Comparative evaluation of halothane anaesthesia in medetomidine–butorphanol and midazolam–butorphanol premedicated water buffaloes (*Bubalus bubalis*)

V Malik[a*], P Kinjavdekar[b], Amarpal[b], H P Aithal[b], A M Pawde[b] and Surbhi[b]

ABSTRACT

Six clinically healthy male water buffaloes (*Bubalus bubalis*) 2–3 years of age and weighing 290–325 kg were used for 2 different treatments (H_1 and H_2). The animals of group H_1 were premedicated with medetomidine (2.5 g/kg, i.v.) and butorphanol (0.05 mg/kg, i.v.), while in group H_2 midazolam (0.25 mg/kg) and butorphanol (0.05 mg/kg) were used intravenously. Induction of anaesthesia was achieved by 5 % thiopental sodium in H_1 (3.85 ± 0.63 mg/kg) and H_2 (6.96 ± 0.45 mg/kg) groups. The anaesthesia was maintained with halothane in 100 % oxygen through a large animal anaesthetic machine. Better analgesia and sedation with a significantly lower dose of thiopental for induction and significantly higher values of sternal recumbency time and standing time were recorded in group H_1 than in group H_2, whereas no significant ($P > 0.05$) difference for the halothane concentration was observed between groups H_1 and H_2. Significant decrease in heart rate was observed in group H_1 whereas it significantly increased in group H_2. In both groups, RR decreased during the preanaesthetic period, which increased significantly ($P < 0.01$) after halothane administration. In both groups a significant ($P < 0.01$) fall in RT was recorded from 20 min to the end of observation period. A significant ($P < 0.05$) fall in MAP was observed in group H_1 from 15 min until the end, while in group H_2 MAP increased nonsignificantly ($P > 0.05$) after premedication and a significant ($P < 0.05$) occurredafter thiopental administration. In both groups a significant ($P < 0.01$) increase in CVP and a significant ($P < 0.01$) decrease in SpO_2 were observed after premedication which persisted up to 120 min. ECG changes included significant ($P < 0.01$) decrease and increase in QRS amplitudes in groups H_1 and H_2 respectively, a significant ($P < 0.05$) increase in PR interval was recorded at 15 min in group H_1, a significant ($P < 0.05$) decrease in PR interval in group H_2, a significant ($P < 0.05$) decrease in T wave amplitude in group H_1, and a significant ($P < 0.01$) increase in duration of T wave in group H_1. It is concluded that both combinations can be used safely in buffaloes for surgery of 2 h duration but better sedation, analgesia and muscular relaxation and more dose sparing effect on anaesthetics and shorter recovery times were observed in group H_1.

Keywords: buffalo, butorphanol, halothane, medetomidine, midazolam, thiopental.

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INTRODUCTION

In large ruminants inhalation anaesthesia maximizes effectiveness and safety, provided appropriate adaptations are made for fasting and positioning of animals. Anaesthesia for major surgery is usually maintained with volatile agents but sedation and induction of anaesthesia with injectable drugs are very important in large, aggressive animals. Medetomidine, the most potent alpha-2 agonist, has been investigated in some species of animals[2,44,51]. This drug has, however, not been widely used in buffaloes, particularly in combination with butorphanol. Butorphanol, a synthetic opioid analgesic, is a partial agonist and agonist at κ opioid receptors. Midazolam has been reported to produce adequate sedation when used as premedicant with thiopental sodium in human beings and several species of animals[35,63,66]. Synergistic interactions have been reported between alpha-2 agonists and opioids and benzodiazepines and opioids in earlier studies[25,35]. However, the suitability of combining butorphanol with medetomidine or midazolam is yet to be established in buffaloes.

Thiopentone sodium is the most widely used intravenous induction agent in ruminants and has been used in cattle and buffalo calves[12,49]. There are few reports on the use of inhalant anaesthesia in large ruminants like cattle and sheep[30,47,61]. However, perusal of literature reveals little information on the use of halothane in adult buffaloes. Considering the importance of this species and the scarcity of information, this study was designed to compare the suitability of halothane anaesthesia with 2 different preanaesthetic protocols.

MATERIALS AND METHODS

Experimental animals

Six clinically healthy male buffaloes 2–3 years of age and weighing 290–325 kg were used. The clinical status of the animals was assessed by recording heart rate, respiratory rate and rectal temperature and by conducting haematological examinations. The animals were fasted for 48 hours and water was withheld for 24 hours prior to the start of the experiment. The animals were secured in right lateral recumbency and the left ventrolateral aspect of the neck and dorsal side of the left ear were aseptically prepared for administration of drugs. A pre-heparinised polythene catheter was introduced into the jugular vein through a 12 gauge hypodermic needle and passed up to the level of the right atrium. This catheter was attached to a central venous pressure (CVP) saline manometer through a 3-way stopcock for recording of CVP. The 3rd end of the stopcock was attached to a glass syringe filled with heparinised saline for flushing the system. The position of the catheter in the anterior *vena cava* or right atrium was confirmed by pressure changes in the saline manometer due to respiration. The cuff of the non-invasive blood pressure (NIBP) monitor (Surgivet, Smith Medical PM, Waukesha, WI, 53186) was applied around the base of the tail for monitoring systolic, diastolic and mean arterial blood pressures. Subcutaneous needle electrodes were placed at the posterior border of the scapula and at the 5th costochondral junction (base apex lead) for recording of

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electrocardiograms at 1 mV and 25 mm/s paper speed (BPL, New Delhi). The baseline data for arterial oxygen saturation were obtained by applying the sensor of a pulse oxymeter (Nonin Medical Inc., Minneapolis, USA) to the tongue after application of a mouth gag in the sedated animals. The animals were stabilised for 30 min before recording the baseline data.

Experimental design

All the animals received 2 treatments randomly at 10-day intervals. In group H_1 medetomidine (2.5 mg/kg) (Domitor; Orion Corporation, Formos Group, Turku, Finland) and butorphanol (0.05 mg/kg) (Butrum; Aristo Pharma, Mumbai) and in group H_2 midazolam (0.25 mg/kg) (Mezolam; Neon Laboratories, Mumbai) and butorphanol (0.05 mg/kg) were administered intravenously. Induction of anaesthesia was achieved with 5 % thiopental sodium (Thiosol sodium; Neon Laboratories, Mumbai) in both groups. Anaesthesia was maintained with halothane (Halothane I.P. 85; Raman and Weil Pvt Ltd, 15, Mumbai) in 100 % oxygen through a large-animal anaesthetic machine (Surgivet; Smith Medical PM, Waukesha, USA). The time of administration of preanaesthetics was taken as time zero.

Technique of drug administration

After 15 min of premedication, the animals were restrained in right lateral recumbency and anaesthesia was induced with intravenous thiopental sodium. An additional dose of thiopental sodium, if required, was administered until the pinprick reflex over the ribs and coronary band ceased to occur. A mouth gag was used to open the jaws and an endotracheal tube was passed and connected to the anaesthetic machine. Halothane in 100 % oxygen was administered *via* a semi- closed rebreathing system for maintenance of anaesthesia for 120 min. The vaporiser setting was adjusted according to depth of anaesthesia after monitoring the animal's response to a pinprick on the tail.

Clinical observations

Sedation. Sedation was evaluated by recording behavioural changes and was graded on a 1–4 scoring scale as: 1 (no sedation) = standing alert, head high, eyes open; 2 (mild sedation) = standing but appearing tired, drooping of head and eyelids; 3 (moderate sedation) = able to sit without support, drooping of head and eyelids; 4 (excellent sedation) = unable to sit without support, drooping of head and eyelids.

Analgesia. Analgesia was assessed by recording the animal's response at 15-min intervals by pricking with a 22 G hypodermic needle on the rib periosteum and at the coronary band. The analgesia was graded on a 1–4 scoring scale as: 1 (no analgesia) = strong reaction to pinpricks; 2 (mild analgesia) = weak response to pin pricks; 3 (moderate analgesia) = occasional response to pinpricks; 4 (excellent analgesia) = no response to pinpricks.

Muscular relaxation. Muscle relaxation was recorded in the muscles of the abdomen, legs and jaws. The ease with which the jaws of recumbent animals could be opened, their hind limbs could be bent without resistance and the flaccid abdomen could be pressed was recorded as the extent of muscle relaxation. It was graded on a 1–4 scoring scale as: 1 (no relaxation) = normal abdominal muscles, tightly closed jaws and stiff limbs; 2 (mild relaxation) = moderate resistance to pressing of abdomen, opening of jaws and bending of limbs; 3 (moderate relaxation) = mild resistance to pressing of abdomen, opening of jaws and bending of limbs; 4 (excellent relaxation) = flaccid abdomen, no resistance to opening of jaws and bending of limbs.

Reflexes. The degree of loss of various reflexes, namely palpebral, corneal, pedal (interdigital skin fold pinching with a artery forceps for 1 second) and pinprick (deep pricking the last thoracic rib periosteum with a 22 G hypodermic needle) were recorded at different intervals in the animals of different groups and were graded on a (–) to (++++) scoring scale as: (–) = completely lost; (+): mild response; (++): moderate response; (+++): good response; (++++): excellent response.

Position of eyeball. Position of the eyeball in the animals of different groups was recorded at different intervals and was graded as C (central) or D (downward rotation).

Extent of salivation. The extent of salivation was recorded at different intervals and was graded on a (–) to (++++) scoring scale as follows: (–): Absent; (+): mild; (++): moderate; (+++): extensive; (++++): profuse.

Dose of thiopental and concentration of halothane. The dose of thiopental sodium (mg/kg) for induction and concentration (%) of halothane (range) for maintenance of anaesthesia was calculated after the completion of each trial.

Weak time. The time that elapsed from the time of injection of preanaesthetic agents to the time when the animals showed ptosis of the head was recorded as weak time.

Recovery time. The time from discontinuation of the administration of halothane and the 1st spontaneous movement of any body part was recorded as recovery time.

Sternal recumbency time. The time from discontinuation of the administration of halothane to the spontaneous regaining of sternal recumbency was recorded as sternal recumbency time.

Standing time. The time from discontinuation of the administration of halothane to spontaneous regaining of standing position was recorded as standing time.

Heart rate (*beats/min*) (*HR*), *respiratory rate* (*breaths/min*) (*RR*) *and rectal temperature* (°C) (*RT*). HR, RR and RT were recorded at 0, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 min of anaesthesia. *Mean arterial pressure, central venous pressure and electrocardiogram.* Mean arterial pressure (MAP) (mm Hg), central venous pressure (CVP) (cm H_2O), haemoglobin oxygen saturation (SpO_2 %) and electrocardiogram (ECG) (base apex lead) at 1 mV and 25 mm/s paper speed were recorded at 0, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 min of anaesthesia.

Statistical analysis

Analysis of variance (ANOVA) and Duncan's multiple-range test (DMRT) were used to compare the means at different intervals among different groups. Paired *'t'* test was used to compare the means at different intervals with their respective base values in each group. For nonparametric observations the Kruskal-Wallis 1-way test was used to compare the means between groups[53,60].

RESULTS

Sedation

In group H_1 the median ± SD (range) of sedation score was 4 ± 0.516 (3–4). Of 6 animals, 4 recorded a score of 4 and 2 animals recorded a score of 3. Group H_2 animals recorded a sedation score of 2 ± 0.632 (1–3) (median ± SD) (range). In this group 4 animals recorded a score of 2, 1 animal recorded 3 and 1 animal scored 1.

In group H_1 the signs of sedation were evident after 2–3 min of medetomidine and butorphanol premedication. Excellent sedation was recorded in this group, with characteristic signs of sedation. Two animals in group H_1 attained sternal recumbency, whereas 2 animals knelt for a short period (1–2 min) and could stand up intermittently. However, other animals remained in the standing position but appeared sedated. None of the animals in this group showed signs of excitement during sedation. In 1 animal the eyelids were closed with moderate depression of palpebral and corneal reflexes

and the eyeball turned ventromedially after 5 min of premedication, but it regained its central position after 10 min of drug administration.

In group H_2 animals, moderate sedation was recorded. Two animals in this group attained sternal recumbency immediately after premedication with midazolam and butorphanol, but these animals stood up after 5–8 min. Other animals remained in the standing position with varying degrees of ataxia and incoordination. All the animals of this group exhibited signs of excitement like vigorous licking of muzzle, shaking of the head and tail, attempts to stand up, if recumbent within 5 min of drug administration. Two animals of this group showed signs of severe excitement and were difficult to restrain before induction. Comparison between the groups revealed that medetomidine and butorphanol produced better sedation than midazolam and butorphanol.

Analgesia

In group H_1 the analgesia was graded as excellent with a score of 4. The median ± SD (range) of analgesia score recorded in group H_1 was 4 ± 0.0 (4–4). However, in group H_2 the analgesia was graded as good. The median ± SD (range) of analgesia score in group H_2 was 2.5 ± 0.81 (2–4). In group H_2, 3 animals recorded a score of 2, while 2 animals recorded 3 and only 1 animal recorded a score of 4.

Muscular relaxation

Median ± SD (range) of muscle relaxation score was 4 ± 0.40 (3–4) in group H_1 and 4 ± 0.51 (3–4) in group H_2, respectively. In group H_1, 5 animals recorded excellent muscle relaxation (score 4) and in 1 animal good muscle relaxation (score 3) was recorded. In group H_2 4 animals recorded excellent muscle relaxation (score 4) and 2 animals recorded good muscular relaxation (score 3). Signs of early muscle relaxation were observed after 8–10 min of premedication and remained so throughout the observation period. Comparison between groups did not reveal significant differences in muscle relaxation scores.

Palpebral reflex

In group H_1 the palpebral reflex was moderately depressed up to 15 min after premedication and remained absent during the rest of the observation period, whereas in group H_2 the palpebral reflex was good to moderately depressed after midazolam and butorphanol administration, but was later completely depressed and remained absent during the rest of the observation period. Comparison between the 2 groups did not show significant differences in the depression of the palpebral reflex.

Corneal reflex

In both groups the corneal reflex showed good response to moderate depression after premedication. However, it disappeared after administration of thiopental sodium in both groups and remained absent up to the end of anaesthesia.

Pedal reflex

After premedication, a good response to moderate depression of pedal reflex was recorded and it remained so up to 15 min of anaesthesia in both groups. After induction of anaesthesia, the pedal reflex disappeared completely and this persisted until the end of maintenance anaesthesia in animals of group H_1. However, in group H_2 the pedal reflex was lost after induction and remained so, but 2 animals in this group showed a mild response up to the end of the observation period. Comparison between groups revealed that the degree of depression of the pedal reflex was higher in group H_1 than in group H_2.

Position of eyeball

The eyeball remained central in position during the sedation period in group H_2, whereas in group H_1 the eyeball rotated downward 5 min after premedication. During the maintenance period it rotated downward in most of the animals of both groups.

Salivation

Mild to moderate salivation was observed after 5–10 min of premedication in both groups. However, in group H_1 the extent of salivation was moderate but group H_2 animals produced only mild salivation during the sedation period. Moderate to profuse salivation was noticed throughout the observation period in both groups. When the concentration of halothane was increased to maintain the desired depth of anaesthesia, the extent of salivation increased immediately. An increase in halothane concentration also increased lacrimation.

Doses of drugs

Thiopental sodium

Mean doses of thiopental sodium for induction of anaesthesia in groups H_1 and H_2 were 3.85 ± 0.63 mg/kg and 6.96 ± 0.45 mg/kg, respectively. Group H_1 required significantly ($P < 0.05$) lower doses than group H_2.

Halothane

Halothane concentration for maintenance of anaesthesia in group H_1 ranged from 2.5 to 3.5 %, whereas in group H_2 it ranged from 2.75 to 4.0 %. Comparison between the groups revealed no significant ($P > 0.05$) differences in the halothane concentration used for maintenance.

Weak time

The median ± SD of weak times recorded in groups H_1 and H_2 were 3.00 ± 1.60 min and 4 ± 1.89 min, respectively, which did not differ significantly between groups (Fig. 1). However, in group H_1 sedation developed smoothly and the onset of limb incoordination was gradual but the animals took less time to show ptosis of the head. In contrast, in group H_2 the onset of limb incoordination was rapid but the animals took longer to show ptosis of the head.

Recovery time

The median ± SD of recovery time recorded in groups H_1 and H_2 were 5 ±

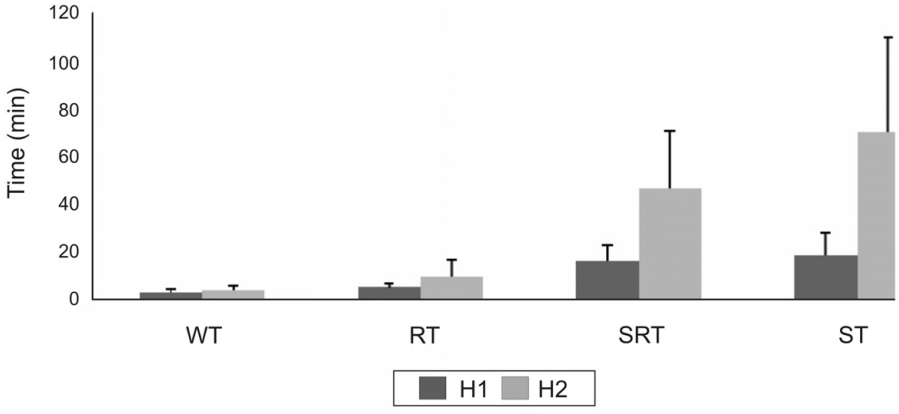

Fig. 1: **Weak time** (WT)**, recovery time** (RT)**, sternal recumbency time** (SRT) **and standing time** (ST) **after halothane anaesthesia in water buffaloes** (n = 6) **induced with thiopental sodium** (5 % to effect i.v.) **and premedicated with medetomidine** (2.5 µg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_1 and midazolam** (0.25 mg/kg i.v. + butorphanol (0.05 mg/kg i.v.) **in group H_2**.

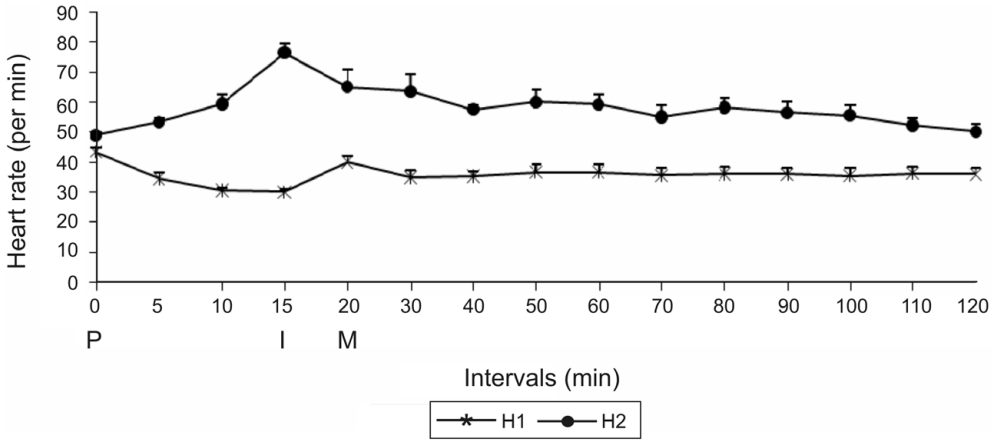

Fig. 2: **Mean ± SE values of heart rates** (beats/min) **at different time intervals during halothane anaesthesia in water buffaloes** ($n = 6$) **induced with thiopental** (5 % to effect i.v.) **and premedicated with medetomidine** (2.5 µg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_1 and midazolam** (0.25 mg/kg i.v.) + butorphanol (0.05 mg/kg i.v.) **in group H_2. P = time of premedication; I = time of induction; M = time of start of maintenance.**

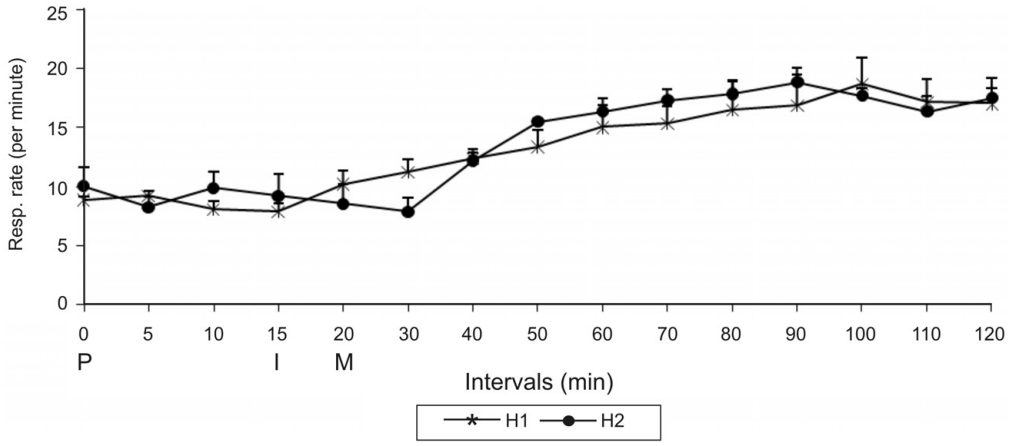

Fig. 3: **Mean ± SE values of respiratory rates** (breaths/min) **at different time intervals during halothane anaesthesia in water buffaloes** ($n = 6$) **induced with thiopental** (5 % to effect i.v.) **and premedicated with medetomidine** (2.5 µg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_1 and midazolam** (0.25 mg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_2. P = time of premedication; I = time of induction; M = time of start of maintenance.**

1.86 min and 9.5 ± 7.00 min, respectively. Group H_1 recovered earlier than group H_2, The recovery times did, however, not differ significantly ($P > 0.05$) (Fig.1) .

Sternal recumbency time

The median ± SD of sternal recumbency time recorded in groups H_1 and H_2 were 16 ± 6.83 min and 46.5 ± 23.86 min, respectively. Group H_2 took significantly ($P < 0.05$) longer to resume sternal recumbency than group H_1 (Fig.1).

Standing time

The median ± SD of standing time recorded in groups H_1 and H_2 were 18.50 ± 9.43 min and 70 ± 39.82 min, respectively. Standing time in group H_2 was significantly ($P < 0.05$) longer than in group H_1 (Fig. 1).

Heart rate (HR)

Medetomidine and butorphanol combination produced significant ($P < 0.01$) bradycardia immediately after premedication in group H_1, which persisted up to 40 min. After 50 min HR improved slightly but remained significantly ($P < 0.05$) decreased until the end of the observation period. In group H_2 HR increased after midazolam and butorphanol administration and remained significantly ($P < 0.05$) increased from 10–40 min and returned to the base value at 120 min. HR remained significantly ($P < 0.05$) higher in group H_2 than in group H_1 (Fig. 2).

Respiratory rate (RR)

In group H_1 a non-significant ($P > 0.05$) decrease in RR was recorded up to 15 min of premedication but an increasing trend in RR was recorded after halothane administration, which was significant ($P < 0.01$) throughout the maintenance period. In group H_2 RR decreased nonsignificantly ($P > 0.05$) after premedication and remained so up to the post-induction period (20 min). It increased after the administration of halothane and remained significantly ($P < 0.01$) increased throughout the maintenance period (Fig. 3).

Rectal temperature (RT)

In groups H_1 and H_2 a significant ($P < 0.01$) decrease in RT was recorded at 20 min which persisted up to the end of the observation period. Significantly higher RT values were recorded in group H_1 up to 15 min, but no significant differences between the groups was recorded in RT after induction until the end of anaesthesia (Fig. 4).

Mean arterial pressure (MAP)

In group H_1 a significant ($P < 0.05$) drop in MAP was recorded after 15 min of premedication and the decrease continued for the entire observation period. However, from 30 to 50 min a highly significant ($P < 0.01$) decrease in MAP was recorded. In group H_2 a nonsignificant ($P < 0.05$) increase in MAP was recorded after 5 min of premedication, but after induction a significant ($P < 0.05$) decrease in MAP was recorded, which persisted for the entire observation period (Fig. 5).

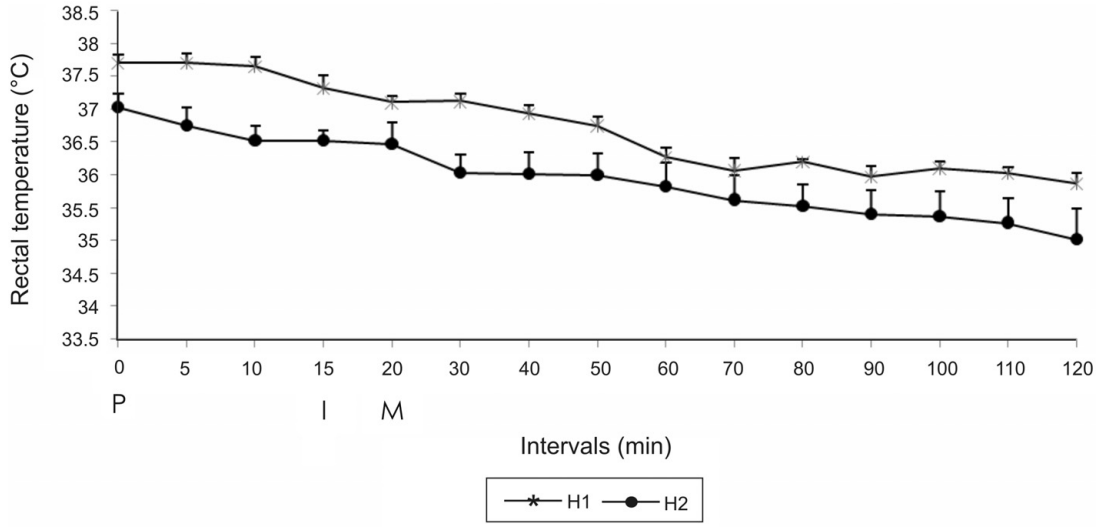

Fig. 4: **Mean ± SE values of rectal temperature** (°C) **at different time intervals during halothane anaesthesia in water buffaloes** (n = 6) **induced with thiopental** (5 % to effect i.v.) **and premedicated with medetomidine** (2.5 µg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_1 and midazolam** (0.25 mg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_2. P = time of premedication; I = time of induction; M = time of start of maintenance.**

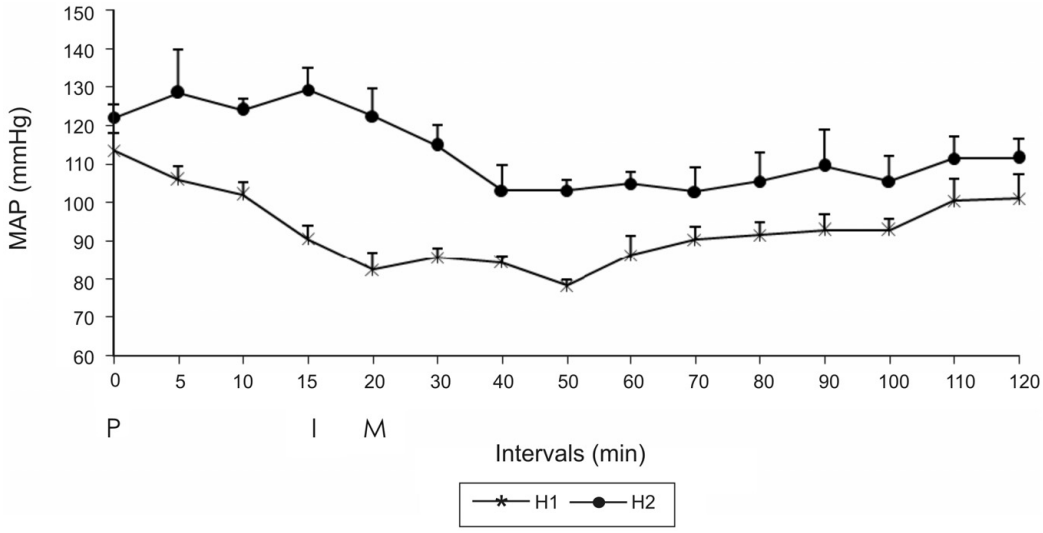

Fig. 5: **Mean ± SE values of mean arterial pressure** (mm Hg) **at different time intervals during halothane anaesthesia in water buffaloes** (n = 6) **induced with thiopental** (5 % to effect i.v.) **and premedicated with medetomidine** (2.5 µg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_1 and midazolam** (0.25 mg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_2. P = time of premedication; I = time of induction; M = time of start of maintenance.**

Central venous pressure (CVP)

In group H_1 CVP increased significantly ($P < 0.01$) 5 min after premedication and this persisted up to 120 min. However, a maximum increase in CVP was recorded at 10 min. CVP increased significantly ($P < 0.01$) after 5 min of premedication in group H_2, which decreased but remained nonsignificantly ($P > 0.05$) higher throughout the observation period. CVP remained significantly ($P < 0.05$) higher in group H_1 thab in group H_2 throughout the observation period (Fig. 6).

Haemoglobin oxygen saturation (SPO_2)

In group H_1 SpO_2 decreased significantly ($P < 0.01$) at 5 min, and this persisted for 120 min. However, the lowest SpO_2 value was observed after induction of anaesthesia. Group H_2 exhibited a significant ($P < 0.01$) decrease in SpO_2 at 10 min, which remained decreased up to the end of the observation period. No significant differences in SpO_2 between groups were recorded throughout the observation period (Fig. 7).

Electrocardiography

Electrocardiographic parameters recorded in both groups are presented in Table 1. A normal sinus rhythm was recorded before premedication in all the animals of both groups. However, sinus bradycardia after premedication was a consistent finding in group H_1. On the other hand sinus tachycardia was consistently observed after premedication in group H_2. After induction of anaesthesia, however, sinus bradycardia disappeared in group H_1 and did not reappear during the rest of the observation period. In group H_1 the QRS amplitude recorded a highly significant ($P < 0.01$) decrease after premedication which remained decreased up to 90 min, whereas in group H_2 the QRS amplitude showed a significant ($P < 0.01$) increase from 15 min until the end of the observation period.

A significant ($P < 0.05$) increase in PR interval was recorded at 15 min in group H_1. A further highly significant ($P < 0.01$) increase was recorded from 45 min to 120 min. By contrast, in group H_2 a significant ($P < 0.05$) decrease in PR interval was recorded at 30 min, which persisted until the end of the observation period. In group H_1 the T wave amplitude decreased significantly ($P < 0.05$) at 30 min

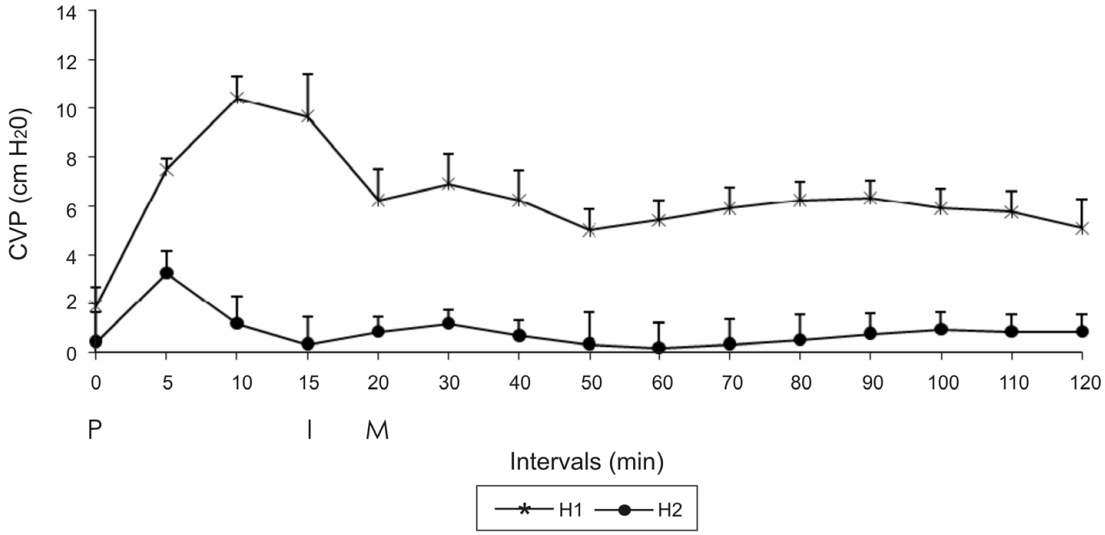

Fig. 6: **Mean ± SE values of central venous pressure** (cm H_2O) **at different time intervals during halothane anaesthesia in water buffaloes** (*n* = 6) **induced with thiopental** (5 % to effect) **and premedicated with medetomidine** (2.5 µg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_1 and midazolam** (0.25 mg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_2. P = time of premedication; I = time of induction; M = time of start of maintenance.**

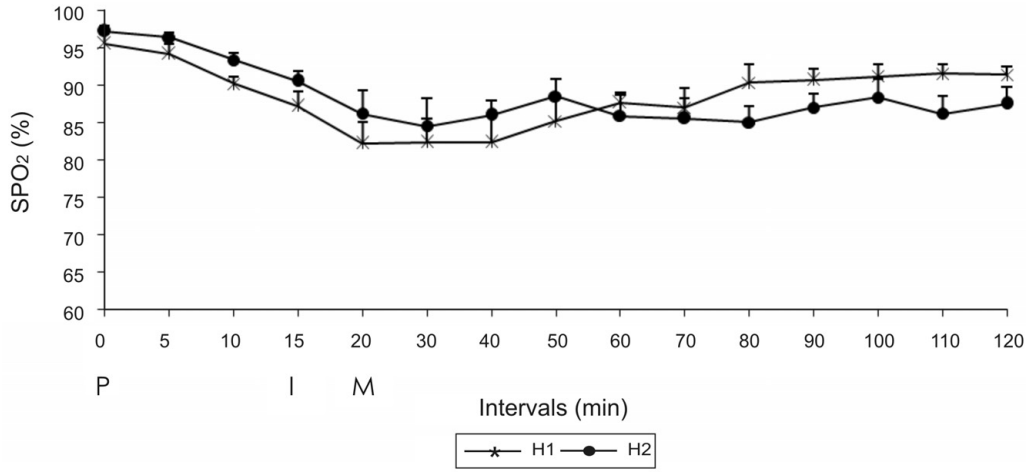

Fig. 7: **Mean ± SE values of heart rates** (beats/min) **at different time intervals during halothane anaesthesia in water buffaloes** (*n* = 6) **induced with thiopental** (5 % to effect i.v.) **and premedicated with medetomidine** (2.5 µg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_1 and midazolam** (0.25 mg/kg i.v.) **+ butorphanol** (0.05 mg/kg i.v.) **in group H_2. P = time of premedication; I = time of induction; M = time of start of maintenance**.

from the baseline and remained decreased until the end of the observation period except at 1 or 2 intervals. In both groups the duration of T wave exhibited a highly significant ($P < 0.01$) increase at 15 min and 30 min and thereafter up to 120 min.

DISCUSSION

The doses of medetomidine (2.5 g/kg) and butorphanol (0.05 mg/kg) were selected on the basis of pilot trials conducted before the start of the experiment. It was found that smaller doses of medetomidine (2.5 g/kg) and butorphanol (0.05 mg/kg) enhanced the sedation and analgesia and reduced the adverse effects. Similarly, decreased doses of medetomidine ranging from 2 to 10 g/kg with butorphanol have been reported to enhance sedation and analgesia, while potentially reducing the duration of the adverse cardiovascular effects associated with its use[45]. Synergistic sedative and analgesic activity between alpha-2 agonists and opioid agonist-antagonists has been reported in horses and ruminants[10,35]. Midazolam and butorphanol produced moderate sedation and adequate analgesia but induced varying degrees of excitement in all the animals. Although midazolam does not have any analgesic effect, addition of butorphanol might have resulted in an adequate level of analgesia. Thiopental and halothane have no or minimal intrinsic analgesic effect[31]. Excellent analgesia throughout the observation period in both groups might be due to the long-lasting analgesic effect of medetomidine and butorphanol and CNS depressant effects of thiopental and halothane. Alpha-2 agonists have been reported to produce profound muscle relaxation alone and in combination with opioid agonist-antagonists[24]. Midazolam possesses muscle-relaxant properties typical of benzodiazepines. The muscle relaxation and motor incoordination induced by midazolam have been reported in different species[32,58]. Moderate depression of all the reflexes was recorded in both groups. Moderate to complete abolition of palpebral and corneal reflexes after medetomidine (10 g/kg) and pentazocine (3mg/kg) in goats, mild to moderate palpebral reflex and full corneal reflex after midazolam administration (0.2 mg/kg, i.v.) in bovine and complete abolition of palpebral and corneal reflexes and ventro-medial rotation of eyeball after thiopental administration and during maintenance with halothane in bovine have been reported[4,5,21,49].

Increased salivation during the maintenance period could be due to the effect of alpha-2 agonists on salivary glands,

Table 1: **Electrocardiographic parameters recorded in groups H_1 and H_2 at different time intervals.**

Parameters	Groups	Time intervals (min)								
		0	15	30	45	60	75	90	105	120
P wave amplitude (mV)	H_1	0.18a*± 0.02	13*b ± 0.01	0.12*bc ± 0.01	0.16a ± 0.02	0.15a ± 0.02	0.15a ± 0.01	0.13b*± 0.01	0.12 ± 0.02	0.13* ± 0.02
	H_2	0.14b ± 0.02	0.16ab ± 0.02	0.16a ± 0.01	0.16a ± 0.02	0.15a ± 0.01	0.15a ± 0.01	0.15ab ± 0.01	0.14 ± 0.02	0.14 ± 0.02
P wave duration (s)	H_1	0.10 ± 0.01	0.09 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.10a ± 0.01	0.10a ± 0.01	0.10a ± 0.01	0.10a ± 0.01	0.09a ± 0.00
	H_2	0.08 ± 0.01	0.10 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.08bc ± 0.00	0.09ab ± 0.00	0.09ab ± 0.00	0.09ab ± 0.00	0.09a ± 0.01
QRS amplitude (mV)	H_1	1.18a ± 0.03	1.10**a ± 0.04	1.10**a ± 0.04	1.08a ± 0.07	1.06**a ± 0.05	1.06**a ± 0.05	1.06**ab ± 0.05	1.10a ± 0.04	1.10a± 0.04
	H_2	0.88bc ± 0.03	1.00**ab ± 0.03	1.08**a ± 0.03	1.12**a ± 0.04	1.08**a ± 0.04	1.06**a ± 0.04	1.06**ab ± 0.04	1.10**a ± 0.04	1.12**a ± 0.04
QRS duration (s)	H_1	0.09a ± 0.00	0.10 ± 0.01	0.11**a ± 0.00	0.11a ± 0.01	0.10ab ± 0.01	0.10a ± 0.01	0.11**a ± 0.00	0.10a ± 0.00	0.10*a ± 0.00
	H_2	0.08b ± 0.01	0.09 ± 0.00	0.09b ± 0.00	0.09ab ± 0.00	0.08b ± 0.00	0.08b ± 0.00	0.08b ± 0.00	0.08c ± 0.01	0.08c ± 0.01
T wave amplitude (mV)	H_1	0.38ab ± 0.02	0.30 ± 0.04	0.25* ± 0.04	0.21** ± 0.03	0.30 ± 0.05	0.25 ± 0.04	0.23*bc ± 0.03	0.22*b ± 0.04	0.21*b ± 0.04
	H_2	0.34ab ± 0.03	0.28 ± 0.03	0.36 ± 0.03	0.34 ± 0.04	0.38 ± 0.06	0.38 ± 0.06	0.40a ± 0.04	0.38a ± 0.04	0.38a ± 0.04
T wave duration (s)	H_1	0.14 ± 0.01	0.16**a ± 0.01	0.16** ± 0.01	0.17*a ± 0.01	0.16** ± 0.00	0.16** ± 0.00	0.16a ± 0.01	0.18**a ± 0.01	0.18**a ± 0.01
	H_2	0.10 ± 0.01	0.12b ± 0.01	0.15* ± 0.01	0.16**ab ± 0.01	0.16** ± 0.02	0.16** ± 0.02	0.16**a ± 0.02	0.16** ± 0.02	0.16**a ± 0.02
PR interval (s)	H_1	0.20a ± 0.00	0.23*a ± 0.01	0.22* ± 0.01	0.23** ± 0.00	0.23**a ± 0.00	0.23*a ± 0.00	0.23**a ± 0.00	0.23** ± 0.00	0.23**a ± 0.00
	H_2	0.21a ± 0.00	0.18b ± 0.01	0.18* ± 0.01	0.17**b ± 0.00	0.17*b ± 0.01	0.17*b ± 0.01	0.17*b ± 0.00	0.18**b ± 0.01	0.18**b ± 0.01
QT interval (s)	H_1	0.48 ± 0.02	0.56a ± 0.05	0.54*ab ± 0.02	0.55*a ± 0.03	0.56**a ± 0.03	0.56**a ± 0.03	0.56**a ± 0.03	0.56**a ± 0.03	0.59**a ± 0.03
	H_2	0.48 ± 0.03	0.45bc ± 0.02	0.48b ± 0.03	0.50ab ± 0.03	0.49ab ± 0.03	0.48b ± 0.05	0.47bc ± 0.05	0.45b ± 0.04	0.45b ± 0.04

*Significantly different from the base value ($P < 0.05$).
**Significantly different from the base value ($P < 0.01$).

decreased swallowing reflex or partially opened jaws for placement of the endotracheal tube[26,50]. Regurgitation, a frequent complication during general anaesthesia in ruminants, could be effectively prevented in the present study by keeping the animals off feed prior to the start of the experiment and by placing the caudal cervical and anterior thoracic region higher than the rest of the body[46].

Reduction in the induction dose of thiopental was recorded in both groups as the usual dose of thiopental in large ruminants is around 8–10 mg/kg. Synergism between medetomidine and butorphanol and thiopental might have played an important role in reducing the induction dose of thiopental in the present study. Synergistic interaction between midazolam and thiopental has also been reported where preanaesthetic medication with midazolam reduced the dose of thiopental by about 25 % and 50 % in cattle and 40 % in buffaloes[5,7,21]. The concentration of halothane required for maintenance in group H_1 was slightly lower than in group H_2, which suggested a greater halothane sparing effect of medetomidine in comparison to midazolam. Similarly, medetomidine (30 g/kg) has been reported to cause a 47.2 % decrease in MAC of isoflurane compared to a 23 % reduction in MAC of isoflurane after midazolam administration in dogs[9,64].

The animals of group H_2 required significantly longer time to stand than those of group H_1. It might be due to the greater induction doses used in group H_2. Consciousness has been reported to return within 15–20 min after discontinuation of halothane in diazepam and chloral hydrate induced calves, which were able to stand within 90 min[55]. However, it has been reported that buffaloes took 190 minutes to stand after thiopental-induced halothane anaesthesia[6]. In another study, return of consciousness, within 15–20 min following halothane anaesthesia, irrespective of induction agents used, has also been reported in different animals[11,31].

Significant bradycardia has been recorded in medetomidine and butorphanol premedicated buffaloes. Inhibition of sympathetic tone from the CNS, vagal activity in response to medetomidine induced vasoconstriction and direct increase in the release of acetylcholine from sympathetic nerves in the heart have been reported as the possible mechanisms by which medetomidine induced bradycardia[32]. Similar effects have been reported in earlier studies after medetomidine administration in different species[28,67]. Midazolam has been reported to cause transient hypotension in humans

and, as the baroreflex is preserved, the increase in HR may be a reflex response to decreased blood pressure in humans[29]. A similar finding has been recorded in the present study, where midazolam caused tachycardia. An appreciable tachycardia with no change in MAP but decreased CVP in calves sedated with diazepam has also been reported[37]. Mild increase in HR after thiopentone administration in both groups in the present study supported the findings in buffaloes administered thiopentone sodium and glyceryl guiacolate[1]. It has been observed that during halothane anaesthesia tachycardia was a consistent finding and during controlled ventilation HR increased approximately 50 % over resting values[68]. Similar findings of tachycardia have also been reported in cattle anaesthetised with halothane[13]. By contrast, bradycardia has been shown to develop after halothane anaesthesia in cattle calves and no change in HR was reported when it was used at clinical doses in these animals[52,65].

Respiratory depression was a consistent finding in both groups. Respiratory depression associated with alpha-2 adrenergic agonists might be secondary to the CNS depression produced by alpha-2 adrenoceptor stimulation or due to direct depression of the respiratory centres by preanaesthetics[27,54]. A similar decrease in RR has also been reported after medetomidine administration in sheep[38,39]. In contrast, only a small effect on RR has been reported after intravenous medetomidine administration in goats[41]. In both groups, shallow and rapid respiration was recorded throughout the observation period. Shallow and rapid respiration has been reported to be a characteristic feature of halothane anaesthesia[36]. Similar observations have been recorded in camels during halothane anaesthesia[68].

Significant hypothermia was recorded in both groups throughout the observation period. Alpha-2 agonists have been reported to induce prolonged depression of thermoregulation[43] and similar findings have also been reported after medetomidine administration in goats[59]. These agents have also been found to depress hypothalamic noradrenergic alpha-2 adrenergic receptors to cause hypothermia[34]. Reduced basal metabolic rate and muscle activity on one hand and depression of thermoregulation on the other might have resulted in hypothermia[43].

Hypotension was a consistent finding in both groups. A biphasic response, *i.e.* transient initial hypertension followed by prolonged hypotension, has been considered a classic response after intravenous administration of alpha-2 adrenergic agonists[48]. However, an initial hypertensive response was not recorded in the present study and instead only a hypotensive phase was recorded. It has been reported that preservation of haemodynamic functions occurred with midazolam, which involves an intact sympathetic reflex as demonstrated by release of endogenous catecholamine[14], and this might be the reason for increase in MAP after midazolam and butorphanol administration. However, in contrast with the findings of the present study, intravenous administration of midazolam and butorphanol has been reported to induce significant decrease in MAP in isoflurane anaesthetised cats[16]. In both groups the MAP remained lower than the baseline during the maintenance period. However, the depression was significant only in group H_1. The hypotensive effect of halothane has been shown in cattle, horses, sheep, buffalo and camels[12,42,52,57,62]. Halothane, when used in clinical doses, produced a decrease in arterial blood pressure, which resulted from the depression of myocardial contractility and cardiac output[65].

The significant and prolonged increase in CVP as recorded in the present study was probably a reflection of medetomidine-induced bradycardia and possibly vasoconstriction resulting in the pooling of blood in the venous circulation[27]. Significant increase in CVP has been demonstrated after medetomidine and butorphanol administration in goats[41]. A slight decrease in CVP was recorded immediately after thiopentone administration in the present study. Similar findings have been reported after thiopentone administration in buffaloes and crossbred calves[5,56]. In group H_1, however, the CVP showed a decline after the start of the maintenance period but it remained significantly higher than the base value. Continued maintenance of CVP at higher levels in both groups might possibly have been due to the depressive influence of medetomidine and butorphanol on the heart that gradually subsided with the elimination of the drugs[20,22]. Compensatory mechanisms might have been affected in the present study, as the CVP did not return completely to the baseline at the end of the observation. In group H_2, the CVP increased significantly after premedication but the increase was less significant than in group H_1 and this trend was recorded for the entire observation period. A lesser rise in CVP in group H_2 might be attributed to increased HR and decreased systemic vascular resistance.

Decrease in SpO_2 was possibly due to a certain degree of respiratory depression in both groups. Low SpO_2 values with medetomidine and ketamine anaesthesia have been reported in rabbits[15,40]. Slightly higher values of SpO_2 recorded during the maintenance period in the present study might be due to the administration of 100 % oxygen with halothane.

In the present study, no abnormality in the ECG except for slight variations in the amplitude of P wave, T wave and QRS complex was recorded under halothane anaesthesia in buffaloes as has also been reported in other studies[6]. Similar findings have also been reported after medetomidine administration in goats[8,19]. Ventricular premature depolarisation has been reported in dogs and cats under halothane anaesthesia[18]. The elevation of ST segment, T wave changes, wandering pacemakers and ectopic pacing in sheep during thiopentone and halothane anaesthesia have been reported[42]. None of the above abnormalities except for some T wave changes like notched or biphasic T waves were observed in the present study during halothane anaesthesia. Similar findings have been reported under thiopentone and halothane anaesthesia in calves[55].

It is concluded that both anaesthetic drug combinations can be used safely in buffaloes for surgery of 2-hour duration However, medetomidine (2.5 g/kg) and butorphanol (0.05 mg/kg) provide better sedation, analgesia and muscle relaxation with transient but slightly more cardiac depression than midazolam (0.25 mg/kg) and butorphanol (0.05 mg/kg) when used as preanaesthetics to thiopental and halothane anaesthesia in buffaloes. Medetomidine and butorphanol combination provides more dose sparing effect on anaesthetics used for induction and maintenance with shorter recovery times than that of the midazolam–butorphanol combination.

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