Clinicophysiological and haemodynamic effects of fentanyl with xylazine, medetomidine and dexmedetomidine in isoflurane-anaesthetised water buffaloes (*Bubalus bubalis*)

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The present study was undertaken to investigate the sedative, analgesic and clinical effects of xylazine, medetomidine and dexmedetomidine with fentanyl as pre-anaesthetics in water buffaloes and to compare the dose-sparing effect of xylazine, medetomidine and dexmedetomidine on thiopental for induction and isoflurane for maintenance of anaesthesia in water buffaloes. Six male water buffaloes randomly received intravenous fentanyl (5.0 µg/kg body weight) and xylazine (0.05 mg/kg body weight), fentanyl (5.0 µg/kg body weight) and medetomidine (2.5 µg/kg body weight), fentanyl (5.0 µg/kg body weight) and dexmedetomidine (5.0 µg/kg body weight) at weekly intervals in groups I1, I2 and I3, respectively. After 15 min, the animals were restrained in right lateral recumbency and anaesthesia was induced by 5% thiopental sodium administered intravenously. The intubated animal was connected to the large animal anaesthesia machine and isoflurane in 100% oxygen (5 L/min) was insufflated for 60 min. The treatments were compared by clinicophysiological, haematobiochemical and haemodynamic parameters. Fentanyl-medetomidine and fentanyl-dexmedetomidine produced more cardiovascular depression during the pre-anaesthetic period but less depression of cardio-respiratory dynamics in the post induction and maintenance period. Quicker recovery was recorded in I2 and I3 groups. A lower dose of thiopental was required in group I3 (4.33 mg/kg ± 0.66 mg/kg) than in groups I2 (4.41 mg/kg ± 0.98 mg/kg) and I1 (4.83 mg/kg ± 0.79 mg/kg). The dose of isoflurane was less in group I3 (45.50 mL ± 5.45 mL) than in group I1 and I2 (48.66 mL ± 5.10 mL and 48.00 mL ± 6.38 mL). Better anaesthesia was recorded with fentanyl-dexmedetomidine-thiopental-isoflurane (group I3) than with fentanyl-medetomidine-thiopental-isoflurane (group I2) and fentanyl-xylazine-thiopental-isoflurane (group I1). Fentanyl-medetomidine and fentanyl-dexmedetomidine were better pre-anaesthetic agents in comparison to fentanyl-xylazine for thiopental and isoflurane anaesthesia. Fentanyl-dexmedetomidine-thiopental-isoflurane and fentanyl-medetomidine-thiopental-isoflurane produced effective surgical anaesthesia and were found to be safe, as cardio-pulmonary functions were well preserved during maintenance anaesthesia with no deleterious effect on vital organ functions in water buffaloes.

Introduction

General anaesthesia in adult water buffaloes or cattle involves complications, such as regurgitation, bloat, aspiration pneumonia, nerve paralysis et cetera, which are not often encountered in small animals. To reduce the risk associated with these potential complications, adult cattle should be fasted from 18 h to 24 h under captive conditions. Additionally, pulmonary functional residual capacity may be better preserved in fasted anaesthetised animals (Tranquilli & Maze 1993).

Xylazine was initially used in cattle and later in horses to sedate or, in higher doses, restrain ruminants and is a more potent sedative in ruminants than in horses. Medetomidine, the most potent alpha-2 agonist, is more lipophilic, selective, potent and efficacious and eliminated faster (Schienin & MacDonald 1989). Sedative and analgesic effects of medetomidine have been studied in sheep (Kastner *et al*. 2001), goats (Pawde *et al*. 1996), calves (Raekallio, Kivalo & Jalanka 1997), dairy cows (Ranheim *et al*. 1999) and water buffaloes (Kinjavdekar *et al*. 2003). Dexmedetomidine has been used as a sedative and as a premedicant in different species. Fentanyl is a highly lipid soluble, short-acting synthetic µ-opioid agonist. In the clinical setting, there are few reports of intravenous fentanyl administration in large animal species, although fentanyl infusions have been employed in a variety of surgical animal research models involving calves (Wilson, Kantrowitz & Pacholewicz 2000).

Thiopental sodium is the most widely used intravenous induction agent in ruminants and has been used in cattle (Rugh *et al*. 1985) and water buffalo calves (Malik 2008). As it is a very short-

acting agent, repeated doses are required to maintain surgical anaesthesia, which produces a cumulative effect (Thurmon, Tranquilli & Benson 1996) and makes this drug unsuitable for maintenance of anaesthesia, especially in procedures of longer duration. Furthermore, injectable anaesthetics are associated with prolonged 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. However, there are few reports on the use of inhalant anaesthesia in cattle and water buffaloes. The present study was therefore undertaken to investigate the sedative, analgesic and clinical effects of xylazine, medetomidine and dexmedetomidine with fentanyl as pre-anaesthetics in water buffaloes and to compare the dose-sparing effect of xylazine, medetomidine and dexmedetomidine on thiopental for induction and isoflurane for maintenance of anaesthesia in water buffaloes.

Materials and methods

Experimental animals

Six clinically healthy male water buffaloes of 1 and 3 years of age were used. The animals were stall-fed, had free access to feed and water and were maintained under uniform managemental conditions. The animals were deprived of feed for 48 h and water was withheld for 24 h prior to the start of the experiment.

Experimental design

All the animals randomly received intravenous fentanyl (5.0 µg/kg body weight) and xylazine (0.05 mg/kg body weight), fentanyl (5.0 µg/kg body weight) and medetomidine (2.5 µg/kg body weight) fentanyl (5.0 µg/kg body weight) and dexmedetomidine (5.0 µg/kg body weight) respectively at weekly intervals in groups I1, I2 and I3. The dose of medetomidine was selected on the basis of the earlier study (Kinjavdekar *et al.* 2003). The doses of fentanyl and dexmedetomidine were standardised and selected after conducting pilot trials. After 15 min of premedication, the animals were restrained in right lateral recumbency and anaesthesia was induced by 5% thiopental sodium administered intravenously. A mouth gag was placed for endotracheal intubation. The tube was connected to the large animal anaesthesia machine and isoflurane in 100% oxygen (5 L/min) was insufflated for 60 min. The different treatments were evaluated on the basis of the following parameters: clinical, physiological, haematological, biochemical and haemodynamic observations.

Clinical observations

Sedation was evaluated before and after induction of anaesthesia at 0 min, 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 60 min and 75 min, as well as after discontinuation of anaesthesia by observing behavioural changes and was graded on a 0–3 scale. Analgesia was evaluated by observing the animals' response at 15 min intervals after a deep prick on periosteum of the rib and at the coronary band with a 22-gauge needle and was graded on a 1–4 scale. Muscle relaxation was observed by 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 and was graded on a 1–4 scale. Degree of abolition of palpebral and corneal reflexes was recorded at different intervals and was graded on a (-) to (++++) scale. The extent of salivation at different intervals of anaesthesia was recorded and graded on a (-) to (++++) scale. The doses of thiopental sodium (mg/kg) and the concentration (%) of isoflurane were calculated after each trial. The indicators used are listed in Table 1.

Physiological observations

The heart rate (HR) (beats/min) by auscultation, respiratory rate (RR) (breaths/min) by observing the thoracic excursions and rectal temperature (RT) (°C) by a clinical thermometer were recorded before administration of any drug (0 min) and then at 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 60 min, 75 min, 90 min, 105 min and 120 min after premedication (Kinjavdekar *et al.* 2003; Malik 2008).

TABLE 1: Parameters used for clinical monitoring of anaesthesia.

Parameters	Score	Interpretation
Depth of anaesthesia	0	No sedation: Alert, eyes open
	1	Mild sedation: Drooping of eyelids, 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	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	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
Palpebral and corneal reflexes	-	Completely abolished reflexes
	+	Mildly abolished reflexes
	++	Moderately abolished reflexes
	+++	Slightly intact reflexes
	++++	Intact reflexes
Salivation	-	Absent
	+	Mild
	++	Moderate
	+++	Extensive
	++++	Profuse
Recovery time	n/a	The time from discontinuation of the inhalant agent to the first spontaneous movement of any body part
Sternal recumbency time	n/a	The time from discontinuation of inhalant agent to the spontaneous regaining of sternal recumbency
Standing time	n/a	The time from discontinuation of inhalant agent to spontaneous regaining of standing position

Haematological observations

Blood samples (1 mL) were collected in sterile, heparinised syringes at time 0 min (baseline) and at 15 min, 30 min, 60 min, 90 min, 120 min, 720 min and 1440 min after administration of different drugs. Haemoglobin (Hb) (g/L) by Sahli's haemoglobinometer, packed cell volume (PCV) (L/L) by microhaematocrit, total leukocyte count (TLC) ($\times 10^9$/L) by haemocytometer and differential leukocyte count (DLC) (%) were estimated.

Biochemical observations

Blood samples (0.5 mL) were collected in sterile, heparinised syringes (sodium fluoride for glucose) at time 0 min (baseline) and at 15 min, 30 min, 60 min, 90 min, 120 min, 720 min and 1440 min for separation of plasma. Urea (mmol/L) by diacetyl monoxime (DAM) method, glucose (mmol/L) by o-Toluidine method, creatinine (µmol/L) by alkaline picrate method, cortisol and insulin by radio immuno-assay (RIA) (nmol/L) and lactate dehydrogenase (LDH) (U/L) by a standard method were estimated.

Haemodynamic observations

Mean arterial pressure (MAP), diastolic blood pressure (DBP), systolic blood pressure (SBP) (mm Hg) were recorded using a non-invasive blood pressure monitor (Surgivet; Smith Medical PM, Inc., Waukesha, USA), after stabilisation for 30 min, at time 0 min (baseline) and at 5 min, 15 min, 30 min, 45 min and 60 min after induction of anaesthesia. For central venous pressure (CVP), a sterile polyethylene catheter was passed through a 12-gauge hypodermic needle into the jugular vein and was advanced up to the anterior vena cava. The catheter was connected to a saline manometer containing heparinised saline through a three-way stop cock. The position of the catheter was confirmed by observing the pressure changes in the saline manometer caused by respiration. A syringe containing heparinised saline was connected to the third end of the stop cock to flush the system. The zero of the manometer was adjusted at the level of the sternal manubrium. The haemoglobin oxygen saturation (SpO_2) (%) was recorded by applying the sensor of the pulse oxymeter (Nonin Medical Inc., Minneapolis, USA) on the anal fold at the same time intervals as recorded for blood pressure. For electrocardiography (ECG), standard base apex lead electrocardiograms (BPL India, Ltd, New Delhi, India) were recorded at 1 mV and 25 mm/s paper speed at the same intervals as blood pressure. The electrocardiograms were analysed for the duration and amplitude of P wave, QRS complex, T wave, PR and QT intervals and rhythm.

Statistical analysis

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

Ethical considerations

Approval for conducting the anaesthetic trials and number of animals used was sought from the Institutional Animal Ethics Committee and the Committee for the Purpose of Control and Supervision of Experimentation in Animals. There were no physical or psychological risks involved in the experimental trials.

Results

Clinical results

In groups I1, I2 and I3 the median sedation scores were 3.00 ± 0.09, 3.00 ± 0.09 and 3.00 ± 0.00, respectively (Figure 1). Good sedation was recorded in groups I1, I2 and I3. Groups I1, I2 and I3 recorded a median analgesia score of 4.00 ± 0.18, 4.00 ± 0.05 and 4.00 ± 0.09, respectively (Figure 2). Group I1 recorded mild pin-prick response up to 10 min after premedication, but in some animals the pin-prick response was absent from 10 min onwards until the end. In group I2, a mild pin-prick response was recorded at 5 min of premedication, but in some animals the pin-prick response was absent from 5 min until the end. In group I3, no pin-prick response was recorded for the entire observation period. Comparison amongst different groups revealed that the pin-prick reflex was absent for a longer period in group I3. In group I1, I2 and I3, muscle relaxation scores of 3.00 ± 0.20, 4.00 ± 0.20 and 4.00 ± 0.20, respectively were recorded (Figure 3). The muscle relaxation was higher in groups I2 and I3 compared with group I1.

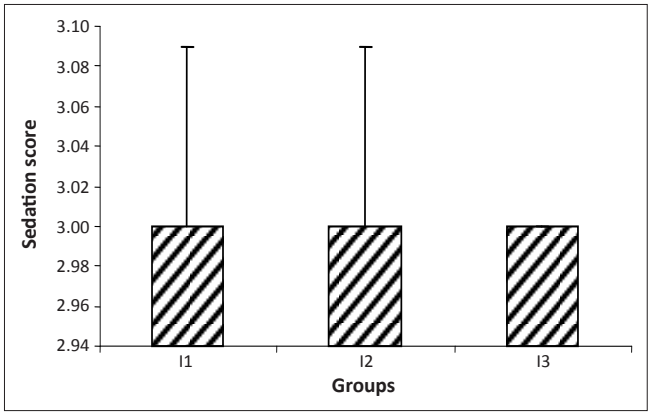


FIGURE 1: Median ± standard deviation of sedation in water buffaloes of different groups.

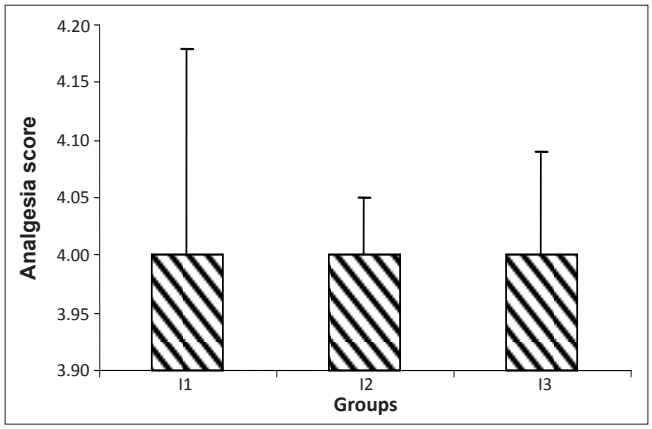


FIGURE 2: Median ± standard deviation of analgesia in water buffaloes of different groups.

The palpebral reflex was completely abolished after premedication until the end, except in group I1, where mild response was recorded up to 10 min. Comparison amongst different groups revealed that in groups I2 and I3 the palpebral reflex was completely abolished after premedication and during the maintenance period. Group I1 revealed mild response to the corneal reflex up to 10 min, after which it was completely abolished until the end. In group I2, moderate response at 5 min and mild response at 10 min was recorded, after which the corneal reflex was completely abolished. In group I3, mild response was recorded up to 10 min after premedication, which was completely abolished until the end. Comparison amongst different groups revealed that the corneal reflex was completely abolished for longer in groups I2 and I3 than group I1. Extensive salivation was recorded in group I1, whilst in group I2, salivation was extensive up to 10 min, becoming moderate from 15 min to 45 min and extensive from 45 min to 60 min. In group I3, extensive salivation was recorded for the entire observation period. Comparison amongst groups I1, I2 and I3 revealed that extensive salivation was recorded for a longer period in group I1 than in group I3 and moderate salivation was recorded for longer period in group I2.

The doses of thiopental sodium (5% solution) in groups I1, I2 and I3 were 4.83 mg/kg ± 0.79 mg/kg, 4.41 mg/kg ± 0.98 mg/kg and 4.33 mg/kg ± 0.66 mg/kg, respectively. Mean doses of isoflurane (mL) in groups I1, I2 and I3 were 48.66 mL ± 5.10 mL, 48.00 mL ± 6.38 mL and 45.50 mL ± 5.45 mL, respectively (Figure 4).

The median recovery time recorded in groups I1, I2 and I3 were 5.66 min ± 0.98 min, 5.16 min ± 0.79 min and 3.00 min ± 1.09 min, respectively. The median sternal recumbency times recorded were 9.16 min ± 1.40 min, 8.16 min ± 0.30 min, 13.83 min ± 3.04 min, respectively. The median times to standing recorded were 12.50 min ± 1.97 min, 19.00 min ± 0.96 min and 18.00 min ± 3.28 min, respectively (Figure 5).

Physiological results

Group I1 recorded a significant ($p < 0.05$) decrease in HR at 5 min and 10 min after premedication up to 30 min. Group I2 and I3 recorded a significant ($p < 0.05$) decrease in HR from 10 min until the end (Figure 6). Comparison between groups I1 and I2 revealed that at 120 min and 135 min the HR was significantly ($p < 0.05$) lower in group I1. Comparison between groups I2 and I3 revealed the same trend as in groups I1 and I2, except that the HR was lower at 120 min and 135 min in group I3. In group I1, the RR increased significantly ($p < 0.05$) at 60 min and 75 min. However, the RR decreased significantly ($p < 0.05$) at 120 min. Group I2 recorded a significant ($p < 0.05$) decrease in RR at 5 min, after which RR increased until the end. In group I3, the RR increased significantly ($p < 0.05$) during the entire maintenance period (Figure 7). In group I1, the RT decreased significantly ($p < 0.05$) from 20 min to 135 min and highly significantly ($p < 0.01$) at 90 min. Group I2 did not reveal any significant change. In group I3, the RT decreased significantly ($p < 0.05$) from 20 min to 90 min and highly significantly ($p < 0.01$) at 60 min. Comparison between groups I1 and I2 revealed that at

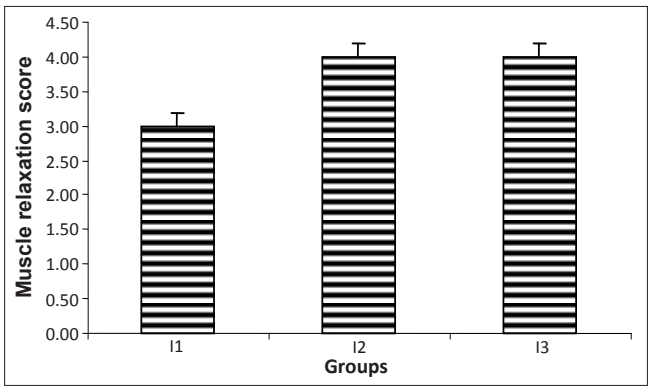


FIGURE 3: Median ± standard deviation of muscle relaxation in water buffaloes of different groups.

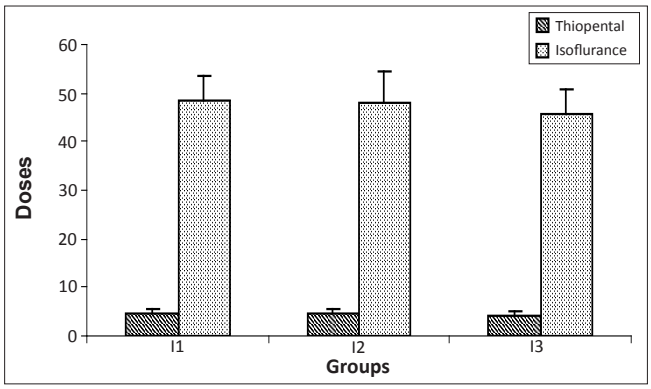
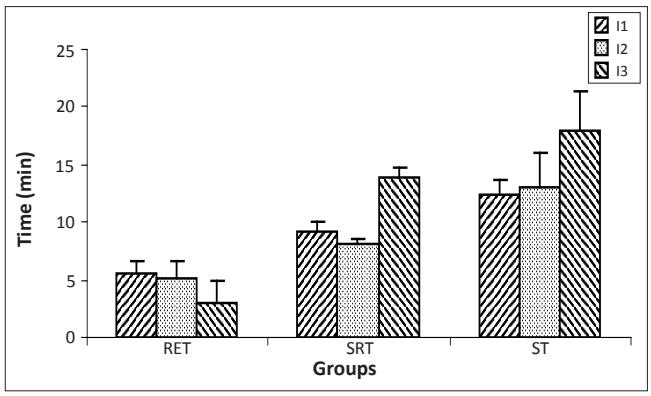


FIGURE 4: Mean ± standard error of doses of thiopental sodium (mg/kg) and isoflurane (mL) in water buffaloes of different groups.



RET, recovery time; SRT, sternal recumbency time; ST, standing time.

FIGURE 5: Mean ± standard error of recovery time, sternal recumbency time and standing time (min) in water buffaloes of different groups.

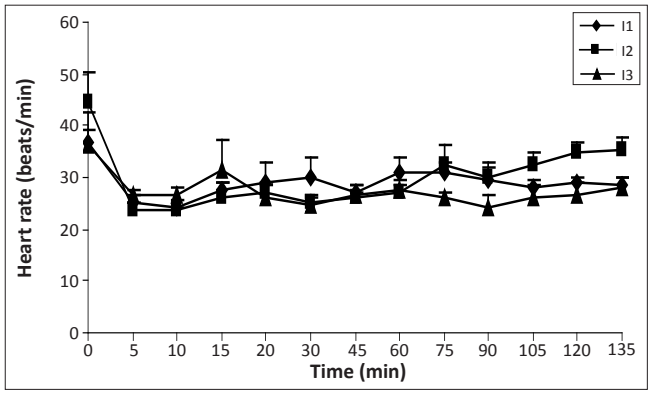


FIGURE 6: Mean ± standard error of heart rate (beats/min) in water buffaloes of different groups.

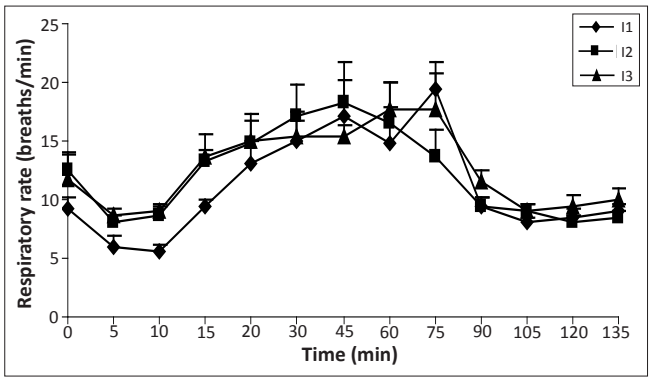


FIGURE 7: Mean ± standard error of respiratory rate (breaths/min) in water buffaloes of different groups.

20 min and 75 min the RT was significantly ($p < 0.05$) lower in group I1. Comparison between groups I2 and I3 revealed that at 20 min the RT was significantly ($p < 0.05$) lower in group I3.

Haematological results

In group I1, a significant ($p < 0.05$) Hb decrease was recorded up to 90 min and this decrease was highly significant ($p < 0.01$) at 30 min and 90 min. Group I2 did not show any significant change. Group I3 showed a significant ($p < 0.05$) decrease from 30 min to 90 min (Table 2). Comparison between groups I1 and I2 revealed that at 120 min significantly ($p < 0.01$) higher Hb was recorded in group I2. In group I1, PCV decreased significantly ($p < 0.05$) up to 120 min and highly significantly ($p < 0.01$) from 30 min to 90 min. In groups I2 and I3 the PCV significantly ($p < 0.05$) decreased from 30 min to 90 min (Table 2). Comparison between groups I1 and I2, as well as between I1 and I3, revealed that at 90 min the PCV was significantly ($p < 0.05$) lower in group I1. In group I1, a significant ($p < 0.05$) decrease in TLC from 15 min to 90 min and a highly significantly ($p < 0.01$) decrease at 90 min were recorded. In group I2, a significant ($p < 0.05$) decrease in TLC from 15 min to 720 min and a highly significant ($p < 0.01$) decrease at 60 min, 90 min and 720 min were recorded. Group I3 showed a significant ($p < 0.05$) decrease in TLC up to 30 min (Table 2). Comparison between groups I1 and I3 revealed that a significantly ($p < 0.05$) lower TLC was recorded from 30 min to 90 min in group I1. A highly significant ($p < 0.01$) decrease in lymphocyte count was recorded in groups I1 and I2 up to 60 min; however, the decrease was significant ($p < 0.05$) at 90 min, 120 min and 1440 min in group I2. Group I3 showed a significant ($p < 0.01$) decrease in lymphocyte count throughout. Comparison between groups I2 and I3 revealed that at 120 min the lymphocyte count was lower in group I1. Group I1 revealed a highly significant ($p < 0.01$) increase up to 60 min and a significant ($p < 0.05$) increase at 90 min in neutrophil count. Group I2 showed a significant ($p < 0.01$) increase up to 30 min, whilst there was a significant ($p < 0.05$) increase up to 60 min in Group I3. Comparison between groups I1 and I2, as well as between I2 and I3, revealed that at 90 min and 30 min, respectively, a significantly ($p < 0.05$) lower value was recorded in group I2.

Biochemical results

Group I1 did not reveal any significant change in the glucose level. Group I2 revealed significantly ($p < 0.05$) higher glucose from 15 min to 30 min and a highly significant ($p < 0.01$) increase at 90 min. Group I3 experienced a significant ($p < 0.05$) increase in glucose at 720 min (Table 2). Comparison between groups I1 and I2 revealed that at 90 min a significantly ($p < 0.05$) lower glucose was recorded in group I1. A comparison of groups I1 and I3 revealed that at 720 min a significantly ($p < 0.05$) lower glucose was recorded in group I1. The creatinine decreased significantly ($p < 0.05$) in group I1, with a highly significant ($p < 0.01$) decrease from 15 min to 720 min. In group I2, the creatinine decreased significantly ($p < 0.05$), with a highly significant ($p < 0.01$) decrease from 30 min to 120 min and at 1440 min. The creatinine decreased significantly ($p < 0.01$) in group I3 (Table 2). Group I1 revealed that from 120 min to 1440 min the urea increased significantly ($p < 0.05$). In group I2 the urea increased significantly ($p < 0.05$). Group I3 recorded a significant ($p < 0.05$) increase in urea at 30 min, 90 min and 1440 min (Table 2). Group I1 demonstrated a significant ($p < 0.05$) decrease in insulin up to 120 min, whereafter a significant ($p < 0.05$) increase was recorded at 720 min and 1440 min. Group I2 showed a highly significant ($p < 0.01$) decrease in insulin up to 60 min, with a significant ($p < 0.05$) decrease up to 120 min. Group I3 showed a significant ($p < 0.05$) decrease in insulin up to 120 min and then an increase at 720 min and 1440 min (Table 2). Groups I1 and I3 demonstrated a significant ($p < 0.05$) decrease in the cortisol. Comparison between groups I2 and I3, as well as between I1 and I3, revealed that at 1440 min the cortisol was significantly ($p < 0.05$) lower in groups I2 and I1, respectively (Table 2). Group I1 revealed a significant ($p < 0.05$) increase in LDH at 15 min, 90 min and 1440 min. However, group I2 revealed that at 120 min a significant ($p < 0.05$) increase in LDH was recorded. Group I3 revealed that at 1440 min a significant ($p < 0.05$) decrease in the LDH was recorded (Table 2). Comparison between groups I1 and I2 revealed a significantly ($p < 0.05$) lower LDH from 15 min to 120 min and at 1440 min in group I1. Comparison between groups I2 and I3 revealed a significantly ($p < 0.05$) lower LDH from 60 min to 90 min and at 1440 min in group I3. Comparison between groups I1 and I3 revealed a significantly ($p < 0.05$) lower LDH in group I3.

Haemodynamic results

In groups I1 and I2, the fall in SBP was significant ($p < 0.01$) up to 30 min. Group I3 showed a significant ($p < 0.05$) decrease at 5 min and 10 min and then from 30 min to 75 min. Comparison between groups I1 and I2 revealed a significantly ($p < 0.05$) lower SBP at 5 min, 10 min and 30 min in group I1. Comparison between groups I1 and I3 revealed a significantly ($p < 0.05$) lower SBP from 5 min to 30 min in group I1. In group I1, the DBP decreased significantly ($p < 0.01$) throughout the observation period. Group I2 revealed a significant ($p < 0.05$) decrease in DBP, with a highly significant ($p < 0.01$) decrease up to 30 min. In group I3 the DBP decreased significantly ($p < 0.05$). Comparison between

TABLE 2: Mean ± standard error of haematological and biochemical parameters in water buffaloes of different groups.

Parameters	Groups	Time (min)							
		0	15	30	60	90	120	720	1440
Haemoglobin (g/L)	I1	105.000^{ab} ± 0.180	93.330* ± 0.280	87.330**^{a} ± 0.240	89.330* ± 0.320	91.330**^{ab} ± 0.080	95.660*^{a} ± 0.230	103.000 ± 0.260	104.660 ± 0.130
	I2	90.000^{a} ± 1.600	95.330 ± 0.280	92.330^{ab} ± 0.260	89.660 ± 0.200	99.330bc ± 0.160	107.330^{b} ± 0.310	108.330 ± 0.180	109.000 ± 0.270
	I3	104.830^{ab} ± 0.340	98.000 ± 0.210	93.000*^{ab} ± 0.190	90.250* ± 0.210	94.660*^{abc} ± 0.140	92.000^{a} ± 0.360	106.330 ± 0.26 0	105.660 ± 0.180
PCV (L/L)	I1	0.300 ± 0.045	0.280* ± 0.0620	0.260** ± 0.068	0.260** ± 0.081	0.270**^{a} ± 0.029	0.290*^{ab} ± 0.053	0.300 ± 0.072	0.310 ± 0.042
	I2	0.310 ± 0.044	0.280* ± 0.091	0.270* ± 0.092	0.270** ± 0.067	0.290*^{b} ± 0.056	0.310^{b} ± 0.062	0.320 ± 0.050	0.300 ± 0.068
	I3	0.300 ± 0.088	0.290 ± 0.046	0.270* ± 0.055	0.270** ± 0.048	0.280*^{b} ± 0.045	0.280^{a} ± 0.097	0.310 ± 0.063	0.320 ± 0.071
TLC (× 10^9/L)	I1	8.510^{a} ± 0.530	5.680*^{a} ± 0.440	5.730**^{a} ± 0.420	5.550*^{a} ± 0.660	6.250**^{a} ± 0.500	7.210^{a} ± 1.070	8.221^{a} ± 0.760	9.160^{a} ± 0.570
	I2	11.060^{abc} ± 0.500	8.860*^{b} ± 1.020	7.730*^{ab} ± 1.190	7.200**^{ab} ± 0.680	8.450**^{ab} ± 0.540	8.900*^{ab} ± 0.740	9.500**^{a} ± 0.540	10.780^{ab} ± 0.400
	I3	10.780^{ab} ± 0.850	9.880*^{b} ± 0.710	9.580*^{b} ± 0.720	9.810^{b} ± 0.880	9.730^{b} ± 0.700	10.460^{ab} ± 0.650	10.830^{ab} ± 0.430	10.780^{ab} ± 0.510
Glucose (mmol/L)	I1	6.510 ± 1.450	7.580^{ab} ± 1.030	6.330^{a} ± 0.630	6.810^{ab} ± 1.150	4.910^{a} ± 0.210	5.980 ± 0.660	5.090^{a} ± 0.660	6.140 ± 0.710
	I2	6.000 ± 0.870	7.190*^{a} ± 0.480	7.290*^{ab} ± 1.080	6.740^{ab} ± 0.730	7.570**^{bc} ± 0.690	6.640 ± 0.540	6.210^{ab} ± 0.520	6.300 ± 0.370
	I3	5.470 ± 0.660	6.520^{a} ± 0.310	6.610^{a} ± 0.450	6.090^{a} ± 0.460	5.820^{ab} ± 0.580	6.540 ± 0.430	6.900*^{bc} ± 0.470	6.430 ± 0.220
Creatinine (µmol/L)	I1	162.340 ± 2.910	140.940** ± 2.810	138.090** ± 3.180	137.770**^{b} ± 2.950	138.890**^{ab} ± 3.360	145.820** ± 3.030	151.320** ± 2.820	157.440* ± 3.240
	I2	162.030 ± 3.300	142.780* ± 4.820	139.660** ± 2.460	136.490**^{b} ± 2.760	138.58**^{ab} ± 2.400	146.350** ± 2.340	152.540* ± 1.940	157.650** ± 3.290
	I3	161.840 ± 2.500	153.200** ± 1.300	145.720** ± 2.530	118.900**^{bc}± 2.100	144.520**^{b} ± 2.550	146.320** ± 2.990	154.160* ± 2.740	160.620 ± 2.660
Urea nitrogen (mmol/L)	I1	9.610 ± 0.330	9.900^{ab} ± 0.340	10.070^{ab} ± 0.280	10.460 ± 0.450	10.990 ± 0.640	10.710* ± 0.510	11.460** ± 0.400	11.770*^{ab} ± 0.980
	I2	9.370 ± 0.270	10.170*^{b} ± 0.400	9.850^{ab} ± 0.110	10.350 ± 0.950	11.700** ± 0.290	11.310* ± 0.800	10.960* ± 0.460	12.760**^{b} ± 0.420
	I3	9.370 ± 0.440	10.070^{b} ± 0.470	11.290**^{b} ± 0.630	10.650 ± 0.340	11.280** ± 0.620	12.08*0 ± 0.660	11.180 ± 0.580	12.270*^{ab} ± 0.580
Insulin (µU/mL)	I1	9.700 ± 1.270	5.660*^{b} ± 0.370	4.940*^{ab} ± 0.360	4.430*^{ab} ± 0.300	4.160*^{a} ± 0.250	4.210*^{ab} ± 0.130	16.030*^{b} ± 1.720	15.110*^{bc} ± 1.960
	I2	9.190 ± 0.620	5.490**^{b} ± 0.520	5.370**^{b} ± 0.450	5.150**^{b} ± 0.390	6.75*^{b} ± 0.750	6.530*^{b} ± 1.120	9.180^{ab} ± 2.670	7.540^{ab} ± 1.090
	I3	8.150 ± 1.250	4.450*^{ab} ± 0.270	3.850*^{a} ± 0.210	4.650^{b} ± 0.260	4.010*^{a} ± 0.140	4.430*^{ab} ± 0.630	12.470^{ab} ± 4.240	13.100^{abc} ± 4.840
Cortisol (nmol/L)	I1	44.860 ± 9.380	18.220*^{a} ± 3.200	11.700* ± 2.680	17.000*^{ab} ± 5.550	23.640*^{abc} ± 6.400	47.800 ± 8.900	13.800* ± 3.110	21.570*^{a} ± 1.920
	I2	59.130 ± 17.880	36.370^{ab} ± 11.850	44.490 ± 20.830	40.920^{b} ± 6.910	38.410^{bc} ± 3.600	43.510 ± 9.600	31.370 ± 6.020	28.530^{ab} ± 6.630
	I3	65.740 ± 9.21	34.340**^{ab} ± 9.860	34.320* ± 18.200	40.770*^{b} ± 14.460	41.420*^{c} ± 5.960	34.660* ± 7.100	24.560* ± 7.200	42.650*^{c} ± 9.360
LDH (U/L)	I1	579.470^{ab} ± 70.190	630.240^{ab} ± 63.240	657.810^{a} ± 46.260	689.590^{a} ± 52.190	693.090*^{a} ± 49.170	702.360^{a} ± 71.390	638.200^{a} ± 57.110	584.520*^{a} ± 44.430
	I2	527.270^{b} ± 39.170	510.940^{bc} ± 41.190	516.880^{ab} ± 56.390	535.770^{c} ± 39.310	423.470^{b} ± 45.100	439.390*^{b} ± 74.390	592.320^{ac} ± 78.290	683.050^{b} ± 61.240
	I3	584.520^{a} ± 56.190	445.710^{b} ± 43.160	501.160*^{b} ± 39.380	453.430^{b} ± 61.140	533.300^{c} ± 35.170	463.660^{bc} ± 71.190	555.660^{bc} ± 39.490	458.220*^{c} ± 67.140

PCV, packed cell volume; TLC, total leukocyte count; LDH, lactate dehydrogenase.
^{a,b,c}, Values bearing different superscripts differ significantly among different groups.
*, Values differ significantly from the base value $p < 0.05$; **, Values differ significantly from the base value $p < 0.01$

groups I1 and I2, as well as between I1 and I3, revealed significantly ($p < 0.01$) lower DBP from 5 min to 30 min in group I1. Comparison between groups I2 and I3 revealed a significantly ($p < 0.01$) lower DBP at 5 min, 10 min and 20 min in group I2. In groups I1 and I2, a highly significant ($p < 0.01$) decrease in MAP was recorded up to 30 min, with a significant ($p < 0.05$) decrease from 45 min to 75 min. Group I3 revealed a significant ($p < 0.05$) decrease in MAP (Figure 8). Comparison between groups I1 and I2 revealed a significantly ($p > 0.05$) lower MAP from 5 min to 10 min and from 20 min to 30 min in group I1, whilst comparison between groups I2 and I3 revealed a significantly ($p > 0.05$) lower MAP from 5 min to 15 min in group I2. Comparison between groups I1 and I3 revealed a significant ($p > 0.05$) decrease in MAP from 5 min to 30 min and at 75 min in group I1. In group I1, the CVP increased significantly ($p < 0.05$) up to 15 min and from 60 min to 75 min. In group I2, the CVP increased significantly ($p < 0.05$) at 5 min. Group I3 recorded a significant ($p < 0.05$) increase in CVP, with a highly significant ($p < 0.01$) increase from 5 min to 20 min (Figure 9). Comparison between groups I1 and I2 revealed that at 5 min the CVP was significantly ($p < 0.05$) lower in Group I2. Group I1 revealed a significant ($p < 0.05$) decrease in the SpO_2 at 5 min. In group I2 the SpO_2 increased significantly during the maintenance period. In

group I3, the SpO_2 decreased significantly ($p < 0.01$) up to 10 min after premedication (Figure 10). Comparison between groups I1 and I3 revealed that the SpO_2 was significantly ($p < 0.01$) lower in group I3 at 10 min.

In group I1, the P wave duration significantly ($p < 0.05$) decreased at 10 min and 75 min. In group I2, the P wave duration significantly ($p < 0.05$) decreased from 10 min to 20 min and from 60 min to 75 min. Comparison between groups I1 and I2 revealed a significantly ($p < 0.05$) lower P wave duration in group I2 at 15 min. Comparison between groups I2 and I3 revealed a significantly ($p < 0.05$) lower P wave duration in group I2 from 15 min to 20 min and 60 min to 75 min. Comparison between groups I1 and I3 revealed a significantly ($p < 0.05$) lower P wave duration at 20 min and from 60 min to 75 min in group I1. A comparison of groups I1 and I2 revealed that in group I1 a significant ($p < 0.05$) decrease in the P wave amplitude was recorded at 15 min, 60 min and 75 min. Comparison between groups I2 and I3 revealed a significantly ($p < 0.05$) lower P wave amplitude at 20 min in group I2. Comparison between groups I1 and I2 revealed that the duration of QRS complex at 20 min was significantly lower in group I1. In groups I1 and I3, a significant ($p < 0.05$) increase in T wave duration was recorded at 10 min and 15 min. Group I2 showed a significant ($p < 0.05$) increase in T wave duration at 45 min and 75 min. Comparison between groups I2 and I3 revealed a significantly ($p < 0.05$) lower T wave duration from 20 min to 45 min in group I3. In group I2, a significant ($p < 0.05$) decrease in PR interval was recorded at 5 min and 75 min. Comparison between groups I1 and I2 revealed a significantly ($p < 0.05$) lower PR interval at 5 min in group I2. Comparison between groups I1 and I3 revealed a significantly ($p < 0.05$) lower PR interval at 10 min in group I3. In group I1, the QT interval increased significantly ($p < 0.05$) at 15 min and from 45 min to 75 min. In group I2, the QT interval increased significantly ($p < 0.01$) from 5 min to 75 min. In group I3, the QT interval increased significantly ($p < 0.05$) from 5 min to 10 min and from 60 min to 75 min. Comparison between groups I1 and I2 revealed a significantly ($p < 0.05$) higher QT interval at 20 min and 45 min in group I1. Comparison between groups I1 and I3 revealed a significantly ($p < 0.05$) higher QT interval in group I1 from 15 min to 20 min and 45 min and 75 min. In group I3, the ST segment increased significantly ($p < 0.05$) at 20 min and 45 min. Comparison between groups I1 and I2 revealed a significantly ($p < 0.05$) higher ST segment at 20 min and 60 min in group I1.

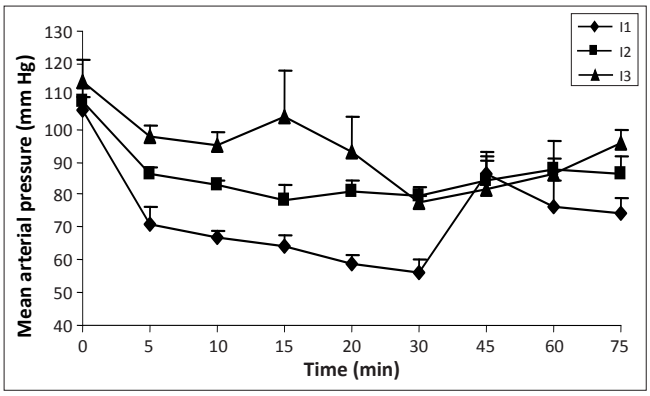


FIGURE 8: Mean ± standard error of mean arterial pressure (mm Hg) in water buffaloes of different groups.

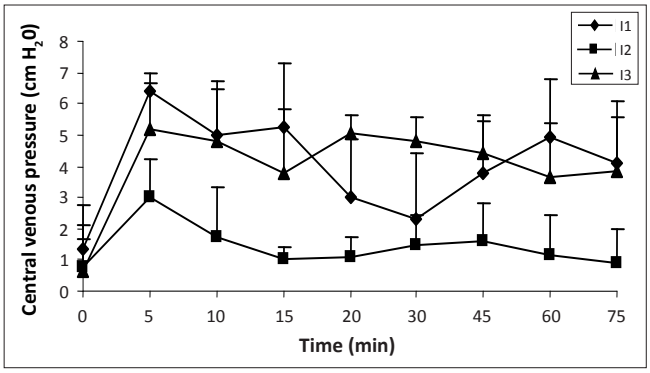


FIGURE 9: Mean ± standard error of central venous pressure (cm H_2O) in water buffaloes of different groups.

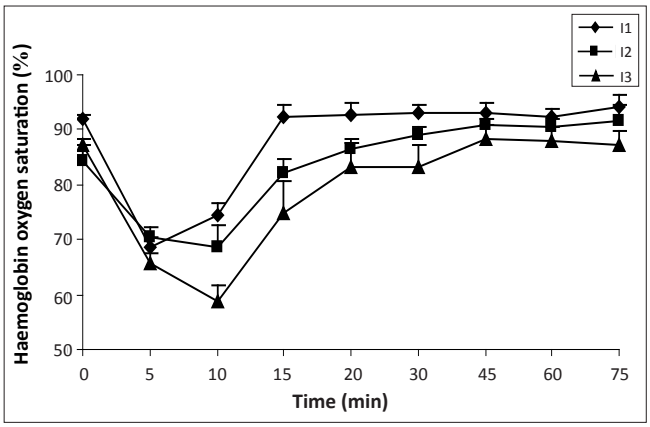


FIGURE 10: Mean ± standard error of haemoglobin oxygen saturation (%) in water buffaloes of different groups.

Discussion

Interpretation of clinical observations

In the xylazine and medetomidine groups, mild sedation was recorded compared with the dexmedetomidine group. Dexmedetomidine is more highly specific to alpha-2 adrenergic receptors than medetomidine and xylazine (Scheinin *et al.* 1989). Stimulation of these presynaptically located receptors inhibits the release of catecholamines (Skarda & Muir 1992). In higher doses, alpha-2 agonists produce profound cardiopulmonary effects, but combinations with opioids at reduced doses make them superior to any other pre-anaesthetic agent (Thurmon *et al.* 1996). Medetomidine and butorphanol produced better sedation than midazolam and butorphanol in water buffaloes (Malik 2008). The doses of dexmedetomidine (5 µg/kg) and fentanyl (5 µg/kg) were selected on the basis of pilot trials and it was recorded that low doses produced adequate sedation. However, deep sedation and analgesia were recorded in water buffalo calves (Kinjavdekar *et al.* 2003) and goats (Hugar, Gupta & Singh 1998) after a higher dose (20 µg/kg) of medetomidine. The animals of all groups showed good to excellent analgesia. It is well documented that alpha-2 agonists produce analgesia by blocking receptors at various sites in the pain pathway within the brain and spinal cord (Stenberg 1989). In the

present study, the combination of dexmedetomidine and fentanyl produced excellent analgesia of longer duration, possibly owing to synergistic action. A similar type of synergism between alpha-2 agonists and opioid analgesics has been reported in goats (Carroll *et al.* 1998). Excellent analgesia in the animals of all groups might be the result of the long-lasting analgesic effects of alpha-2 agonists and fentanyl, as well as the CNS depressant effects of isoflurane.

In all groups, adequate muscle relaxation was recorded. The excellent muscle relaxation immediately after medetomidine-fentanyl and dexmedetomidine-fentanyl might be attributable to the synergistic effect of both drugs. The muscle relaxant effect that accompanies sedation is caused by inhibition at alpha-2 adreneoceptors at the inter-neuron level of the spinal cord (Cullen 1996). Although isoflurane is devoid of any muscle relaxation capacity, thiopental and alpha-2 agonists produce muscle relaxation that might be responsible for good muscle relaxation in different groups.

Palpebral and corneal reflexes were depressed after premedication in all groups. The degree of depression at maximal sedation was higher in groups I2 and I3. Moderate to complete abolition of these reflexes after medetomidine (10 µg/kg) and pentazocine (3 mg/kg) in goats has been reported (Amarpal *et al.* 1998). Thiopental in all groups produced abolition of palpebral reflexes; however, the corneal reflex showed mild response at a few intervals in group I1. A similar finding was observed in dogs with thiopental and isoflurane anaesthesia (Singh *et al.* 2010). In the present study during isoflurane administration in all groups, the palpebral and corneal reflexes remained completely abolished at all intervals.

The extent of salivation during the sedation period was higher in groups I1 and I3 than group I2. Alpha-2 agonists have been reported to exert their effects on salivary glands through alpha-1 adrenergic receptors, thus increasing the secretion (Rusoaho 1986). Another reason for increased salivation during maintenance could be a decreased swallowing reflex (Kokkonen & Eriksson 1987).

Groups I1 and I2 required less thiopental sodium (4.41 mg/kg ± 0.66 mg/kg and 4.33 mg/kg ± 0.79 mg/kg, respectively) for induction than group I3 (4.83 mg/kg ± 0.79 mg/kg). A synergism between medetomidine, butorphanol and thiopental might have played an important role in reducing the induction doses of thiopental in water buffaloes (Malik 2008). Alpha-2 agonists, along with opioids, have been reported to decrease the anaesthetic requirement (Tranquilli & Maze 1993). Synergism between alpha-2 agonists and thiopentone has also been reported (Cullen & Reynoldson 1993). A significant reduction in thiopental induction dose has been reported in water buffaloes after premedication with medetomidine and butorphanol (Malik 2008). Thiopental and isoflurane produce dose-dependent cardiovascular and respiratory side effects. Therefore, a reduction in the dose of these agents may lead to improved cardiovascular stability. An adequate level of anaesthesia could be maintained by 2.5% – 4.0% isoflurane in all groups. The vaporiser setting in group I3 was slightly lower than other groups, which suggested a greater minimum alveolar concentration sparing effect of dexmedetomidine in comparison to xylazine and medetomidine. Similarly, in another study, intramuscular medetomidine (5 µg/kg and 10 µg/kg) has been found to reduce the isoflurane requirement of maintenance of anaesthesia in sheep (Kastner *et al.* 2006).

The recovery time in groups I1, I2 and I3 was comparable. The high volatility of isoflurane, coupled with low blood solubility, provided relatively rapid induction and recovery and easy control of the depth of anaesthesia. In another study, the recovery time has been reported to be significantly shorter after isoflurane anaesthesia, in comparison to propofol infusion in dexmedetomidine premedicated dogs (Kuusela *et al.* 2003). The short recovery time observed in these groups might be caused by a lower blood gas partition coefficient of isoflurane and faster changes in the alveolar concentration that induced recovery from anaesthesia more rapidly than other inhalant anaesthetics. The early recovery associated with isoflurane could also be attributed to its better cardiovascular function, reduced stress response and less alteration in the hepatic blood flow with quicker elimination.

The lower and comparable SRT recorded in groups I1, I2 and I3 might be the result of the low blood solubility of isoflurane allowing early resumption of sternal recumbency. However, the SRT was higher in group I3 because of the more potent sedative and analgesic effect of dexmedetomidine, compared with xylazine and medetomidine.

Interpretation of physiological observations

Alpha-2 agonists and fentanyl resulted in a significant decrease in HR in the different groups. Changes in the HR and rhythm are generally caused by effects of the drug on the CNS, autonomic nervous system or cardiac automaticity and the compensatory response to cardiovascular depression. Inhibition of sympathetic tone caused by reduction in norepinephrine release from the CNS, vagal activity in response to alpha-2 agonist-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 & Virtanen 1992). Similar effects have been reported in earlier studies after dexmedetomidine and medetomidine administration in different species (Kuusela *et al.* 2000). Hypotension is attributed to bradycardia and vasodilation because of the stimulation of central alpha-2 adrenoceptors, peripheral sympatholytic action and enhanced parasympathetic outflow (Tibirica, Feldman & Mermet 1991).

A decrease in respiration was recorded in all groups during sedation. Respiratory depression associated with alpha-2 agonists might be secondary to the CNS depression produced by alpha-2 adrenoceptor stimulation (Sinclair 2003) or to the result of direct depression of the respiratory centres by pre-

anaesthetics (Kumar & Thurmon 1979). A similar decrease in RR has been reported after medetomidine administration in sheep (Muge, Chambers & Livingston 1994). A decrease in RR after medetomidine and butorphanol in water buffaloes was reported (Malik 2008). The respiratory depressant effect of opioids was compounded by the co-administration of alpha-2 agonists and/or anaesthetic agents.

A significant decrease in RT was recorded in all groups during the post-anaesthetic period. This might be attributed to a decrease in the skeletal muscle tone, reduced metabolic rates and muscle relaxation, along with depression of thermoregulatory centres. Alpha-2 agonists have been reported to induce prolonged depression of thermoregulation (Ponder & Clarke 1980). Hypothermia tends to be the most common response, particularly when opioids are used in the presence of other CNS depressants (Branson, Gross & Booth 2001). During the course of the trials, the ambient temperature fluctuated between 35 °C and 39 °C. In the present study, a highly significant and early hypothermia occurred in the animals of different groups during the maintenance period.

Interpretation of haematological observations

Haemoglobin, PCV and TLC decreased significantly in all groups during the post-anaesthetic period. Pooling of circulatory blood cells in the spleen or other reservoirs secondary to sympathetic activity may explain the decrease in Hb, PCV and TLC recorded in the present study (Wagner, Muir & Hinchcliff 1991). The decrease in PCV and Hb during anaesthesia or sedation may be caused by the shifting of fluid from the extravascular compartment to the intravascular compartment in order to maintain normal cardiac output (Wagner *et al.* 1991). In the present study, inter-compartmental fluid shift or splenic pooling of cells might have occurred and caused a decrease in Hb, PCV and TLC. Neutrophilia and lymphocytopenia were recorded in all groups and might have been the result of the stress caused by the pre-anaesthetic and anaesthetic drugs and subsequent stimulation of adrenal glands. Similar findings have been reported after medetomidine and ketamine (Kinjavdekar *et al.* 2003) and medetomidine, butorphanol, thiopental and halothane (Malik 2008) in water buffaloes.

Interpretation of biochemical observations

Plasma glucose increased in all groups. The high glucose was probably the result of increased muscular activity and sympathetic stimulation caused during restraining of the animals, resulting in increased secretion of adrenocortical hormone. Similar findings were also recorded in buffalo calves under thiopental anaesthesia (Mirakhur, Sobti & Nigam 1984). Hyperglycemia might be attributed to alpha-2 adrenergic inhibition of insulin released from beta-pancreatic cells and to increased glucose production in the liver (Gasthuys *et al.* 1987). Increase in plasma glucose after medetomidine administration in goats (Hugar *et al.* 1998), xylazine in cattle (Thurmon *et al.* 1996), water buffaloes (Peshin & Kumar 1979), sheep (Brockman 1981) and goats (Kumar & Thurmon 1979) and butorphanol-medetomidine-halothane in water buffaloes (Malik 2008) has been reported. Relaxation of all body muscles during anaesthesia may also lower the utilisation of glucose at tissue level, leading to hyperglycaemia. A significant decrease in creatinine in all groups might be the result of the well maintained renal blood flow during isoflurane anaesthesia. However, urea increased significantly in all groups. Increased hepatic urea production from amino acid degradation could also account for the observed increase in urea values (Eichner, Prior & Kvascnicka 1979). However, it is unlikely that this could be caused by renal damage because all the reported values were within the normal physiological limits. A slight variation in urea was reported after administration of xylazine in cows (Eichner *et al.* 1979) and medetomidine in goats (Hugar *et al.* 1998).

Lactate dehydrogenase showed a significant increase in groups I1 and I2. However, a significant decrease in LDH value was observed in groups I3. It is therefore unlikely that the increase in LDH was a result of injury to any particular organ because the values were within the normal physiological range. As the animals were in lateral recumbency during the period of anaesthesia, the increase in serum LDH activity may be attributed to possible muscle damage. It has been observed that isoflurane may act directly upon skeletal muscles, perhaps influencing intracellular calcium homeostasis to alter membrane permeability and increase enzyme efflux, resulting in a degree of post-anaesthetic muscle damage (Mitchell *et al.* 1999). Insulin decreased significantly after premedication and during anaesthesia in all the groups. Alpha-2 agonists have been reported to induce an increase in serum glucose by suppressing insulin release, stimulating glucagon release, or both in alpha and beta cells of the pancreas, respectively (Brockman 1981). A significant decrease in cortisol was recorded after premedication in all groups. Alpha-2 agonists have been known to influence the pituitary response and may decrease adrenocorticotropic hormone output (Masala *et al.* 1985). Various studies have shown that alpha-2 agonists reduce the perioperative levels of stress-related hormones and thus attenuate the stress response to surgery in dogs (Ambrisko & Hikasa 2002). An increase in plasma cortisol was reported in water buffaloes after administration of butorphanol and medetomidine (Malik 2008).

Interpretation of haemodynamic observations

Blood pressure (SBP, DBP and MAP) decreased significantly after premedication in all groups. Intravenous administration of alpha-2 agonists results in a transient initial hypertension followed by a prolonged hypotension (Ruffolo, Nichols & Stadel 1993). The biphasic response of blood pressure after intravenous administration of alpha-2 agonists was not recorded in the present study; instead, only hypotension was recorded. 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 and butorphanol

and induction with thiopental, a significant decrease in SBP, DBP and MAP was recorded in water buffaloes (Malik 2008). This is in agreement with the reduction in blood pressure after induction with thiopentone in the present study. Blood pressure remained significantly low in all groups during the maintenance period. Isoflurane causes a greater fall in peripheral vascular resistance with a decrease in arterial blood pressure and a smaller decrease in cardiac output in goats (Hikasa *et al.* 2002). The present study recorded that alpha-2 agonists and fentanyl produced a highly significant increase in CVP. It would appear that this haemodynamic change might be attributed primarily to the cardiovascular effect of alpha-2 agonists. The significant and prolonged increase in CVP was a likely reflection of alpha-2 agonist-induced bradycardia and possibly vasoconstriction. Other possible contributory factors include pooling of blood in the venous circulation as a result of low HR; that is, central shift of blood to the venous compartment (Venugopalan *et al.* 1994), decrease in myocardial contractility and an increase in the afterload (Serteyn *et al.* 1993). The increase in MCVP is caused by vasoconstriction as a result of stimulation of peripheral postsynaptic alpha-2 adrenoceptors (Venugopalan *et al.* 1994). A highly significant increase in CVP recorded in the present study could be attributed to the synergistic action of dexmedetomidine and fentanyl. Continued maintenance of CVP at a higher level in all groups might possibly be to the result of the depressive influence of alpha-2 agonists and fentanyl on the heart that gradually subsided with the elimination of the drugs. Compensatory mechanisms might have been affected in the present study as the CVP did not return completely to the baseline at the end. A slight decrease in CVP was recorded after thiopentone in the present study. The combination of medetomidine and butorphanol produced a highly significant increase in CVP in water buffaloes (Malik 2008).

The decrease in SpO_2 after premedication recorded in all groups was possibly to the result of a certain degree of respiratory depression. Xylazine was also reported to decrease partial pressure of oxygen in arterial blood (PaO_2) in cattle (De Moor & Desmet 1971) and goats (Kumar & Thurmon 1979). It has been reported that detomidine, medetomidine and romifidine also produce severe hypoxaemia when administered intravenously at equipotent sedative doses in conscious sheep. The hypoxaemia was not caused by hypoventilation, neither was it the result of postural changes after drug administration (Celly *et al.* 1997). A similar finding was recorded in the present study, where all three alpha-2 agonists produced a comparative degree of fall in SpO_2. Higher values of SpO_2 observed during isoflurane anaesthesia in the present study might be caused by the administration of 100% oxygen along with isoflurane. A decrease in SpO_2 after medetomidine and butorphanol was recorded in water buffaloes (Malik 2008).

A decrease in atrial depolarisation area was recorded in groups I1 and I2. A slight decrease in atrial depolarisation area was recorded after administration of medetomidine and butorphanol in water buffaloes (Malik 2008). Similar observations have been reported after medetomidine administration in goats (Hugar *et al.* 1998). The QS pattern recorded in all the animals suggested that the impairment of conduction is above the bifurcation of the bundle of His. Decrease in conduction velocity in the AV-node because of vagal activity after xylazine administration has been reported in water buffaloes (Peshin & Kumar 1979). A decrease in the T wave amplitude was noticed in group I2. The deviation and inconsistency of the T wave might be to the result of transient changes in acid base balance on account of retention of CO_2 (Peshin & Kumar 1979). The increase in T wave duration observed in this study might be caused by the slow repolarisation of ventricles (Tilley 1985). Similar changes were reported after the administration of xylazine in water buffaloes (Peshin & Kumar 1979) and medetomidine and ketamine in goats (Hugar *et al.* 1998). An inverted T wave was recorded in one animal of group I2 at 15 min. The increase in amplitude of the T wave and inverted T wave might be the result of myocardial hypoxia (Tilley 1985), as decreased SpO_2 was recorded at the same time intervals. Electrocardiograms of different groups revealed sinus bradycardia. Alpha-2 agonists are known to cause different types of arrhythmias. Bradycardia and AV blocks probably occur from increased vagal activity caused by the vasopressor effect of xylazine (Knight 1980). The PR interval decreased in group I2 after premedication. The PR interval changes are dependent on conduction velocity between the SA node and AV conduction system. A prolonged PR interval would indicate a decrease in conduction velocity within the atrial muscles, the SA conduction system, or both (Venugopalan *et al.* 1994). An increased QT interval was recorded in all groups. PR and QT intervals are governed by sympathetic neurons and these may or may not be activated together. Furthermore, the increase in PR and QT intervals might be caused by a decreased HR and corresponding increase in oxygen requirement of the heart after xylazine or medetomidine administration (Peshin & Kumar 1979). A reciprocal relation between the HR, PR and QT intervals exists (Tilley 1985).

Conclusion

On the basis of the findings of the study described above, it is concluded that dexmedetomidine, in combination with fentanyl, thiopental sodium and isoflurane, produced better clinical, physiological and haemodynamic stability in water buffaloes than medetomidine and xylazine.

Acknowledgements

Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

G.D.S. (Indian Veterinary Research Institute) performed experimental trials. P.K. (Indian Veterinary Research Institute) developed the concept and designed the experiment. A. (Indian Veterinary Research Institute) monitored haemodynamic parameters. H.P.A. (Indian Veterinary Research Institute) recorded clinicophysiological parameters. A.M.P. (Indian

Veterinary Research Institute) measured haematobiochemical parameters. M.M.S.Z. (Indian Veterinary Research Institute) coordinated different activities. J.S. (Indian Veterinary Research Institute) performed experimental trials and collected blood samples. R.T. (Indian Veterinary Research Institute) performed experimental trials and collected blood samples.

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