RESPIRATORY DEPRESSION EFFECTS OF DIAZEPAM, MIDAZOLAM PREMEDICATION AND THIOPENTAL-ISOFLURANE COMBINATION ANAESTHESIA IN WATER BUFFALOES (*BUBALIS BUBALIS*)

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ABSTRACT

Study was designed to evaluate respiratory depression and blood gas, acid base and electrolyte changes in twelve water buffaloes subjected to general anaesthesia while performing diaphragmatic herniorrhaphy in dorsal recumbency. Animals were randomly divided into two groups comprising of six animals each. Anaesthetic protocol included midazolam (Group I) and diazepam (Group II) preanaesthesia 0.2 mg/kg bwt. followed by induction with thiopental and maintenance with isoflurane in both the groups. Estimation of blood gas, acid base and electrolyte values showed no major alterations in blood electrolyte (Sodium, Potassium, Chloride) values in both groups. However, the electrolyte values were better maintained in animals subjected to midazolam preanaesthesia (Group II). Blood gas and acid base values in two groups showed significant decrease in blood pH, PaO_2 and increase in $PaCO_2$ during the anaesthesia indicating respiratory acidosis. It was observed that respiratory acidosis was the predominant acid base alteration in animals subjected to general anaesthesia owing to dorsal recumbency and depressed respiration.

Keywords: *Bubabus bubalis*, buffaloes, isoflurane, diazepam, midazolam, diaphragmatic hernia, anaesthesia

INTRODUCTION

General anaesthesia is a challenge for large animal anesthesiologists. Bovine are generally not considered good subjects to general anaesthesia. Regurgitation, delayed recovery and disturbances in haemodynamic parameters in dorsal and lateral recumbency are the important complications. Diaphragmatic hernia is one of the very common affections of water buffaloes. Disease results in high morbidity and mortality. General anaesthesia in dorsal recumbency is prerequisite for diaphragmatic herniorrhaphy in bovine. Combinations of preanaesthetic, induction and maintenance agents have been used for inducing general anaesthesia in bovine (Thurmon *et al*., 1996). Preanaesthetic agents help in reducing the dose of induction agents, improve the quality of induction, and minimises the adverse effects caused by injectable or inhalant maintenance agents. Diazepam and midazolam are commonly used benzodiazepine preanaesthetic agents. Diazepam enhances the effect of neuro transmitter gamma-aminobutyric acid, by binding

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to the benzodiazepine site on the receptor leading to central nervous system depression (Riss *et al*., 2008). It possesses anxiolytic, anticonvulsant, hypnotic, sedative, skeletal muscle relaxant and amnestic properties (Mandrioli *et al*., 2008). It has been used as preanaesthetic agent for buffaloes in combination with thiopental sodium (Mirakhur *et al*., 1989). Midazolam, a short-acting imidazo-benzodiazepine has a potent anxiolytic, hypnotic, sedative, anticonvulsant and skeletal muscle relaxant action. It provides minimal adverse effects on cardiovascular system (Riss *et al*., 2008; Barash *et al*., 2009). Thiopentone sodium, an ultrashort acting barbiturate, has been used in buffaloes for induction and maintenance (Alexander *et al*., 1985; Gwinnutt, 1996). Combination of thiopentone sodium with various preanaesthetics or tranquilizers reduces its induction and maintenance dose and helps in reducing the recovery time (Mirakhur *et al*., 1989).

For maintenance of anaesthesia parenteral or inhalant routes can be followed. Intravenous anaesthesia is easy to administer, technically simple and requires no sophisticated equipment. However, when used for long procedures, supplemental doses of intravenous anaesthesia may lead to drug over dose, increased recumbency, delayed recovery and greater involvement of renal and hepatic systems. Inhalant anaesthetics are considered better for maintenance of long and risky procedures as they provide control on depth of anaesthesia, facilitate rapid recovery and their systemic absorption is less when compared to injectable anaesthetic agents. A combination of injectable and inhalant anaesthetic drugs can be used to achieve many of the ideal properties of general anaesthesia (Kehlet and Dahl, 1993).

Isoflurane and halothane, the most commonly used inhalant anaesthetic agents for maintenance produces dose dependent depression of the respiratory system. Isoflurane exists as a clear non-flammable, halogenated methyl ethyl ether with a blood-gas partition coefficient of 1.46 (Stoelting, 1999; Steffey and Mama, 2007). It is a safer inhalant anaesthetic agent for use in veterinary patients. Its combination with midazolam has been reported suitable for maintenance of haemodynamic and fluid balance studies in pigs (Filho *et al*., 1998), dogs (Husby *et al*., 1998) and horses (Gangl *et al*., 2001). Isoflurane maintains respiratory parameters better than halothane. A reduction of tidal volume is observed with halothane. However, increase in tidal volume and decrease in the respiratory rate is observed at the beginning of deep anaesthesia withisoflurane. Isoflurane also has minimal effects on bronchial smooth muscle secretion (Alexander *et al*., 1985; Muir *et al*., 1995; Gwinnutt, 1996; Mutoh *et al*., 1997). Because the animals being operated for diaphragmatic herniorrhaphy have high chances of respiratory insufficiency, especially due to lateral and dorsal recumbency and at the time of opening of thoracic cavity, any change in the acid base balance may have metabolic consequences. Affect on respiratory system makes the monitoring of arterial blood gas, acid base and electrolyte changes essential whenever, administration of general anaesthesia is performed. Monitoring of blood electrolyte and acid base changes is useful as it is important to compensate adverse changes at the earliest. Continuous monitoring of these parameters during the anaesthetic procedure may increase the safety of the procedure. Present study was conducted to monitor alterations in blood gas, acid base and electrolyte changes in animals being operated for diaphragmatic herniorrhaphy in general anaesthesia.

MATERIALS AND METHODS

The study included twelve female buffaloes subjected to general anaesthesia for the repair of diaphragmatic hernia. History regarding age, body weight, pregnancy and parturition status was recorded. Condition was diagnosed by radiography, ultrasonography and rumenotomy. Rumen was emptied completely by performing laparo-rumenotomy a day before diaphragmatic herniorrhaphy. No feed or water was given till surgery and the animals were maintained on intravenous fluids. Animals were restrained in lateral recumbency before starting the anaesthetic protocol by randomly dividing them into two groups of six animals each. Midazolam or Diazepam 0.2 mg/kg b.wt. were used intravenously as preanaesthetic drugs in Groups I and II, respectively. Anaesthesia was induced with 5% Thiopental, 5 minutes after administration of preanaesthetic drugs in both groups (I_5). Initially two-third of the total calculated dose (10 mg/kg b.wt.) was given, which was topped up "till effect". Animals were intubated with cuffed endotracheal tube of appropriate sizes and connected to the anaesthesia workstation. Isoflurane 2.0 to 3.0% was used during induction, followed by 1.5 to 2.0% for maintenance. After proper induction as judged from eye reflexes and muscle relaxation, animals were positioned in dorsal recumbency for performing diaphragmatic herniorrhaphy. The respiration throughout the procedure was either spontaneous and was maintained by IPPV at a pressure of approx. 20 cm of H_2O, 3 to 4 times a minute throughout the time for which thorax was open. One ml heparinised blood samples from auricular artery were collected for estimation of acid base and electrolyte status at zero interval (base), 5 minutes after preanaesthetic administration (P_5) and 5 minutes after induction of anaesthesia (I_5). Thereafter, samples were taken at 15, 30, 45, 60, 90 and 240 minutes intervals. Acid base and electrolyte parameters like pH, PaO_2 (mm of Hg), $PaCO_2$ (mm of Hg), HCO_3^-(mmol/L), Na^+(mmol/L), K^+(mmol/L) and Cl^-(mmol/L) were estimated using IBL-80 Radiometer blood gas analyzer. Data was analysed using SPSS 16.0 version for windows. Analysis of Variance (ANOVA) and paired t test were used to compare the means among two groups at various time intervals and to compare the mean values at various intervals from base values.

RESULTS AND DISCUSSION

Recurrent tympany, anorexia and decreased milk yield were the common complaint in all the animals presented. All animals under study were female buffaloes and were either in advanced stages of pregnancy or had calved recently. The animals had a mean body weight of 310.00±8.72 kg and 329.00±9.49 kg, and mean age of 4.50±0.52 and 5.63±0.45 years in Groups I and II, respectively. Four animals of Group I and 3 animals in Group II were in their advanced stage of pregnancy varying from 6 to 8 months, other animals had a history of recent calving varying from 1 to 3 months. Pregnancy is one of the important predisposing causes of diaphragmatic hernia. Weight of the fetus and presence of potential foreign bodies are some of the important factors responsible for diaphragmatic hernia (Singh *et al*., 1977). Buffaloes suffering from diaphragmatic hernia are generally poor risk patients. Surgery and anaesthetic procedures in compromised patients should be therefore, aimed to keep various physical, haematobiochemical and acid base parameters within the normal range. The combination anaesthetic protocol used in both

groups was satisfactory considering induction, maintenance, muscle relaxation, ease of intubation and recovery.

Diaphragmatic herniorrhaphy was performed in dorsal recumbency. Dorsal recumbency is abnormal position for the animal. Large size of body viscera may be responsible for additional stress on the animal. Regurgitation and aspiration pneumonia, have been reported to be the most important complications in cattle subjected to general anaesthesia (Weaver, 1971). Complete emptying of rumen by laparo-rumenotomy one day before surgery helped in preventing these complications. Complete emptying of rumen was also helpful in reducing the weight of body viscera and ease of operative manoeuvres.

Analysis of arterial blood samples showed no significant alterations in sodium, potassium and chloride levels in both the groups (Table 1). Values fluctuated within normal limits throughout the observation period. Comparison between two groups showed no definitive information. The results indicated that anaesthetic combinations used in the study did not have any untoward effect on blood electrolyte values. Regulation of electrolyte levels is important as any disturbance can be having serious consequences. Changes in sodium can have significant impact on the plasma osmolality (Marks and Taboada, 1998). Kidneys regulate sodium and water balance in the body (Di Bartola, 1998). Potassium plays a critical role in neuromuscular transmission. Imbalances in potassium manifest skeletal muscle dysfunction (Phillips and Polzin, 1998). Progressive decrease in plasma chloride during anaesthetic procedure suggests a tendency towards hypochloraemic acidosis which is one of the major complications during spontaneous ventilation (Bailey and Pablo, 1998). No significant changes in plasma electrolyte concentrations during the anaesthetic period and between two groups indicated that anaesthetic combinations used in the study did not have any untoward effect on the blood electrolyte values. Similar observations have been reported after thiopental-halothane anaesthesia in calves (Singh, 1988), diazepam-thiopental administration in calves (Mirakhur *et al*., 1988) and by diazepam, thiopental and halothane anaesthesia in buffaloes (Singh *et al*., 2013). Administration of intravenous fluids during perioperative period might also be helpful in maintenance of electrolyte balance.

Arterial blood pH values showed non-significant decrease (Table 2) immediately after administration of preanaesthetics in both groups. After induction, pH decreased non significantly in Group I, whereas it decreased significantly ($P<0.05$) in Group II. In animals of Group I, significant ($P<0.01$) decrease in pH from base value was observed from 30 to 60 minutes of maintenance. pH values however, showed recovery and reached close to their respective base levels at the end of observation period (240 minutes). In animals of Group II, highly significant ($P<0.001$) decrease in pH from base levels was observed during 15 to 90 minutes of maintenance. However, 240 minutes values were near the base levels. Comparison between two groups revealed no significant variation at various anaesthetic intervals. Trends in arterial O_2 saturation were similar to pH (Table 2). No significant change was observed following administration of preanaestetic agents in both the groups. Decrease was however, observed after induction. Decrease was statistically significant at 10 and 30 minutes intervals in Group II. In comparison, the decrease in PaO_2 of Group I were statistically non significant. Improvement in PaO_2 values was observed after 45 minutes, so that the values at the end of observation period were near

the base levels. Comparison between two groups revealed no significant difference in PaO_2. Values of $PaCO_2$ in the animals of both the groups showed non-significant increase after premedication. In Group I, significant increase ($P<0.05$) from base value was observed 5 minutes after induction and thereafter, highly significant increase was recorded from 15 to 60 minutes interval. In group II, significant increase in $PaCO_2$ from base value was observed between 10 to 60 minutes intervals. Normalization of values was observed afterwards in both the groups and values after 90 minutes were near the base levels. Comparison between two groups showed significantly ($P<0.05$) high values in Group II at 5, 10, 30 and 45 minutes intervals. Bicarbonate (HCO_3^-) levels (Table 2) showed non significant decrease in Group II. However, values in Group I, were near their base levels. Comparison between two groups showed significant ($P<0.05$) lowered values of HCO_3^- levels in Group II in comparison to Group I throughout the observation period. However, recovery values were comparable between the groups and values were close to the base levels.

Decreased pH, PaO_2 and increase in $PaCO_2$ levels during anaesthetic period indicated that the changes in blood pH were of respiratory origin. Lateral and dorsal recumbency and opening of thorax might be responsible for respiratory acidosis. Ventilation-perfusion mismatch during dorsal recumbency might have led to respiratory compromise. The findings are in corroboration with the observations of Fujimoto *et al.* (1985); Singh *et al*. (2013) who reported decreased pH, decreased PaO_2 and increased $PaCO_2$ during halothane anaesthesia in sheep and buffaloes. Similar findings were recorded by Hikasa *et al.* (2000) during isoflurane anaesthesia in sheep. Ruminants are generally prone to hypoxemia in lateral and dorsal recumbency. Large animals tend to develop a big imbalance in the distribution of ventilation relative to pulmonary blood flow. This results in a large alveolar to arterial oxygen tension difference (Tagawa *et al*., 1994).

Depression of the respiratory and cardiovascular centres has been reported to be a common finding throughout general anaesthesia in horses, with more dramatic effects induced by dorsal than lateral recumbency (Hall *et al*., 1968; Day *et al*., 1995). Arterial hypoxemia may be induced by hypoventilation, alveolar-capillary membrane diffusion impairment, low inspired oxygen concentration, mismatching of pulmonary ventilation and perfusion, intrapulmonary shunt, decreased cardiac output and pharmacological depression of the respiratory centre by anaesthetic drugs (Hall *et al*., 1968; Fujimoto *et al*., 1985; Muir and Hubbell, 1991).

Decreased PaO_2, pH and HCO_3 values makes it desirable that buffaloes being administered general anaesthesia should be mechanically ventilated. Comparing two preanaesthetic agents the electrolyte, acid base and PaO_2 values were better maintained by midazolam. However, maintenance of acid base balance in both groups was not adequate. Natalini *et al*. (2008) attributed the changes in respiratory, heart rate and arterial blood pressure to the anaesthetic drugs and lack in response to respiratory stimulation from elevated $PaCO_2$. Drugs for premedication are recommended to avoid respiratory depression and irritation in the anaesthesia with isoflurane (Mutoh *et al*., 1997). However, in present study most of the changes in both groups did not have any significant difference. Values seemed primarily to be respiratory in origin.

Table 1. Blood electrolyte (mmol/L) profile in different groups at various intervals.

Parameter	Group	Base	Time (Minutes)							
			Pre-anaesthesia	Induction	Maintenance					Recovery
		0	5 (P_5)	10 (I_5)	15	30	45	60	90	240
Na	I	139.00±1.75	142.17±1.77	141.17±1.78	140.17±1.78	141.17±1.78	142.17±1.78	141.17±1.7	139.00±1.75	139.00±1.75
	II	137.00±1.63	140.00±1.63	138.00±1.63	138.50±1.64	140.00±1.64	138.50±1.65	138.00±1.63	137.00±1.63	141.17±1.70
K	I	4.28±0.10	4.17±0.10	4.24±0.10	4.16±0.10	4.19±0.10	4.03±0.10	4.03±0.11	4.08±0.10	4.15±0.09
	II	4.06±0.15	3.92±0.15	3.90±0.15	3.92±0.15	3.88±0.15	3.89±0.22	3.89±0.20	3.89±0.20	3.85±0.15
Cl	I	111.00^{b}±1.79	113.00^{b} ±1.79	115.00^{b}±1.78	109.00±1.79	109.00±1.79	110.00±1.79	109.00±1.79	109.00±1.79	111.00±1.79
	II	102.30^{a}±1.14	103.30^{a}±1.15	104.33^{a}±1.14	108.33±1.15	107.33±1.15	106.33±1.14	107.33±1.14	105.33±1.14	103.33±1.16

Values with different alphabets differ significantly between the groups at the corresponding intervals (P<0.05)

Table 2. Blood acid base profile in different groups at various intervals.

Parameter	Group	Time (Minutes)								
		Base	Pre-anaesthesia	Induction	Maintenance					Recovery
		0	5 (P_5)	10 (I_5)	15	30	45	60	90	240
pH	I	7.39±0.04	7.36±0.04	7.30±0.03	7.24±0.04	7.19^{**}±0.04	7.17^{**}±0.03	7.14^{**}±0.04	7.34±0.03	7.37±0.04
	II	7.45±0.07	7.38±0.03	7.32^{*}±0.04	7.28^{***}±0.03	7.20^{***}±0.03	7.18^{***}±0.03	7.15^{***}±0.02	7.27^{***}±0.03	7.38±0.03
PaO_2	I	77.00±1.39	75.67±1.42	70.80±3.85	67.00±2.58	70.33±1.76	73.67±1.43	75.67±1.43	77.67±1.43	79.67±1.43
	II	80.67±1.56	78.33±1.80	68.50^{**}±1.52	67.00±1.90	63.67^{*}±5.27	72.50±0.99	73.17±5.12	79.67±1.56	81.67±1.56
$PaCO_2$	I	42.33±1.60	43.16^{a} ±2.44	48.50^{a*}±1.52	51.83^{*}±1.49	55.16^{a**}±1.66	53.50^{a**}±2.66	57.50^{***}±4.50	47.50±4.50	47.66±2.81
	II	43.16±1.24	48.83^{b}±1.24	52.16^{b**}±1.24	49.16^{*}±1.24	61.16^{b***}±1.24	62.16^{b***}±1.19	53.00^{**}±4.01	44.50±2.51	44.83±2.05
HCO_3 mmol/L	I	25.50±1.08	23.50^{b}±0.89	25.33^{b}±0.95	23.33^{b}±0.95	25.00^{b}±1.03	24.83^{b}±0.83	25.33^{b}±0.95	27.83^{b}±1.93	25.67±0.84
	II	23.50±1.23	20.33^{a}±0.84	18.83^{a}±0.79	18.16^{a}±0.792	20.16^{a}±0.48	21.83^{a}±0.83	20.22^{a}±0.75	21.83^{a}±0.70	24.22±1.30

Asterisked values differ significantly from the base value of the group (*P<0.05; **P<0.01; ***P<0.001).

Values with different alphabets differ significantly between the groups at the corresponding intervals (P<0.05).

CONCLUSIONS

Study showed that both anaesthetic combinations had no major alterations in blood electrolyte levels, however, electrolyte balance was better maintained in animals given midazolam as preanaesthetic. Significant decrease in blood pH, PaO_2 and increase in $PaCO_2$ noticed during the observation period primarily suggested respiratory acidosis which was dependent on recumbency and depression of respiratory centres by both anaesthetic combinations.

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