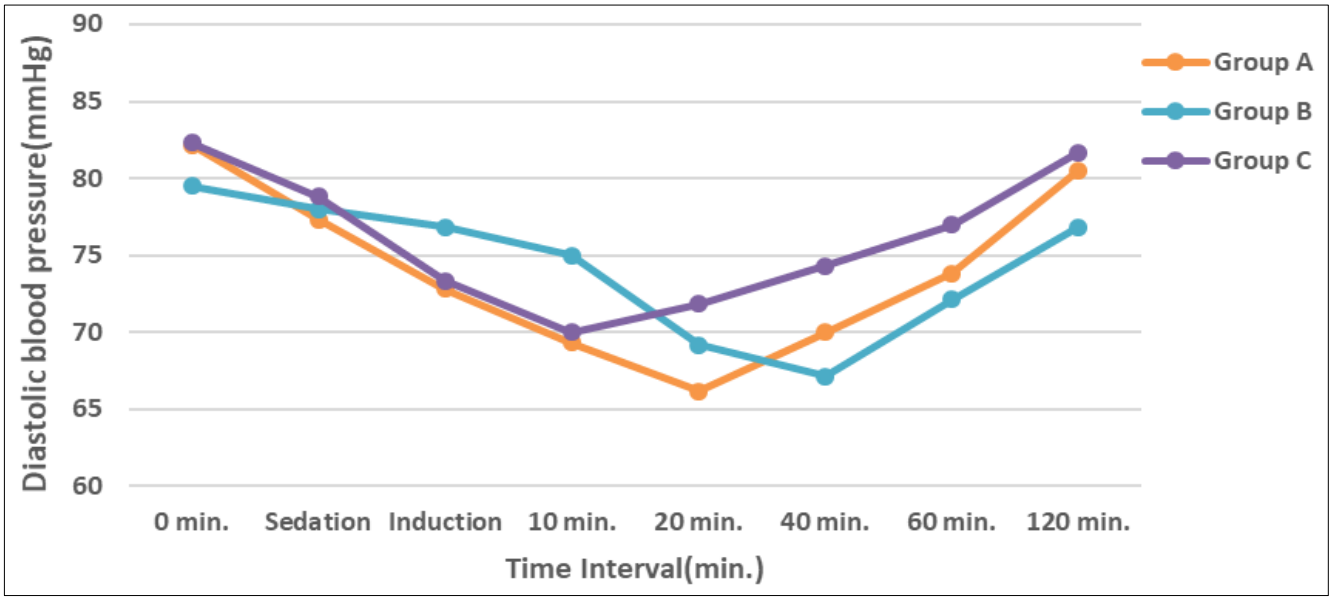

Fig 5: Showing Diastolic blood pressure (mmHg) after various anaesthetic protocol in different groups

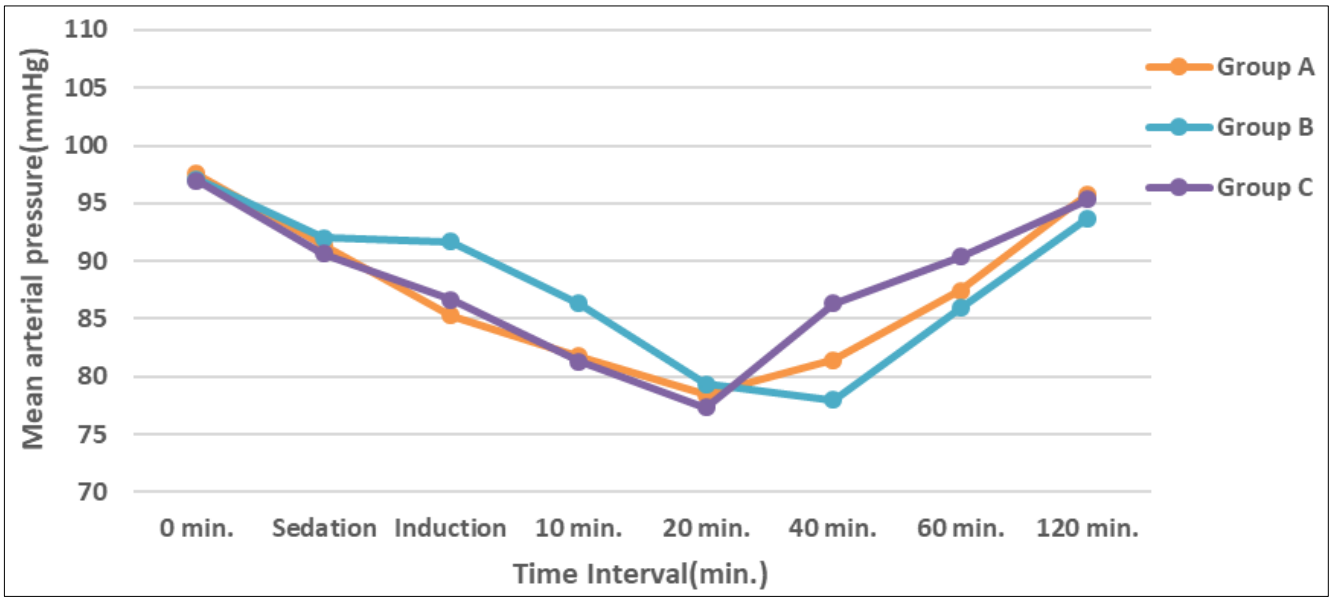

Fig 6: Showing Mean arterial pressure (mmHg) after various anaesthetic protocol in different groups

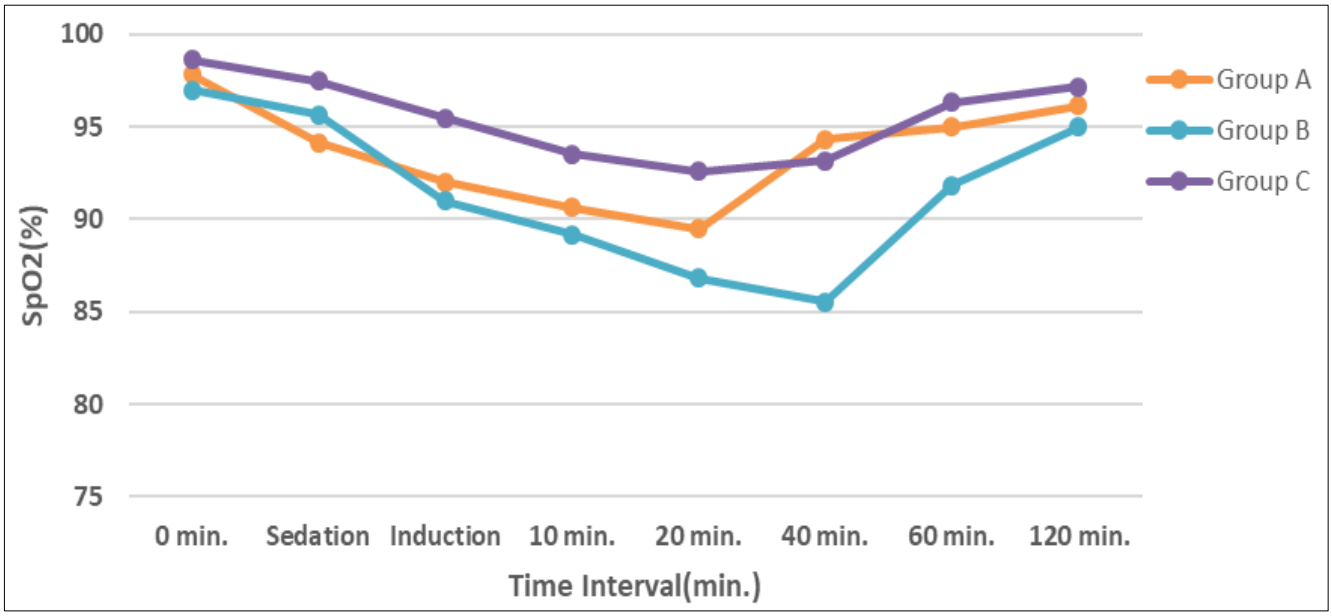

Fig 7: Showing SpO_2 (%) after various anaesthetic protocol in different groups

Conclusion

Physiological and haemodynamic parameters showed a temporary shift during anaesthesia but remained within physiological limits and eventually returned to normal during the research period. The present findings revealed that thiopentone sodium can be used safely as an induction agent in dogs premedicated with glycopyrrolate-butorphanol, glycoprrolate-dexmedetomidine and glycopyrrolate-acepromazine combination respectively.

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