



Clinicophysiological and haemodynamic effects of fentanyl with dexmedetomidine in halothane and isoflurane anaesthetized buffaloes

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ABSTRACT

The clinical, physiological, haemodynamic and anaesthetic effects of halothane and isoflurane in buffaloes premedicated with dexmedetomidine and fentanyl, were studied. Clinically healthy male buffaloes (6) were used. All the animals received 2 treatments randomly at weekly interval in groups H (halothane) and I (isoflurane). In both groups sedation was accomplished by fentanyl (5 µg/kg body wt) and dexmedetomidine (5 µg/kg body wt) intravenously. Induction of anaesthesia was achieved by 5% thiopental sodium in both groups. Maintenance of anaesthesia was done by halothane in group H and by isoflurane in group I respectively in 100% oxygen through a large animal anaesthesia machine. The different treatments were evaluated on the basis of clinical, physiological, haematological, biochemical and haemodynamic parameters.

It is concluded that dexmedetomidine-fentanyl-thiopental and isoflurane provided better clinical, physiological and haemodynamic stability than dexmedetomidine-fentanyl-thiopental and halothane in buffaloes.

Key words: Buffaloes, Dexmedetomidine, Fentanyl, Halothane, Isoflurane

General anaesthesia in adult buffaloes or cattle involves complexities like regurgitation, bloat, aspiration pneumonia, nerve paralysis etc. To reduce the risk associated with these complications, adult cattle should be fasted 18 to 24 h and deprived of water for 12 to 18h which decreases the likelihood of tympany and regurgitation. Additionally, pulmonary functional residual capacity may be better preserved in fasted anaesthetized animals (Tranquilli and Maze, 1993).

Intravenous anaesthesia in large ruminants, is simple and easy to administer requiring no sophisticated instruments, but is associated with prolonged recovery and recumbency time. On the other hand, inhalant anaesthetics offer comparative safety as the depth of anaesthesia can be easily controlled. Moreover, early recovery from inhalant anaesthesia offers an additional advantage in large ruminants, minimizing the recumbency time and hence the anaesthetic complications. Balanced anaesthesia is induced by a combination of drugs from different pharmacological groups which helps in rapid and smooth induction, adequate hypnosis, proper analgesia for surgical intervention, minimal

suppression of vital organ functions, rapid, uncomplicated and complete recovery (Thurmon *et al.* 1996).

Medetomidine, the most potent alpha-2 agonists, used in small animals to induce sedation, analgesia and muscle relaxation, is more lipophilic, selective, potent and efficacious, and eliminates faster (Schienin and MacDonald, 1989). Sedative and analgesic effects of medetomidine were studied in sheep (Kastner *et al.* 2001), goats (Pawde *et al.* 1996), calves (Raekallio *et al.* 1997), dairy cows (Ranheim *et al.* 1999) and buffaloes (Kinjavdekar *et al.* 2003). Dexmedetomidine is used as a sedative and as a premedicant in dogs, cats and horses (Ansah *et al.* 1998, Kuusela *et al.* 2001, Bettschart-Wolfens-berger *et al.* 2005). It is as safe and effective as medetomidine prior to propofol-isoflurane anaesthesia (Kuusela *et al.* 2001) and propofol-halothane anaesthesia in dogs (Hayashi *et al.* 1991).

In large ruminants, general anaesthesia can be induced by either injectable or inhalation techniques. Thiopental sodium is the most widely used intravenous induction agent in ruminants and is used in cattle (Rugh *et al.* 1985) and buffaloes (Malik *et al.* 2011). Being an ultrashort acting agent, its repeated doses are required to maintain surgical anaesthesia, which produces a cumulative effect (Thurmon *et al.* 1996) and makes this drug unsuitable for maintenance of anaesthesia, especially in longer duration procedures. Anaesthesia in ruminants can be maintained with injectable or inhalant agents. However, injectable anaesthetics are

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associated with prolonged recovery, and additional doses are required for maintenance in prolonged procedures, increasing the recovery and recumbency time. Therefore, inhalant agents like halothane, isoflurane, or sevoflurane, offer a better choice for maintenance of general anaesthesia in large ruminants, after induction with injectable drugs.

There are few reports on the use of inhalant anaesthesia in cattle and buffaloes. In large ruminants halothane anaesthesia was investigated in camel (Singh *et al.* 1994) and cattle (Riazuddin *et al.* 2004). In a recent study, in buffaloes, halothane was found to be a better maintenance agent in terms of clinicophysiological and haematobiochemical stability as compared to propofol or ketamine (Malik *et al.* 2011). Inhalation anaesthesia with halothane and isoflurane is commonly used in goat (Hikasa *et al.* 1998) and bulls (Greene *et al.* 1998). Halothane has a greater sensitizing effect than isoflurane or sevoflurane (Steffey *et al.* 1977). Nevertheless, inhalant anaesthesia is becoming increasingly popular now-a-days, especially in veterinary teaching hospitals and institutions, due to compelling needs. Surgical conditions requiring general anaesthesia are frequently encountered in buffaloes. Keeping in mind, the importance of this species and scarcity of literature regarding inhalant anaesthesia in buffaloes, the present study was undertaken to compare the clinical, physiological, haemodynamic and anaesthetic effects of halothane and isoflurane in buffaloes premedicated with dexmedetomidine and fentanyl.

MATERIALS AND METHODS

Clinically healthy male buffaloes (6) of 1 and 3 years of age were used. All the animals were dewormed with fenbendazole (5 mg/kg) orally. The animals were stall-fed and had free access to feed and water. Uniform managemental conditions were maintained for all the animals throughout the period of the study. The animals were kept off feed for 48 h and water was withheld for 24 h prior to the start of the experiment. All the animals received 2 treatments randomly at weekly interval in groups H (halothane) and I (isoflurane). In both groups sedation was accomplished by fentanyl (5 µg/kg body wt) and dexmedetomidine (5 µg/kg body wt) intravenously. The doses of fentanyl and dexmedetomidine were standardized and selected after conducting pilot trials in a few buffaloes before the start of the study. Induction of anaesthesia was achieved by 5% thiopental sodium in both groups. Maintenance of anaesthesia was done by halothane in group H and by isoflurane in group I, respectively, in 100% oxygen through a large animal anaesthesia machine.

The animals were restrained in right lateral recumbency and after 15 min of premedication, anaesthesia was induced by thiopental sodium intravenously. The animals were orotracheally intubated by the palpation technique through a mouth gag. The animals were connected to the large animal anaesthesia machine and halothane in group H and isoflurane

in group I in 100% oxygen (5 L/min) was used via an open breathing circuit to maintain anaesthesia for 60 min. The different treatments were evaluated on the basis of the following parameters.

Clinical observations: The following parameters were evaluated in both groups during the period of anaesthesia at 0, 5, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min.

Sedation was evaluated before induction of anaesthesia and after discontinuation of anaesthesia by observing behavioural changes and was graded on a 0 to 3 scoring scale as follows: 0 (no sedation): Alert, eyes open; 1 (mild sedation): Drooping of eye lids, mild sensory and motor deficit; 2 (Moderate sedation): Drooping of eye lids, moderate sensory and motor deficit; 3 (deep sedation): Drooping of eye lids, severe sensory and motor deficit.

Analgesia was evaluated by observing the animals' response at every 15 min interval after a deep prick on the rib of the periosteum and at the coronary band with a 22G needle. The analgesia was graded on a 1 to 4 scoring scale as follows: 1 (no analgesia): Strong reaction to pin pricks; 2 (mild analgesia): Weak response to pin pricks; 3 (moderate analgesia): Occasional response to pin pricks; 4 (excellent analgesia): No response to pin pricks.

Muscle relaxation was observed in the muscles of abdomen, legs and jaws. The ease with which the jaws of recumbent animals could be opened and their hind limbs could be bent without resistance, as well as the flaccid abdomen could be pressed was recorded. The muscle relaxation was graded on a 1 to 4 scoring scale as follows: 1 (no relaxation): Tightly closed jaws and stiff limbs, no flaccidity of abdomen; 2 (mild relaxation): Moderate resistance to opening of jaws and bending of limbs, no flaccidity of abdomen; 3 (moderate relaxation): Mild resistance to opening of jaws and bending of limbs, no flaccidity of abdomen; 4 (excellent relaxation): No resistance to opening of jaws and bending of limbs and flaccid abdomen.

Reflexes like degree of abolition of palpebral and corneal reflexes were recorded and graded on a (-) to (+++++) scoring scale as follows: (-): Completely abolished; (+): Mild response; (++) Moderate response; (+++) Good response; (++++): Excellent response.

Extent of salivation was recorded and graded on a (-) to (+++++) scoring scale as follows: (-): Absent; (+): Mild; (++) Moderate; (+++) Extensive; (++++): Profuse.

Recovery time (RET) was the time from discontinuation of inhalant agent and the first spontaneous movement of any body part.

Sternal recumbency time (SRT) was the time from discontinuation of inhalant drug administration to the spontaneous regaining of sternal recumbency.

Standing time (ST) was the time from discontinuation of inhalant drug administration to spontaneous regaining of standing position.

Required doses and concentration of different drugs: The

required doses of thiopental sodium (mg/kg) for induction and the concentration (%) of halothane and isoflurane for maintenance of anaesthesia were calculated after the completion of each trial.

Physiological observations: Heart rate (HR) (beats/min), respiratory rate (RR) (breaths/min) and rectal temperature (RT) (°C) Physiological observations were recorded before administration of any drug and then at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min after administration of sedative agents.

Hematological observations: The blood samples (1 ml) were collected in clean, dry syringes containing heparin at time 0 (base line) and at 15 min, 30 min, 1 h, 1 h, 2 h, 12 h and 24 h after administration of different drugs and were subjected to the estimation of haemoglobin (Hb) (g/L) as per Schalm (1988) using Hellige Sahli's haemoglobinometer, packed cell volume (PCV) (L/L) by microhaematocrit method as per Schalm (1988), total leukocyte count (TLC) ($\times 10^9/L$) by haemocytometer with improved Neubauer's counting chamber, differential leukocyte count (DLC) after staining the smear with Leishman's stain and examined under oil immersion for cellular differentiation in percentage.

Biochemical observations: The blood samples (5 ml) were collected in sterile syringes containing heparin (1 ml in sodium fluoride for glucose) at time 0 (base line) and at 15 min, 30 min, 1 h, 1 h, 2 h, 12 h and 24 h after the administration of different drugs. The plasma samples were subjected to estimation of urea nitrogen (mmol/L) by DAM method (Netelson 1961), glucose (mmol/L) by O' toluidine method (Cooper and MacDaniel 1970), creatinine ($\mu\text{mol/L}$) by alkaline picrate method (Levinson and McFate 1969), cortisol (nmol/L) and insulin (nmol/L) by radio immuno-assay (RIA) using cortisol kit and lactate dehydrogenase (LDH) (U/L) by a standard method.

Haemodynamic observations: The cuff of the noninvasive blood pressure monitor was applied around the metatarsal region for monitoring systolic, diastolic and mean arterial blood pressure. The animals were stabilized for half an hour. Mean arterial pressure (MAP), diastolic blood pressure (DBP), systolic blood pressure (SBP) (mm Hg) were recorded at time 0 (base line) and at 5, 15, 30, 45 and 60 min after induction of anaesthesia. Central venous pressure (CVP) was recorded by passing a polyethylene catheter through 12 gauge hypodermic needle anchored in the jugular vein and was advanced up to right atrium. The catheter was connected to a saline manometer containing heparinized saline through a 3-way stop cock. The position of the catheter was confirmed by observing the pressure changes in the saline manometer due to respiration. A syringe containing heparinized saline was connected to the third end of the stop cock to flush the system. The zero of the column was adjusted at the level of sternal manubrium. Subcutaneous needle electrodes were placed at the posterior border of scapula and at the fifth costochondral junction for base apex lead

electrocardiography (ECG) at 1 mV and 25 mm/sec paper speed at the same intervals as in blood pressure. The electrocardiogram was analyzed for the duration and amplitude of P wave, QRS complex, T wave, P-R and Q-T intervals and rhythm. Haemoglobin oxygen saturation (SpO_2) (%) was recorded by applying the sensor of the pulse oxymeter on the anal fold.

Statistical analysis: Analysis of variance (ANOVA) and Duncan's multiple range test (DMRT) were used to compare the means at different time intervals between groups. Paired 't' test was used to compare the mean values at different intervals with their respective base values in each group (Snedecor and Cochran 1980). For non-parametric observations, Kruskal-Wallis one-way test (Siegel 1988) was used to compare the means between groups at corresponding intervals.

RESULTS AND DISCUSSION

Clinical observations

Median sedation: Median sedation scores Sedation in the animals of groups H and I were 3.00 ± 0.12 and 3.00 ± 0.00 respectively. Comparison between 2 groups did not reveal any significant difference (Fig.1). Good sedation was recorded in both groups. Dexmedetomidine is highly specific to alpha-2 adrenergic receptors than medetomidine (Scheinin *et al.* 1989). Malik *et al.* (2011) reported that medetomidine and butorphanol produced good sedation in buffaloes. The sedative action of dexmedetomidine is mainly mediated through activation of central alpha-2 adrenergic receptors. Stimulation of these presynaptically located receptors is believed to inhibit the release of catecholamines. In this study an attempt was made to decrease the side effects by using a small dose of drugs acting at different CNS receptor population which seems to produce synergistic responses with lessened side effects (Thurmon *et al.* 1996). The doses of dexmedetomidine ($5 \mu\text{g/kg}$) and fentanyl ($5 \mu\text{g/kg}$) were selected on the basis of pilot trials conducted before the start of the experiment. Deep sedation and analgesia were recorded in buffalo calves (Pawde *et al.* 1996, Kinjavdekar *et al.* 2003)

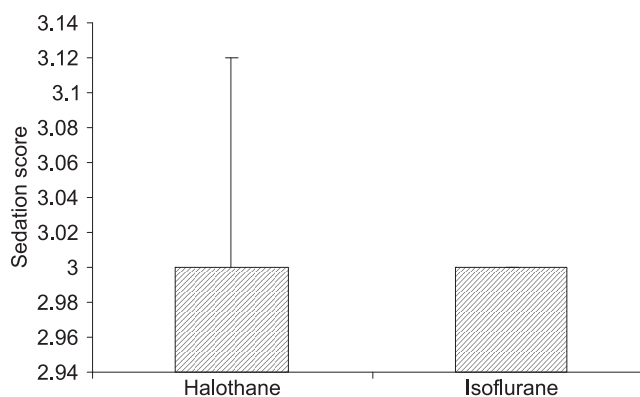


Fig.1. Median $\pm$ SD of sedation in the animals of groups H and I.

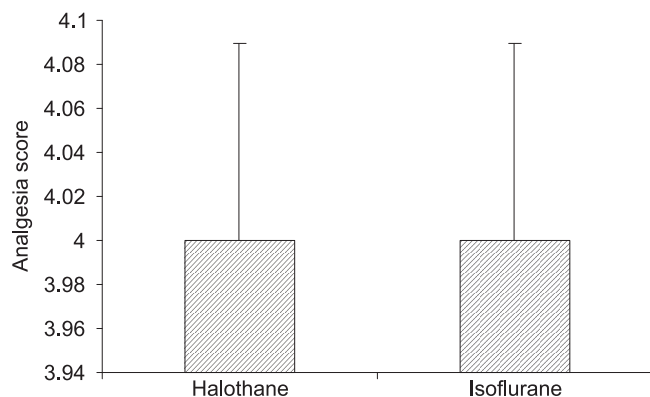


Fig. 2. Median $\pm$ SD of analgesia in the animals of groups H and I.

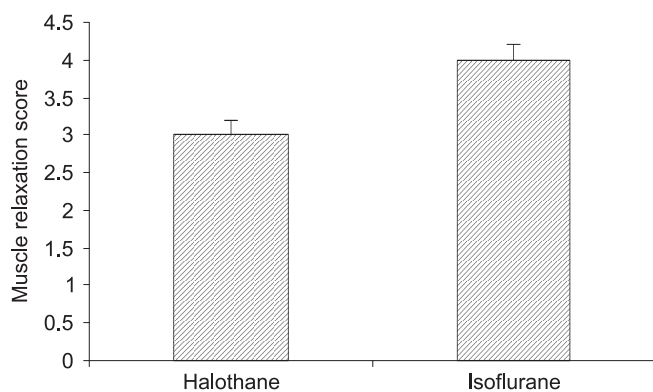


Fig. 3. Median $\pm$ SD of muscle relaxation in the animals of groups H and I.

after medetomidine administration of higher dose (20 μ g/kg). Decreased doses of medetomidine ranging from 1 to 10 μ g/kg with butorphanol have been reported to enhance sedation and analgesia (Pypendop and Verstegen 1998).

Median analgesia scores in analgesia the animals of groups H and I were 4.00 ± 0.09 and 4.00 ± 0.09 respectively. In both groups no pin-prick response was recorded till the end. Good to excellent analgesia was recorded in both groups (Fig.2). It is well documented that alpha-2 agonists produce analgesia by stimulating receptors at various sites in the pain pathway within the brain and spinal cord (Stenberg, 1989). Dexmedetomidine and fentanyl produced excellent analgesia for longer duration, possibly owing to synergistic action on the CNS. Similar type of synergism between alpha-2 agonists and opioid analgesics has been reported in goats (Carroll *et al.* 1998). In ruminants, opioid analgesics have not been used extensively as they might cause excitement, so they were generally combined with other drugs. In the present study dexmedetomidine was combined with fentanyl which achieved adequate analgesia and reduced excitement. Thiopental and halothane have no or minimal intrinsic analgesic property (Thurmon *et al.* 1996) however, excellent analgesia in both groups might be due to the long-lasting

analgesic effects of alpha-2 agonists, fentanyl and CNS depressant effects of the halothane and isoflurane.

Muscle relaxation scores in the animals of groups H and I muscle relaxation were 3.00 ± 0.20 and 4.00 ± 0.20 respectively. In both groups adequate muscle relaxation was recorded (Fig.3). The degree of muscle relaxation immediately after dexmedetomidine and fentanyl was excellent and that might be attributable to the combined effect of both drugs. Alpha-2 agonists have been reported to produce profound muscle relaxation alone and in combination with opioid agonist-antagonist (Ko *et al.* 1996). Malik *et al.* (2011) and Ahmad (2009) reported that good muscle relaxation was recorded in halothane maintained buffaloes which might be due to the long lasting muscle relaxation effect of medetomidine. Although halothane and isoflurane are devoid of any muscle relaxation property, however, thiopental and dexmedetomidine produced good muscle relaxation in both groups.

Palpebral reflex in both groups was completely abolished after premedication till the end.

Corneal reflex in halothane group recorded good response at 5 min after which mild response was recorded however, in some animals good response was recorded at 60 and 75 min. In group I mild response was recorded up to 10 min after premedication, thereafter it completely abolished. Palpebral and corneal reflexes were depressed after premedication till the end in both groups. Moderate to complete abolition of these reflexes have been reported after medetomidine and pentazocine in goats (Amarpal *et al.* 1998). Malik *et al.* (2011) and Ahmad (2009) reported that palpebral and corneal reflexes were depressed after medetomidine and butorphanol and abolished by halothane in buffaloes.

In group H mild salivation was recorded after premedication up to 10 min after which moderate salivation up to 60 min and then at 75 min extensive salivation was recorded. In group I extensive salivation was recorded except at 10 min after premedication where moderate salivation was recorded. The extent of salivation during sedation was higher in both groups. Alpha-2 agonists have been reported to exert their effects on salivary gland through alpha-1 adrenergic receptors and thus increasing the secretion (Rusoaho, 1986). In the present study, it was recorded that regurgitation could be very well prevented by fasting and positioning the caudal cervical and anterior thoracic region higher than other parts of the body (Malik *et al.* 2011).

Mean doses of 5% thiopental sodium required for induction of anaesthesia in groups H and I were 2.58 ± 0.80 mg/kg and 4.33 ± 0.66 mg/kg respectively. Mean dose of halothane (mL) for maintenance was 26.16 ± 2.61 mL.

Mean dose of isoflurane (mL) for maintenance was 45.50 ± 5.45 mL. Halothane group (2.58 ± 0.80 mg/kg) required less amount of thiopental sodium for induction than isoflurane group (4.83 ± 0.79 mg/kg). However, reduction in

the induction dose of thiopental was recorded in both groups (normal dose of thiopental in large ruminants 8–10 mg/kg) (Fig.4). A synergism between dexmedetomidine, butorphanol and thiopental might have played an important role in reducing the induction dose of thiopental in buffaloes (Malik *et al.* 2011, Ahmad 2009). A reduction in the dose of these agents might have led to improved cardiovascular stability. The drug sparing action may result from both intrinsic potency of medetomidine and a reduction in the rate of hepatic metabolism of other drugs (Riazuddin *et al.* 2004). The adequate level of anaesthesia could be maintained by administration of 2.5 to 4% halothane and isoflurane in both groups. The vaporizer setting in both groups was slightly lower, which suggested a greater minimum alveolar concentration (MAC) sparing effect of dexmedetomidine. In another study, intramuscular medetomidine (5 and 10 µg/kg) reduced the isoflurane requirement of maintenance of anaesthesia in sheep (Kastner *et al.* 2006). In the present study medetomidine might have played a role in the reduction of halothane requirement (Malik *et al.* 2011, Ahmad 2009).

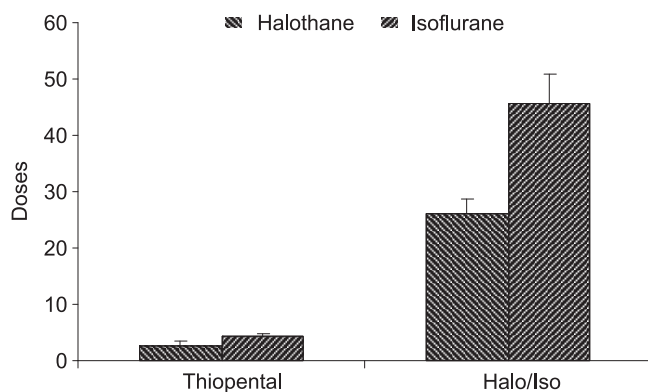


Fig. 4. Mean±SE of doses of thiopental sodium (mg/kg), halothane and isoflurane (mL) in the animals of groups H and I.

The median values of recovery time in groups H and I were 10.50 ± 2.84 min and 3.00 ± 1.09 min respectively. The median values of sternal recumbency time in groups H and I were 24.33 ± 4.82 min and 13.83 ± 3.04 min, respectively.

The median values of standing time in groups H and I were 28.00 ± 5.57 min and 18.00 ± 3.28 min, respectively (Fig.5). The halothane group took more time to recover in comparison to isoflurane. The high volatility of isoflurane, coupled with low blood solubility, provided relatively rapid induction and recovery and easy control of the depth of anaesthesia than halothane. Lower recovery time recorded in isoflurane group might be due to a lower blood gas partition coefficient and faster changes in the alveolar concentration better cardiovascular function, less stress response and lesser alteration in the hepatic blood flow and quicker elimination (Riazuddin *et al.* 2004). Following halothane maintenance anaesthesia, recovery was slower, which could be attributed to increased stress leading to catabolic pathways and

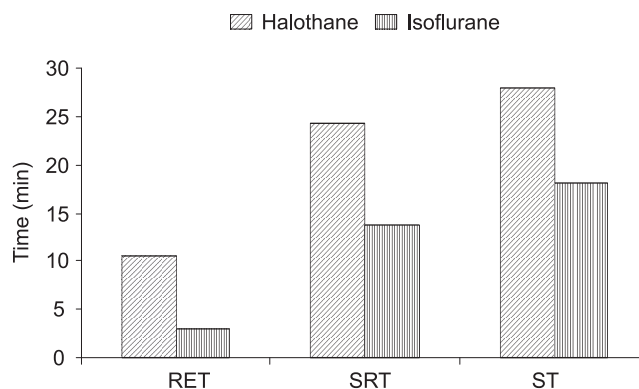


Fig. 5. Mean±SE of recovery time (RET), sternal recumbency time (SRT) and standing time (ST) (min) in the animals of groups H and I

depletion of energy sources (Wagner *et al.* 1991). The halothane group took longer time to resume sternal recumbency than isoflurane which might be due to low blood solubility of isoflurane that allowed early sternal recumbency from anaesthesia as compared to halothane. The time taken for standing by halothane group was longer than isoflurane. Early recovery in the isoflurane group might be due low blood gas partition coefficient of isoflurane than halothane. Rose *et al.* (1988) reported that isoflurane may be indicated to promote rapid recovery than halothane.

Physiological observations

In group H a significant ($P < 0.05$) decrease in heart rate was recorded from 5 to 90 min after premedication with a highly significant ($P < 0.01$) decrease at 45 min. In group I a highly significant ($P < 0.01$) decrease in HR at 5 min was recorded. The HR from 10 min of the premedication decreased significantly ($P < 0.05$) and remained so till the end (Fig.6). Dexmedetomidine and fentanyl resulted in significant decrease in HR in both groups. These changes were related to the CNS sedative and the autonomic and peripheral vascular effects of dexmedetomidine. Inhibition of sympathetic tone due to reduction in norepinephrine release from the CNS, vagal activity in response to alpha-2 agonists induced vasoconstriction and direct increase in the release of acetylcholine from parasympathetic nerves in the heart have been reported as the possible mechanisms by which alpha-2 agonists induced bradycardia (MacDonald and Virtanen 1992). Similar effects have been reported in earlier studies after dexmedetomidine and medetomidine in different species (Kuusela 2000). The biphasic response of blood pressure produced by alpha-2 agonists was not recorded in the present study probably due to the synergistic effect of dexmedetomidine and fentanyl causing hypotension predominantly. Heart rate decreased in both groups during the maintenance period. The major cardiovascular changes during halothane anaesthesia are hypotension which has also been reported in buffaloes (Gahlawat *et al.* 1986).

In group H after induction of anaesthesia RR increased significantly ($P<0.05$) at 60 and 75 min. However, the RR decreased significantly ($P<0.05$) at 120 min. In group I, after induction of anaesthesia the RR increased significantly ($P<0.05$) (Fig.7). Decrease in respiration was recorded in both groups during the sedation period. Respiratory depression associated with alpha-2 agonists might be secondary to the CNS depression produced by alpha-2 adrenoceptors stimulation or due to direct depression of the respiratory centers by preanaesthetics (Kumar and Thurman 1979). A decrease in RR has also been reported after medetomidine in sheep (Mohammad *et al.* 1993, Muge *et al.* 1994) and, medetomidine and butorphanol in buffaloes (Malik *et al.* 2011, Ahmad 2009). The respiratory depressant effect of opioids was compounded by the co-administration of alpha-2 agonists. It is well known that halothane and isoflurane reduce the respiration rate in bulls (Greene *et al.* 1998), although the RR was higher for isoflurane than for halothane in sheep (Gencelep *et al.* 2004). In the present study also the respiratory depression was more in halothane group as compared to isoflurane group.

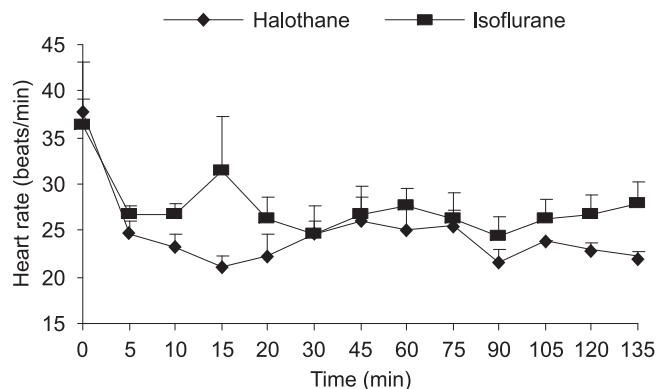


Fig. 6. Mean±SE of heart rate (beats/min) in the animals of groups H and I

In group H the RT decreased significantly ($P<0.05$) from 20 to 135 min and this decrease was highly significant ($P<0.01$) from 60 to 135 min. In group I the RT decreased significantly ($P<0.05$) from 20 to 90 min however, this decrease was highly significant ($P<0.01$) at 60 min. Significant decrease in rectal temperature was recorded in both groups during the post anaesthetic period. This might be attributed to a decrease in the skeletal muscle tone, reduced metabolic rates, muscle relaxation along with depression of thermoregulatory centers (Ponder and Clarke 1980, Matsukawa *et al.* 1995). Significant decrease in rectal temperature was recorded during halothane anaesthesia in buffaloes (Malik *et al.* 2011, Ahmad 2009) and after medetomidine administration in goats (Mohammad *et al.* 1991). Hypothermia tends to be the most common response, particularly when opioids are used in the presence of other CNS depressants (Branson *et al.* 2001). These agents depress

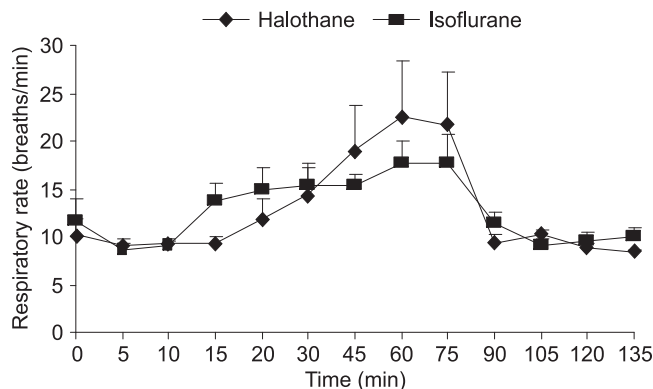


Fig. 7. Mean±SE of respiratory rate (breaths/min) in the animals of groups H and I

hypothalamic non-adrenergic alpha-2 adrenergic receptors to cause hypothermia (McDonald *et al.* 1988). In the present study, a highly significant and early hypothermia was recorded in both groups during the maintenance period however, halothane caused more respiratory depression than isoflurane.

Haematological observations

In group H the Hb decreased significantly ($P<0.05$) up to 120 min however, a highly significant ($P<0.01$) decrease in Hb was observed from 30 to 90 min. Group I revealed a significant ($P<0.05$) decrease from 30 to 90 min after premedication. In group H the PCV decreased significantly ($P<0.01$) from 60 to 120 min. In group I the PCV significantly ($P<0.05$) decreased from 30 to 90 min. In group H a significant ($P<0.05$) decrease in TLC was recorded from 30 to 120 min but the decrease was highly significant ($P<0.01$) at 60 min. Group I revealed a significant ($P<0.05$) decrease in lymphocyte was recorded in group H from 15 to 720 min. Group I revealed a significant ($P<0.01$) decrease in lymphocyte count throughout the observation period. A highly significant ($P<0.01$) increase was recorded in group H in the neutrophil count up to 60 min. A significant ($P<0.05$) increase was recorded in group I up to 60 min (Table). Haemoglobin, PCV and TLC decreased significantly in both groups during the post anaesthetic period. Pooling of circulatory blood cells in the spleen or other reservoirs secondary to sympathetic activity and shifting of fluid from extravascular compartment to intravascular compartment to maintain normal cardiac output in the animals may explain the decrease in Hb, PCV and TLC (Wagner *et al.* 1991). Neutrophilia and lymphocytopenia were recorded in both groups, which might be due to the stress caused by the preanaesthetic and anaesthetic drugs and subsequent stimulation of adrenal glands. Similar findings have been reported after medetomidine-ketamine in goats (Hugar *et al.* 1998; Kinjavdekar *et al.* 2000) and after medetomidine,

butorphanol, thiopental and halothane anaesthesia in buffaloes (Malik *et al.* 2011).

Biochemical observations

Glucose: A significantly ($P<0.05$) higher value of glucose was recorded in group H. Group I revealed a significant ($P<0.05$) increase in glucose at 720 min (Table). An increase in the plasma glucose recorded in both groups was probably due to increased muscular activity and sympathetic stimulation caused during restraining of the animals resulting into increased secretion of adrenocortical hormone. Hyperglycemia has been attributed to an alpha-2 adrenergic inhibition of insulin released from beta-pancreatic cells and to an increased glucose production in the liver (Gasthuys *et al.* 1987). Increase in plasma glucose after medetomidine

has been reported in goats (Mohammad *et al.* 1991, Hugar *et al.* 1998, Kinjavdekar *et al.* 2000) and in buffaloes during butorphanol, medetomidine and halothane anaesthesia (Malik *et al.* 2011, Ahmad 2009). Muscle relaxation during anaesthesia may lower the utilization of glucose at tissue level leading to hyperglycaemia. In group H creatinine decreased non-significantly ($P>0.05$) and decreased significantly ($P<0.01$) in group I. Group H revealed a significant ($P<0.05$) increase in urea nitrogen at 120 and 1440 min. A significant ($P<0.05$) increase was recorded in group I at 30, 90 and 1440 min (Table 2). Creatinine decreased in both groups with more decrease in isoflurane group and this might be due to the well maintained renal blood flow during isoflurane anaesthesia. The increase in urea nitrogen might be attributed to the temporary inhibitory effects of these drugs

Table 1. Mean $\pm$ SE of haematological and biochemical parameters in the animals of groups H (halothane) and I (isoflurane)

Parameters	Groups	Time (min)							
		0	15	30	60	90	120	720	1440
Haemoglobin (g/L)	Halothane	100.70 ± 0.21	92.33* ± 0.35	87.33** ± 0.24	86.33**a ± 0.23	89.50** ± 0.23	97.66* ± 0.09	104.00a ± 0.21	109.00a ± 0.40
	Isoflurane	104.83 ± 0.34	98.00 ± 0.21	93.00* ± 0.19	90.25*b ± 0.21	94.66* ± 0.14	92.00 ± 0.36	106.33b ± 0.26	105.66b ± 0.18
PCV (L/L)	Halothane	0.31a ± 0.060	0.32 ± 0.451	0.28a ± 0.170	0.26**a ± 0.062	0.26**a ± 0.068	0.29* ± 0.026	0.30a ± 0.068	0.31a ± 0.01
	Isoflurane	0.30b ± 0.088	0.29 ± 0.046	0.27* ± 0.055	0.27**b ± 0.048	0.28*b ± 0.045	0.28 ± 0.097	0.31b ± 0.063	0.32b ± 0.071
TLC ($\times 10^9$ /L)	Halothane	10.45 ± 1.14	9.11*a ± 1.14	8.51* ± 1.06	8.08** ± 0.97	9.10*a ± 0.84	9.30 ± 0.65	10.35 ± 0.94	10.50 ± 0.90
	Isoflurane	10.78 ± 0.85	9.88*b ± 0.71	9.58* ± 0.72	9.81b ± 0.88	9.73b ± 0.70	10.46 ± 0.65	10.83 ± 0.43	10.78 ± 0.51
Glucose (mmol/L)	Halothane	5.13a ± 0.72	6.96 ± 0.66	7.80* ± 0.76	6.74* ± 0.49	6.04 ± 0.55	6.44*a ± 0.81	7.61* ± 0.25	7.54*a ± 0.20
	Isoflurane	5.47b ± 0.66	6.52 ± 0.31	6.61 ± 0.45	6.09 ± 0.46	5.82 ± 0.58	6.54b ± 0.43	6.90* ± 0.47	6.43b ± 0.22
Creatinine (μ mol/L)	Halothane	142.89a ± 2.36	119.36a ± 3.90	123.52a ± 1.78	118.90a ± 2.75	128.37a ± 3.17	133.21a ± 5.73	132.11a ± 2.79	135.48a ± 3.38
	Isoflurane	161.84b ± 2.50	153.20**b ± 1.30	145.72**b ± 2.53	118.90**b ± 2.10	144.52**b ± 2.55	146.32**b ± 2.99	154.16*b ± 2.74	160.62b ± 2.66
Urea (mmol/L)	Halothane	9.69 ± 0.44	8.95 ± 0.55	9.81 ± 0.30	8.84 ± 0.35	9.74 ± 0.44	11.07* ± 0.35	9.66 ± 0.85	12.41a ± 0.36
	Isoflurane	9.37 ± 0.44	10.07 ± 0.47	11.29** ± 0.63	10.65 ± 0.34	11.28** ± 0.62	12.08* ± 0.66	11.18 ± 0.58	12.27*b ± 0.58
Insulin (μ U/mL)	Halothane	11.13a ± 1.84	5.85* ± 0.80	4.78* ± 0.77	4.29* ± 0.71	4.67* ± 1.12	5.07* ± 1.37	14.43 ± 2.47	16.19a ± 3.73
	Isoflurane	8.15b ± 1.25	4.45* ± 0.27	3.85* ± 0.21	4.65 ± 0.26	4.01* ± 0.14	4.43* ± 0.63	12.47 ± 4.24	13.10b ± 4.84
Cortisol (nmol/L)	Halothane	56.39 ± 18.49	54.16 ± 13.04	30.06 ± 7.40	28.15 ± 8.60	21.11a ± 9.70	32.00 ± 6.40	31.42 ± 8.88	27.24a ± 3.81
	Isoflurane	65.74 ± 9.21	34.34** ± 9.86	34.32* ± 18.20	40.77* ± 14.46	41.42*b ± 5.96	34.66* ± 7.10	24.56* ± 7.20	42.65*b ± 9.36
LDH (U/L)	Halothane	538.78a ± 30.09	492.53a ± 41.19	472.37a ± 43.68	471.98*a ± 58.16	507.75a ± 62.39	524.52 ± 72.16	517.03 ± 61.09	534.05a ± 47.72
	Isoflurane	584.52b ± 56.19	445.71b ± 43.16	501.16*b ± 39.38	453.43b ± 61.14	533.30b ± 35.17	463.66 ± 71.19	555.66 ± 39.49	458.22*b ± 67.14

on the renal blood flow, which in turn might have caused a rise in plasma urea nitrogen (Kinjavdekar *et al.* 2000). Increased hepatic urea production from amino acid degradation could also account for the observed increase in plasma urea nitrogen values (Eichner *et al.* 1979). However, it is difficult to suggest that it might be due to renal damage because all the values were within the normal physiological limits. In groups H and I a significant ($P<0.05$) decrease in insulin was recorded up to 120 min and then an increase was recorded at 720 and 1,440 min. Group H did not reveal any significant change in cortisol. A significant ($P<0.05$) decrease was recorded in group I in the cortisol (Table 1). Insulin decreased significantly after premedication and during anaesthesia in both groups. Alpha-2 agonists have been reported to increase serum glucose by suppressing insulin release, stimulating glucagon release, or both in alpha and beta cells of pancreas respectively (Angel and Langer 1988). A significant decrease in cortisol was recorded after premedication in isoflurane group. Alpha-2 adrenergic agonists have been known to influence the pituitary response and may decrease ACTH output (Masala *et al.* 1985). An increase in plasma cortisol was recorded in buffaloes after butorphanol and medetomidine (Malik *et al.* 2011, Ahmad 2009).

In group H the LDH decreased significantly ($P<0.05$) at 60 min. Group I revealed a significant ($P<0.05$) decrease at 1440 min. Lactate dehydrogenase recorded a significant decrease in LDH in both groups (Table 1). This is in agreement with the findings of Kumar *et al.* (1998) where LDH activity decreased significantly after acepromazine in yaks. It was observed that halothane and isoflurane may act directly upon skeletal muscles, perhaps influencing intracellular calcium homeostasis to alter membrane permeability and increase enzyme efflux reflecting a degree of post-anaesthetic muscle damage (Mitchel *et al.* 1999).

Haemodynamic observations

In group H the fall in SBP was highly significant ($P<0.01$) after premedication however, the fall was significant ($P<0.05$) from 30 to 75 min. A significant ($P<0.05$) decrease was recorded at 5 and 10 min and then from 30 to 75 min in group I. In group H a significant ($P<0.01$) decrease was recorded in the DBP throughout the observation period. In group I the DBP decreased significantly ($P<0.05$). A highly significant ($P<0.01$) decrease in MAP was recorded in group H. A significant ($P<0.05$) decrease in MAP was recorded in group I (Fig.8). Blood pressure (SBP, DBP and MAP) decreased significantly after premedication in both groups. Hypotension is attributed to bradycardia and vasodilation, stimulation of central alpha-2 adrenoceptors, peripheral sympatholytic action and enhanced parasympathetic outflow (Tibirica *et al.* 1991). After premedication with medetomidine-butorphanol and induction with thiopental, a significant decrease in SBP, DBP and MAP was recorded in

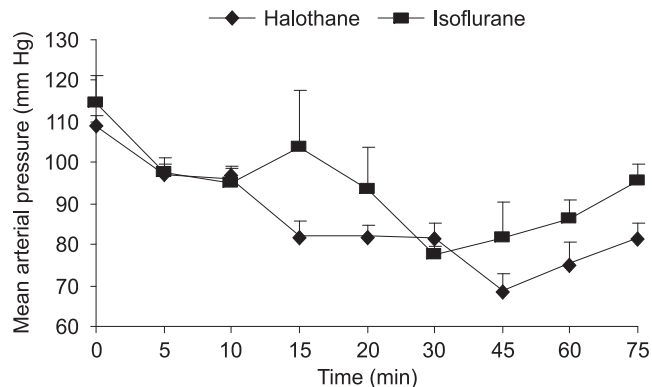


Fig. 8. Mean±SE of mean arterial pressure (mm Hg) in the animals of groups H and I

buffaloes (Malik *et al.* 2011, Ahmad 2009). Blood pressure remained significantly low in both groups during the maintenance period. Isoflurane, sevoflurane and desflurane cause a decrease in arterial blood pressure and systemic vascular resistance and at higher doses, myocardial depression and a decrease in cardiac output (Steffey *et al.* 2005). In group H the central venous pressure increased significantly ($P<0.05$) however, the increase in CVP was highly significant ($P<0.01$) up to 30 min. A significant ($P<0.05$) increase in CVP was recorded in group I. However, the increase in CVP value was highly significant ($P<0.01$) from 5 to 20 min (Fig.9). Dexmedetomidine and fentanyl produced a highly significant increase in CVP. The significant and prolonged increase in CVP was a likely reflection of dexmedetomidine induced bradycardia, possibly vasoconstriction and the synergistic action and pooling of blood in the venous circulation as a result of low heart rate i.e. central shift of blood to the venous compartment and decrease in myocardial contractility and an increase in the after load (Venugopalan *et al.* 1994). Continued maintenance of CVP at higher level in both groups might possibly be attributed to depressive effect of dexmedetomidine and fentanyl on the heart that gradually subsided with the elimination of the drugs (Kallio *et al.* 1990; Kinjavdekar *et*

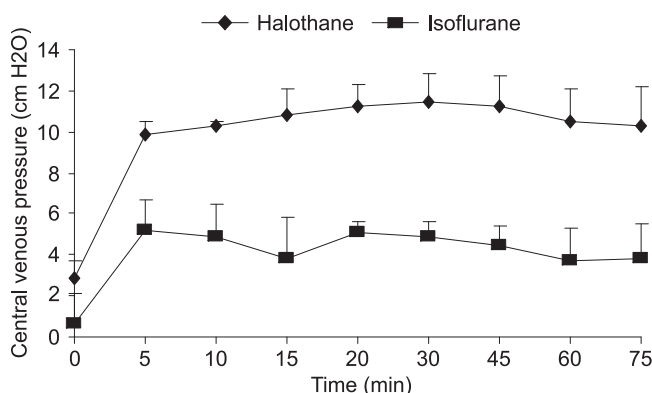


Fig. 9. Mean±SE of central venous pressure (cm H₂O) in the animals of groups H and I

al. 2005). Compensatory mechanisms might have been affected in the present study by the drugs as the CVP did not return completely to the baseline at the end. An increase in CVP values during halothane anaesthesia (Ahmad 2009) and medetomidine and butorphanol (Malik *et al.* 2011) has been reported. A slight decrease in CVP was observed immediately after thiopentone administration in the present study. In group H the SpO₂ decreased significantly ($P < 0.01$) up to 10 min. Group I recorded the same pattern of decrease where the SpO₂ decreased significantly ($P < 0.01$) up to 10 min (Fig. 10). Decrease in SpO₂ after premedication was observed in both groups possibly due to certain degree of respiratory depression. Xylazine in cattle (De Moor and Desmet 1971), goat (Kumar and Thurmon 1979), and medetomidine and butorphanol in buffalo calves (Malik *et al.* 2011, Ahmad 2009) has been reported to decrease SpO₂. It has been reported that detomidine, medetomidine and romifidine also produce severe hypoxaemia when administered IV at equipotent sedative doses in conscious sheep (Celly *et al.* 1997). Higher SpO₂ recorded during halothane and isoflurane anaesthesia in the present study might be due to the administration of 100% oxygen. A significant ($P < 0.05$) increase was recorded in the duration of T wave in both groups at 15 min. In group H a significant ($P < 0.05$) increase in amplitude of T wave at 5 min and a significant ($P < 0.05$) decrease at 15 min was recorded. Group I did not reveal any significant change. P-R interval. In group H a significant ($P < 0.05$) decrease in P-R interval was recorded at 10 min. Group I revealed no significant change. Group H recorded significant ($P < 0.01$) increase at 10 min Q-T interval. In group I the Q-T interval increased significantly ($P < 0.05$) from 5 to 10 min and from 60 to 75 min. In group H, the S-T segment increased significantly ($P < 0.05$) at 75 min. A significant ($P < 0.05$) increase was recorded in group I at 20 and 45 min. The atrial depolarization area did not show any significant changes in both groups. However, the atrial depolarization area and time remained stable during the maintenance period in both groups. Similar observations have been reported after medetomidine in goats (Hugar *et al.*

1998). No change in the QRS-complex was recorded in this study which indicates that ventricular depolarization time and area remained the same throughout the observation period. No significant difference in ventricular depolarization was recorded after medetomidine and butorphanol in buffaloes (Malik *et al.* 2011, Ahmad 2009). Decrease in conduction velocity in AV-node due to vagal activity after xylazine administration has been reported by Peshin and Kumar (1979) in buffaloes. Increase in the amplitude of T-wave was recorded in halothane group after premedication. The duration of T-wave increased in both groups. The deviation and inconsistency of T-wave might be due to transient changes in acid base balance on account of retention of CO₂ (Peshin and Kumar 1979). The increase in T-wave duration recorded in this study might be due to slow repolarization of ventricles (Tilley 1985). Similar changes were reported after xylazine in buffaloes (Peshin and Kumar 1979) and medetomidine/medetomidine and ketamine in goats (Hugar *et al.* 1998). Electrocardiograms of both groups showed sinus bradycardia probably due to increased vagal activity caused by the vasopressor effect of medetomidine (Knight 1980). PR interval, however, did not show a definite pattern. Increased QT intervals were recorded in both groups. Further, the increase in PR and QT intervals might be due to a decreased HR and corresponding increase in oxygen requirement of the heart after medetomidine administration (Peshin and Kumar 1979).

It is concluded that dexmedetomidine-fentanyl-thiopental and isoflurane provided better clinical, physiological and haemodynamic stability than dexmedetomidine-fentanyl-thiopental and halothane in buffaloes.

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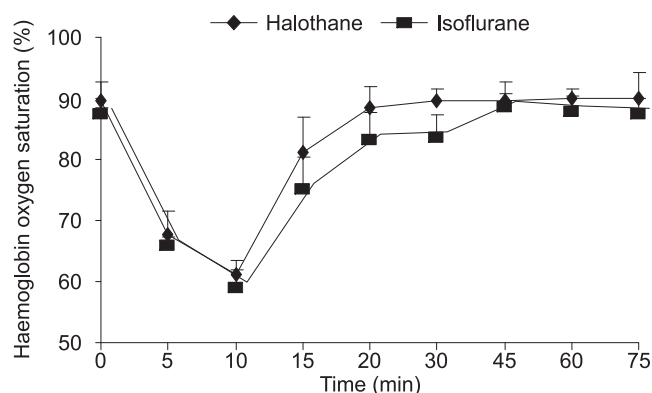


Fig. 10. Mean ± SE of haemoglobin oxygen saturation (%) in the animals of groups H and I

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