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Comparative evaluation of isoflurane and sevoflurane for maintenance of anaesthesia in buffaloes undergoing diaphragmatic herniorrhaphy

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ABSTRACT

The study was conducted in 12 adult female buffaloes suffering from diaphragmatic hernia (DH). The animals were randomly divided in 2 groups of 6 each. DH was repaired under general anaesthesia using glycopyrrholate-xylazine-butorphanol-thiopentone maintained with isoflurane and sevoflurane in group TI and TS, respectively. Clinical and behavioural parameters were observed during herniorrhaphy while physiological, haematological and biochemical parameters were recorded at different intervals (before rumenotomy, before premedication, 5 min after thiopentone injection, at 15 min and 30 min of inhalant anaesthesia, at recovery and at 24 h of recovery). No significant difference was seen in sedation, muscle relaxation and analgesia scores between the groups. The respiratory rate was less depressed and corneal reflex was mostly intact during maintenance in TS group. Recovery and standing with ataxia in TS group was significantly earlier than TI group. There was no significant difference in haematological and blood biochemical parameters between the groups. The results indicated that sevoflurane is a better maintenance agent than isoflurane for maintenance of general anaesthesia in buffaloes undergoing DH.

Key words: Anaesthesia, Buffalo, Isoflurane, Sevoflurane

Diaphragmatic hernia (DH) is an internal hernia where abdominal viscera pass into the chest cavity through an acquired rupture or congenital aperture in the diaphragm. It results in 100% death if left untreated (Krishnamurthy *et al.* 1985). Treatment of the disease involves two stage surgical procedure, viz. laparo-rumenotomy and diaphragmatic herniorrhaphy. Laparo-rumenotomy is done under local anaesthesia with or without mild sedation. But diaphragmatic herniorrhaphy, a complex and longer duration surgery, needs general anaesthesia along with controlled/assisted ventilation.

The buffaloes reported for diaphragmatic herniorrhaphy usually belong to category IV of ASA (American Society of Anaesthesiologists) classification and their physiological status is compromised. Also, a "low pressure-low flow" circulatory state exists during anaesthesia in adult buffaloes in supine position during trans-abdominal diaphragmatic herniorrhaphy, which is aggravated during pregnancy (Peshin *et al.* 1987). So, an anaesthetic combination that produces least depression of cardiopulmonary system is preferred. An intravenous agent like thiopentone on repetitive use, for longer duration surgeries, has a cumulative effect, resulting in prolonged recovery (Thurmon *et al.* 1996). The metabolism and elimination of thiopentone will increase the stress on already compromised liver and kidneys. However, inhalant anaesthetics like isoflurane and sevoflurane have very little metabolism inside the body. The anaesthetic depth can be easily controlled and recovery is faster once the inhalant is discontinued.

At present, isoflurane is the most widely used inhalant agent in veterinary as well as medical anaesthesia but sevoflurane is gaining popularity among professionals. Its qualities are lesser blood gas partition coefficient, which provides more rapid induction of and recovery from anaesthesia; a rapid alteration of anaesthetic depth (Kazma and Ikeda 1988); non-irritant to respiratory mucosa; offers a more stable heart rate profile in animals (Ebert *et al.* 1995); does not lead to 'coronary steal' in dogs with myocardial ischemia (Akazawa *et al.* 1988); causes rapid recovery in cattle (seller *et al.* 2013); and maintains better anaesthesia in puppies (Jadon *et al*. 2008). However, the other pharmacodynamic properties are alike isoflurane.

There is no information available regarding the use of sevoflurane as maintenance agent in the water buffaloes, however, the pharmacokinetic characteristics of sevoflurane promises it to be a better agent for maintenance of anaesthesia in buffaloes like cattle and dog. So, it was planned to evaluate the comparative efficacy of isoflurane and sevoflurane in clinical cases of buffaloes undergoing diaphragmatic herniorrhaphy.

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MATERIALS AND METHODS

Buffaloes (12) presented for treatment of DH were used for the study. The DH was suspected on the basis of clinical symptoms such as recurrent tympany, recent history of parturition, black hard scanty faeces and refractory to medicinal treatment. It was confirmed by radiography followed by rumenotomy. Ruminal contents were evacuated completely and diaphragmatic herniorrhaphy was done the next day.

The animals were randomly divided in 2 groups (TI and TS) having 6 animals each. All the animals were premedicated with glycopyrrolate (0.01 mg/kg, IM)-xylazine (0.05 mg/kg, IM)-butorphanol (0.03 mg/kg, IV) combination. At the onset of ataxia, the animals were restrained in lateral recumbency on a padded bed for induction of anaesthesia. The animals were intubated after induction with 5% solution of thiopentone sodium (5.0 mg/kg, IV). The endotracheal tube was connected to large animal anaesthetic machine. For maintenance of anaesthesia, isoflurane (group TI) or sevoflurane (group TS) was used through agent specific vaporizer along with oxygen through a semi-closed rebreathing system. The animals were restrained in dorsal recumbency for surgery through post-xiphoid trans-abdominal approach. Concentration of inhalation anaesthetic agents was regulated to maintain adequate depth of anaesthesia after monitoring body reflexes and animal's response to surgical stimulation. Inhalation of anaesthetic agent was discontinued at the completion of surgery. All the animals were administered normal saline throughout the period of surgery.

The clinical and behavioural observation were recorded during anaesthesia, however, the physiological, haematological and blood biochemical parameters were recorded before rumenotomy, the next day before premedication, at 5 min of anaesthetic induction, at 15 min and 30 min during inhalation using iso-/sevoflurane, at recovery and at 24 h of recovery.

Clinical observations: A fixed criterion as per Bodh *et al*. (2015) was followed for evaluation of quality of anaesthesia. Scoring was done by a blind folded observer to assign numerical values; starting from 1 to 4 (1-poor, 2-fair, 3-good, 4-excellent) for the quality of premedication, induction, maintenance and recovery. Qualitative or subjective effects (sedation, analgesia, muscle relaxation) of drugs were judged by observing physical response of the medicated animal to surgical stimulation during diaphragmatic herniorrhaphy. Numerical values starting from 0 to 3 (0–nil, 1-mild, 2-moderate, 3-deep) were used for scoring sedation, analgesia and muscle relaxation during maintenance of anaesthesia. The animals were observed to record different behavioural changes including loss and regain of body reflexes in relation to time during anaesthesia. Rectal temperature along with ambient temperature, heart rate and respiratory rate were recorded at each interval.

Blood samples were collected from jugular vein at each designated interval in 2 sets of test tubes, containing 3.8% sodium fluoride solution (10 mg/ml of blood) and heparin (10 IU/ml) for estimation of glucose and other biochemical parameters, respectively and plasma was harvested by centrifugation at 3,000 rpm for 20 min and stored at –20 °C. Also, at each designated interval, 2 ml of blood was collected in vials containing EDTA for haematology. Haemoglobin (Hb), packed cell volume (PCV), total erythrocyte count (TEC), total leukocyte count (TLC), neutrophil (N%) and lymphocyte (L%) were estimated in automatic analyser MS4 (Melet Schloesing Laboratoires - , France) after collecting blood samples in vials containing EDTA. Plasma glucose, lactate dehydrogenase (LDH), alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP), gammaglutamyl transferase (GGT), plasma urea, creatinine, total plasma proteins (TP), albumin and globulin were estimated using commercially available Transasia XL (EM 200™ - automated random access clinical chemistry analyzer, Erba Mannheim, Germany) system pack kits procured from M/S Transasia Biomedical Limited, Mumbai. Sodium, potassium, chloride and calcium were analyzed by automatic electrolyte analyser Easylyte™ (Easylyte™-Electrolyte analyser for Na, K, Cl, Ca/Li. Medica Corporation, USA).

The statistical analysis of data was done by one-way-analysis of variance and Duncan's multiple range test (DMRT).

RESULTS AND DISCUSSION

All the animals included in the study were of ASA category IV. The average duration of illness, surgery, administration of inhalants as well as average age and body weight of the buffaloes of group TI and TS, and the quality of anaesthesia during herniorrhaphy are given in Table 1. The comparisons of behavioural parameters are given in

Table 1. Mean±S.E. of quality of anaesthesia in buffaloes maintained on iso-/sevoflurane

Parameter	TI	TS
Duration of illness (days)	65.83±13.0	38.7±8.37
Age of animals (years)	5.75±1.23	6.50±0.85
Body weight of animals (kg)	294.16±36	353.3±15.47
Time of surgery (min)	35.16±2.94	46.0±3.18
Time of inhalation of anaesthetic agent (min)	46.33±2.70	60.0±3.93
Score of clinical observations		
Premedication	3.00±0.26	2.83±0.21
Induction	3.33±0.33	3.17±0.31
Maintenance	2.83 ±0.31	3.50±0.34
Recovery	3.00±0.45	3.50±0.22
CNS sedation	2.33±0.21	2.00±0.26
Analgesia	2.67±0.21	3.00±0.0
Muscle relaxation	2.67 ±0.21	2.50±0.22

Table 2. Mean±SE of behavioral characteristics of anaesthesia in buffaloes maintained on iso-/sevoflurane

Parameter	TI	TS
Muzzle dryness°	16.50±1.20	13.17±1.08
Weak time°°	13.33±1.33	11.17±0.95
Down time°°	20.00±1.32	21.67±2.82
Loss of palpebral reflex*	2.17±0.48	1.83±0.31
Relaxation of jaw muscle*	2.50±0.34	2.50±0.22
Loss of tongue reflex*	2.17±0.31	1.83±0.17
Loss of swallowing reflex*	3.00±0.26	2.67±0.21
Intubation*	3.50±0.34	3.17±0.31
Regain of alar reflex†	6.00±1.37^{B}	1.67±0.62^{A}
Extubation†	10.00±1.32	7.67±0.96
Regaining of muscle tone†	16.67±1.69	15.0±2.60
Regaining of head righting reflex†	23.67±2.32	23.17±4.61
Return to sternal recumbency†	31.83±4.29	30.00±3.87
Standing with ataxia†	62.83±6.05^{B}	42.50±4.51^{A}
Complete recovery†	72.50±4.96^{B}	51.33±3.13^{A}

°After administration of glycopyrrolate;°°after administration of xylazine; *after administration of thiopentone; †after discontinuation of sevoflurane/isoflurane; means with different superscripts (A/B) in a row show significant difference between groups (P<0.05).

Table 2. There was no significant difference in clinical observations between the groups. Induction score was consistently very good in both the groups owing to pharmacokinetic and muscle relaxant properties of thiopentone. The synergism of thiopentone with α_2-agonists and opioids decreases its dose for induction of anaesthesia in the water buffalo (Malik 2008, Singh *et al.* 2013). In the present study, thiopentone @ 5 mg/kg was found excellent for induction of anaesthesia in buffaloes premedicated with glycopyrrolate-xylazine-butorphanol. There was significant difference (P<0.05) between the groups in regain of alar reflex after discontinuation of inhalation agent (Table 3). The time of muzzle movement, standing with ataxia and complete recovery was significantly lower in buffaloes maintained on sevoflurane than on isoflurane. The substitution of fluorine for chlorine in sevoflurane decreases its blood gas partition coefficient and so the blood solubility which allows a rapid increase in alveolar anaesthetic concentration during induction and a faster decrease during recovery, thus shorter anaesthetic induction and recovery times (Stoelting 1999). The duration of recovery to standing has always been shorter with sevoflurane than with isoflurane in horses, sheep and dogs (Hikasa *et al.* 2000, Johnson *et al.* 1998, Kazama and Ikeda 1988).

A significant decrease in rectal temperature (RT) was recorded (Table 3) from pre-operative value in both groups during the anaesthettic period (mainly at 15–30 min of inhalation anesthesia). This might be attributed to a decrease in the skeletal muscle tone, reduced metabolic rates, muscle relaxation, along with depression of thermoregulatory center and vasodilatation (Singh *et al.* 2013, Bodh *et al*. 2015). Hypothermia tends to be the most common response, particularly when opioids are used in the presence of other CNS depressants (Branson *et al.* 2001).

Respiratory rate decreased significantly from preoperative value in group TI after induction and during inhalation, however, in group TS the decrease was non-significant during inhalation. Sevoflurane and isoflurane reportedly caused dose dependent decrease in respiratory

Table 3. Mean±SE of rectal temperature, heart rate and respiratory rate in buffaloes undergoing diaphragmatic herniorrhaphy after induction with thiopentone and maintenance with iso-/sevoflurane

Parameter (Units)	Before rumen-otomy	Diaphragmatic herniorrhaphy							
		Before drug admn	At 15 min of glycopy-rrolate	At 15 min of xylazine	At 5 min of thiope-ntone	At 15 min of inhalation anaesthesia	At 30 min of inhalation anaesthesia	At recovery	At 24 h of recovery
Rectal temperature (°C)									
TI	37.80^{bc}± 0.38	36.87^{abc}± 0.37	36.92^{abc}± 0.36	36.78^{ab}± 0.37	36.50^{a}± 0.34	36.37^{a}± 0.36	36.30^{a}± 0.36	36.53^{a} ± 0.40	37.97^{c}± 0.23
TS	37.24^{ab}± 0.22	37.02^{ab}± 0.50	37.17^{ab}± 0.36	36.95^{ab}± 0.38	36.43^{ab}± 0.31	36.30^{a}± 0.32	36.23^{a}± 0.30	36.67^{ab} ± 0.25	37.45^{b}± 0.35
Respiratory rate (breaths/min)									
TI	14.33^{e}± 0.62	12.00^{bc}± 0.58	12.50^{cd}± 0.50	11.17^{bc}± 0.40	07.17^{a}± 0.40	10.33^{b}± 0.67	10.50^{b}± 0.56	16.67^{f}± 0.72	14.17^{Bde}± 0.75
TS	12.00^{b}± 0.52	12.00^{b}± 0.89	11.83^{b}± 0.48	10.33^{b}± 0.62	8.17^{a}± 0.48	11.33^{b}± 0.62	12.67^{b}± 1.41	16.17^{c}± 0.54	12.33^{Ab}± 0.42
Heart rate									
TI	56.33^{ab}± 2.09	58.17^{ab}± 2.99	63.17^{b}± 3.29	57.33^{ab}± 3.89	56.17^{ab}± 3.47	54.33A^{ab}± 3.16	52.67 ^{a}± 2.85	58.83^{ab}± 2.85	56.17^{ab}± 2.34
TS	56.67^{a}± 2.62	61.83^{a}± 4.51	65.67^{a}± 3.98	59.83^{a}± 3.47	59.50^{a}± 3.30	58.33B^{a}± 1.89	58.33^{a}± 1.82	64.17^{a}± 1.94	58.17^{a}± 2.93

Means with different superscripts (A/B/C) in a column show significant difference between groups (P<0.05). Means with different superscripts (a/b) in a row show significant difference within group (P<0.05).

rate and an increase in $PETCO_2$ (end tidal concentration of CO_2) in dogs, horses, and goats when maintained at one MAC (Aida *et al.* 1996, Galloway *et al.* 2004, Hikasa *et al.* 1998, Johnson *et al.* 1998, Mutoh *et al.* 1997). Alpha 2-agonist and butorphanol might be also associated with respiratory depression (Sinclair 2003). Heart rate increased significantly in both groups at 15 min of glycopyrrolate due to its parasympatholytic action. The heart rate decreased in both groups after xylazine injection as reported by Potaliya (2015). During inhalation of either isoflurane or sevoflurane, there was decrease in heart rate which increased at recovery and stabilized near base value at 24 h of recovery. The cardiovascular effects of sevoflurane are similar to isoflurane as both anaesthetics cause dose dependent decrease in blood pressure, cardiac output and systemic vascular resistance in humans, dogs, horses, sheep and goats (Aida *et al.* 1996, Ebert *et al.* 1995, Hikasa *et al.* 1994, 1998, 2000, Mutoh *et al.* 1997, Steffy and Mama 2007, Stoelting 1999). The buffaloes maintained with sevoflurane had more uniform cardiac rhythm than with isoflurane. Heart rate increased in both groups at recovery due to decrease in blood pressure, cardiac output and systemic vascular resistance causing stimulation of baroreceptor reflex (Stoelting 1999).

The pre-operative PCV of group TI (26.78±2.32%) was significantly lower than group TS (36.52±3.81%) due to longer duration of illness and lesser Hb (9.90± 0.76 g/dl) concentration in animals of group TI. This difference was maintained throughout the period of study irrespective of inhalant agent administered. There was no significant difference in Hb, TEC, TLC, N% and L% between the groups.

A significant increase in plasma glucose level was observed in both the groups during anesthesia due to increased sympathetic stimulation (Mirakhur *et al.* 1984), inhibition of insulin release and gluconeogenesis in liver (Gasthuys *et al.* 1987) and lower the utilization of glucose during anaesthesia. However, no significant difference was recorded between 2 groups. An increase in blood glucose level in buffaloes after butorphanol-medetomidine-halothane (Malik 2008), after midazolam-butorphanol-isoflurane (Bodh *et al.* 2015) and after glycopyrrolate-xylazine-ketamine/propofol-isoflurane (Potaliya 2015) was also reported.

The lactate dehydrogenase (LDH) level was high (3954.50± 639.50 IU/L for TI and 2904.83± 671.68 IU/L for TS) preoperatively, which increased after rumenotomy, at recovery and at 24 h of recovery; but no significant difference was recorded between and within the groups. Tear in muscles of diaphragm and injury to muscles by

Table 4. Mean±SE of different biochemical parameters in buffaloes undergoing diaphragmatic herniorrhaphy using iso-/sevoflurane as maintenance agent

Parameters (units)	Before rumen-otomy	Diaphragmatic herniorrhaphy					
		Before drug admn.	At 5 min of thiope-ntone	At 15 min of inhalation anaesthesia	At 30 min of inhalation anaesthesia	At recovery	At 24 h of recovery
Total plasma proteins (g/dl)							
TI	7.52^{bc}±0.53	7.97^{c}±0.45	7.59^{c}±0.33	6.26^{ab}±0.63	6.67^{abc}±0.18	6.00^{a}±0.26	7.79^{c}±0.38
TS	7.13^{bc}±0.33	7.75^{c}±0.41	7.02^{bc}±0.39	6.34^{ab}±0.39	6.15^{ab}±0.29	5.65^{a}±0.16	7.72^{b}±0.29
Plasma urea (mg/dl)							
TI	63.75^{a}± 4.36	80.35^{b}±4.80	85.55^{bc}±4.70	90.10^{bc}±5.05	92.50^{bc}±4.02	96.78^{c}±4.36	95.45^{c}±4.57
TS	52.33^{a}± 4.30	68.37^{b}±3.47	72.07^{bc}±4.46	81.48^{cd}±3.44	86.08^{de}±2.77	95.08^{e}±4.30	96.43^{e}±3.59
Plasma creatinine (mg/dl)							
TI	1.85^{a}±0.08	2.25^{b}±0.11	2.28^{b}±0.10	2.32^{bc}±0.13	2.29^{b}±0.14	2.32^{bc}±0.12	2.65^{c}±0.10
TS	2.32^{a}±0.16	2.59^{ab}±0.14	2.64^{ab}±0.14	2.81^{b}±0.09	2.67^{ab}±0.15	2.74^{ab}±0.14	2.53^{ab}±0.14
Sodium (mmol/l)							
TI	128.28^{a}± 0.93	127.08^{a}±1.95	128.87^{a}±0.54	129.27^{a}±1.48	127.77^{a}±1.12	128.88^{a}±0.90	136.23^{b}±1.81
TS	125.73^{a}±1.29	130.72^{ab}±1.62	132.52^{ab}±4.44	132.50^{ab}±2.83	133.05^{ab}±2.84	129.42^{ab}±1.89	137.77^{b}±2.68
Potassium (mmol/l)							
TI	3.98^{c}±0.06	3.77^{bc}±0.27	3.19^{a}±0.08	3.09^{a}±0.19	3.24^{ab}±0.20	3.39^{ab}± 0.19	3.96^{c}±0.21
TS	3.33b^{c}±0.21	3.29^{abc}±0.14	2.932^{ab}±0.18	2.98^{ab}±0.13	2.79^{a}±0.14	2.75^{a}± 0.13	3.51^{c}±0.22
Chloride (mmol/l)							
TI	93.63^{a}±2.29	97.80^{ab}±1.18	97.90^{ab}±2.67	102.57^{b}±3.01	99.38^{ab}±2.16	100.30^{b}± 0.77	103.28^{b}±1.09
TS	92.88^{a}±1.35	97.93^{ab}±3.50	97.53^{ab}±3.71	99.07^{ab}±3.84	99.05^{ab}±3.82	98.23^{ab}± 3.20	104.53^{b}±3.96
Calcium (mmol/l)							
TI	0.79^{a}±0.06	0.98^{ab}±0.06	0.94^{ab}±0.08	0.93^{ab}±0.04	0.91^{ab}±0.07	0.89^{ab}±0.06	1.04^{b}±0.06
TS	0.69±0.07	0.98±0.13	0.78±0.20	0.77±0.16	0.74±0.14	0.77±0.14	0.98±0.13

Means with different superscripts (A/B/C) in a column show significant difference between groups (P<0.05). Means with different superscripts (a/b) in a row show significant difference within group (P<0.05).

potential foreign bodies might be responsible for increased LDH level preoperatively. Incision of muscles during rumenotomy and herniorrhaphy as well as restraining might be the cause of rise in LDH level before premedication and after herniorrhaphy. The levels of AST, ALT, and GGT were not significantly different between the 2 groups and within the groups. Total plasma proteins revealed a significant decrease (Table 4) in the both groups, without significant difference between the groups, during the period of anaesthesia may be attributed to expanded intravascular volume due to shifting of fluid from extravascular compartment to intravascular compartment to maintain normal cardiac output (Brock 1994), protein degradation caused by surgical stress and trauma (Traynor and Hall 1981) and fluid therapy causing haemodilution during intraoperative period. Plasma urea and creatinine levels at 24 h of recovery were significantly ($P<0.05$) higher than the pre-operative values in both groups but there was no significant difference between the groups. The variation within the group was also non-significant as per the criteria laid by Hou *et al.* (1983) for clinical cases.

Both isoflurane and sevoflurane produce similar mild, reversible, dose related decrease in renal blood flow and glomerular filtration rate (GFR) due to decrease in cardiac output (Stoelting 1999). Sevoflurane is primarily metabolized in liver unlike methoxyflurane where both hepatic and renal sites are important (Kharasch *et al.* 2001). The buffaloes in this study were maintained on a semi-close rebreathing system using oxygen flow rates (7–8 l/min) almost twice of their metabolic requirement to dilute and flush out the compound A which might have been generated by interaction of sevoflurane with CO_2 absorbent in the breathing circuit (Muir and Gadawski 1998). The buffaloes anaesthetized with sevoflurane in the present study had no complaint of renal problem till 6 months post-operatively. Hikasa *et al.* (1994, 2000) also reported no renal tubular injury in cattle and sheep maintained on sevoflurane. The buffaloes were hyponatremic, hypochloremic and hypocalcemic preoperatively due to DH. The plasma level of these electrolytes improved at 24 h of recovery, without any significant difference between the groups, might be due to corrected physiology after surgery and infusion of normal saline during anaesthesia to maintain cardiac output. Owners were also advised to add salt in animals drinking water offered post-operatively. Potassium plasma concentration varied non-significantly at different intervals in both groups.

Comparative analysis of the cost of both anaesthetic combinations, as per the current market rates, was done considering equal body weight and same duration of surgery for diaphragmatic herniorrhaphy in buffaloes. The anesthetic combination used for group TS was almost two times costlier than for group TI.

It may be concluded that Sevoflurane is better maintenance agent than isoflurane after glycopyrrholate-xylazine-butophanol-thiopentone anaesthesia in buffaloes, owing to lesser respiratory depression, earlier recovery and similar haemato-biochemical changes but the cost of sevoflurane may outweigh its advantages in large animal practice.

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