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Comparative Evaluation of the Isoflurane-sparing Effects of Butorphanol and Pentazocine in Buffaloes Undergoing Diaphragmatic Herniorrhaphy

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ABSTRACT

Background: Isoflurane is commonly used as an inhalant anaesthesia in animals. Foreign body syndrome ultimately results into diaphragmatic hernia which is common in buffaloes. Diaphragmatic herniorrhaphy is generally performed under isoflurane anaesthesia. But there are adverse effects of isoflurane like respiratory depression, hypotension, reduced cardiac output and its metabolites cause atmospheric pollution. So, the present study was planned with the hypothesis that inclusion of opioid analgesic in the balanced anaesthesia might have isoflurane sparing effect.

Methods: The present study was conducted in 15 female buffaloes which were suffering from diaphragmatic hernia which was diagnosed by radiography and later confirmed on rumenotomy. Animals were randomly divided in three groups - group I (Atropine (0.04 mg/kg) - xylazine (0.05 mg/kg) - propofol (till effect) - isoflurane; AXPI), group II (Atropine - xylazine - butorphanol (0.03 mg/kg) - propofol - isoflurane; AXBPI) and group III (Atropine - xylazine - pentazocine (0.75 mg/kg) - propofol - isoflurane; AXPPI) having five animals in each. Group I was taken as control as no analgesic was used in anaesthetic combination for animals of this group. The total isoflurane vapour delivered (mL) for the total duration of anaesthesia was calculated and the values so obtained were equated to 400 kg body weight and 40 minute duration for each animal for statistical comparison.

Result: The Mean volume of isoflurane (ml) utilized for group I (65.58±8.8) was significantly higher than in Group II (38.54±5.7) and Group III (41.01±4.8). There were no significant changes in the haematological and biochemical profile of these buffaloes among three groups.

Key words: Atropine, Buffaloes, Butorphanol, Diaphragmatic herniorrhaphy, Isoflurane, Pentazocine.

INTRODUCTION

Diaphragmatic hernia is a common sequel of foreign body syndrome in buffaloes. Isoflurane is the most commonly used maintenance agent in balanced anaesthetic protocol for diaphragmatic herniorrhaphy in buffaloes (Chaudhary and Tayal 2020). Sparing effect is the effect of a less essential drug in the balanced anaesthesia, such that it reduces the requirement of main drug. When isoflurane is used as sole anaesthetic agent it may lead to inadequate peri- and post operative analgesia, as alone it is not sufficient to abolish appropriately autonomic and nociceptive responses to the surgical stimulus (Steffey and Mama 2007). The reduction in isoflurane requirements for maintaining general anaesthesia is important as use of less isoflurane will obtund common adverse effects of isoflurane like respiratory depression, hypotension and reduced cardiac output (Hikasa *et al*., 2002). Isoflurane and its metabolic products are also hazardous to the atmosphere and cause atmospheric pollution (Joubert 1999). Therefore, any reduction in dose of isoflurane will be advantageous for patient, surgical team as well as environment. Opioid analgesics are reported to have inhalant sparing effect and reduce the minimum alveolar concentration (MAC) required to maintain surgical plain of anesthesia owing to their potent analgesic effect (Tranqulii *et al*., 2007). The inclusion of butorphanol in the anaesthetic protocol had reduced isoflurane requirement in dogs (Ko *et al*., 2000) and cattle (Senthilkumar *et al*., 2013). Sharma *et al*. (2019) have reported that pentazocine produces good analgesia in

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balanced anaesthetic combination for buffaloes undergoing diaphragmatic herniorrhaphy. However, there is scarcity of literature showing the sparing effect of inclusion of these analgesics on isoflurane in buffaloes until now. So it was decided to work out isoflurane sparing effects of butorphanol and pentazocine in buffaloes undergoing diaphragmatic herniorrhaphy (DH) premedicated with xylazine and atropine with propofol induction as it was hypothesized that butorphanol and pentazocine might spare the isoflurane significantly.

MATERIALS AND METHODS

Animals

A total of 15 buffaloes suffering from diaphragmatic hernia were selected after clinical examination, radiography and rumenotomy which were reported to Veterinary Clinical Complex, LUVAS, Hisar during the period of July, 2019 to April, 2020. DH was performed next day of the rumenotomy. Animals were kept off feed and off water after rumenotomy and weighed before doing herniorrhaphy for calculating the dose of drugs used for general anaesthesia. Blood samples were collected for haematological and biochemical variables analysis of buffaloes at preoperative, during anaesthesia and at recovery. Unequal randomization method was followed in the study.

Anaesthetic procedure

All buffaloes were premedicated with atropine (0.04 mg/kg; Atro (1.0 mg/mL); Prem Pharmaceuticals Ltd., Indore, Madhya Pradesh, India), then after 15 minutes with xylazine (0.05 mg/kg; Xylazin (20 mg/mL); Indian Immunologicals Ltd., Guntur, Andhra Pradesh, India). Buffaloes were easily restrained in lateral recumbency for induction of anaesthesia after fifteen minutes of xylazine administration. Then, butorphanol (0.03 mg/kg; Butadol 2 (2 mg/mL); Neon Laboratories Ltd., Mumbai, India) or pentazocine (0.75 mg/kg; Riddof (30 mg/mL); Neon Laboratories Ltd., Mumbai, India) was administered intravenously, in group II and III respectively. However, no opioid analgesic was given in group I. After 5 minutes of analgesics administration induction was done using propofol (1.3 mg/kg; Neorof (10 mg mL-1); Neon Laboratories Ltd., Mumbai, India). After induction, intubation was performed with cuffed endotracheal tube (inner Diameter 20mm, Surgivet, Smith medical company, UK) and connected to large animal anaesthetic machine (Vetland; Vetland medical sales and services, Louisville, KY, USA). For maintenance, isoflurane (Isotroy 250; Troikaa pharmaceuticals Ltd., Gujarat, India) was used through agent specific vaporizer (Dräger, USA) with oxygen through a semi closed rebreathing system. The oxygen flow rate was 10 L/minute for first 3 minutes and then reduced to 6 L/minute along with variable vaporizer setting and uniform surgical plane of surgical anaesthesia was maintained by monitoring body reflexes and animal's response to surgical stimulation. A fixed criterion was followed for evaluation of quality of anaesthesia. Scoring was done to assign numerical values; starting from 1 to 4 (1-poor, 2-fair, 3-good, 4-excellent) for premedication quality, induction quality, maintenance quality and recovery quality. Qualitative and 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-no effect, 1-mild effect, 2-moderate effect, 3-deep effect) was used for sedation, analgesia and muscle relaxation during maintenance of anaesthesia. The animal was placed in dorsal recumbency for surgery through post-xiphoid trans-abdominal approach for diaphragmatic herniorrhaphy. All the animals were administered normal saline (10 mL/kg/hr; 0.9% NSS (1000 mL); Soxa Formulations andResearch Pvt. Ltd., Gujarat, India) throughout the period of surgery. Isoflurane was discontinued with the application of last skin suture but animals were allowed to breathe oxygen until swallowing and coughing reflexes returned. Buffaloes were recovered in the same room, first they placed to lateral recumbency and after removal of endotracheal tube, the animals were placed in sternal recumbency. Post-operatively; strepto-penicillin (5 g Animal-1; Dicrysticin-S (15,00,000 units Procaine Penicillin-G, I.P. and 5,00,000 units of Penicillin G Sodium I.P., Streptomycin – 2.5 g); Zydus AHL - Cadila Healthcare Ltd., Vadodra, India) and meloxicam (0.5 mg/kg; Meloxivet-20 (20 mg/mL); Carus Laboratories Pvt. Ltd., New Delhi, India) were administered intramuscularly after recovery and for five and three days respectively along with antiseptic dressing of incision sites.

Calculation of amount of liquid isoflurane utilized

The changes made in the fresh gas flow rate (FGF) and vaporizer setting at different times was recorded. The data so obtained was calculated for the quantity of isoflurane consumed in different groups by following formulas.

Isoflurane vapour delivered (mL) =Vapourizer setting (%) x FGF (Litre/minute) x Duration (minute) x 10

The total isoflurane vapour delivered (mL) for the total duration of anaesthesia was calculated by summing the isoflurane vapour delivered for each of the FGF and vapourizer setting employed. The total isoflurane vapour value so obtained was equated to 400 kg body weight and 40 minute duration of surgery for statistical comparison as follows:

Isoflurane vapour delivered for 400 kg and 40 minute basis (mL) = (Total isoflurane vapour delivered (mL) x 400 x 40)/ (Body weight x Duration of maintenance).

The volume of liquid isoflurane consumed was calculated by using Avagadro's principle and correction factors were applied for effect of ambient temperature and atmospheric pressure of Operation Theater

= (Isoflurane vapour delivered for 400 kg and 40 minute basis (mL) x181.4) x (ambient temp/ 273) x (760/ barometric pressure mm/Hg)

Blood samples were processed for haematology using Automatic haematoanalyzer (MS4; MeletSchloesing Laboratoires, Evalic, France)) and and plasma from heparinized blood was obtained by centrifugation at 2500 rpm for 15 minutes for biochemical variables using chemistry analyzer (EM 200; automated random access clinical chemistry analyzer, Erba Mannheim, Germany) with their respective commercially available kits.

Statistical analysis

The data so obtained was analysed by one-way-analysis of variance and Duncan's multiple range tests.Differences were considered significant at a value of $p < 0.05$.

RESULTS AND DISCUSSION

The mean volume of isoflurane utilized by buffaloes of control

Table 1: Haematological parameters (Mean ± Standard Error) of female buffaloes under study at different time intervals.

Variable	Group	Time point		
		Pre-anaesthesia	Anaesthesia	Recovery
Haemoglobin (g dL^{-1})	I	9.1 ± 0.3	8.2 ± 0.3	8.4± 0.2
	II	10.2 ± 0.7	9.0 ± 0.6	8.8 ± 0.4
	III	8.9 ± 0.7	8.5 ± 0.6	8.6 ± 0.7
Packed cell volume (%)	I	27.0 ± 1.3	24.2 ± 0.5	26.4 ± 0.9
	II	31.6 ± 0.9	26.6 ± 1.2	26.0 ± 1.4
	III	27.2 ± 1.5	25.8 ± 1.6	26.0 ± 1.2
Total leukocyte Count (x 10^3 mm^{-3})	I	11.2 ± 1.3	8.9 ± 1.1	8.6 ± 0.7
	II	12.9 ± 1.1	12.4 ± 0.7	12.5 ± 1.2
	III	12.1 ± 1.2	10.2 ± 1.4	10.1 ± 1.6

Table 2: Biochemical parameters (mean ± standard deviation) of female buffaloes under study at different time intervals.

Variable	Group	Time point		
		Pre-anaesthesia	Anaesthesia	Recovery
Cortisol (µg dL^{-1})	I	18.7 ± 2.8	49.8 ± 14.4	22.7 ± 3.9
	II	24.45 ± 5.9	30.7 ± 8.7	20.3 ± 4.1
	III	16.3 ± 4.4	11.9 ± 5.1	20.6 ± 8.4
Sodium (mmol L^{-1})	I	131.1 ± 0.4	131.8± 0.4	132.1 ± 0.3
	II	131.1 ± 0.2	131.8 ± 0.2	132.1± 0.1
	III	131.1 ± 0.1	131.8± 0.1	132.1± 0.0
Potassium (mmol L^{-1})	I	2.9 ± 0.1	2.6 ± 0.1	2.5 ± 0.1
	II	2.4 ± 0.2	2.9 ± 0.1	2.7 ± 0.2
	III	2.6 ± 0.1	2.8 ± 0.1	3.0 ± 0.1
Blood Glucose (mg dL^{-1})	I	108.8 ± 11.6	195.8 ± 17.5	267.8 ± 30.0
	II	100.6 ± 20.7	241.6 ± 25.2	198.6 ± 24.2
	III	115.2 ± 9.4	239.0 ± 17.5	227.2 ± 16.3
Urea (mg dL^{-1})	I	80.6 ± 3.8	84.2 ± 8.7	83.1 ± 11.6
	II	74.3 ± 13.2	72.3 ± 12.8	85.8 ± 11.8
	III	44.5 ± 5.3	56.1 ± 14.0	32.5 ± 6.2
Total proteins (g dL^{-1})	I	7.9 ± 0.4	7.5 ± 0.4	7.4 ± 0.2
	II	8.2 ± 0.4	7.3 ± 0.5	8.2 ± 0.3
	III	7.0 ± 0.9	7.6 ± 0.3	8.4 ± 0.4
Albumin (g dL^{-1})	I	2.4 ± 0.2	2.4 ± 0.1	2.5 ± 0.1
	II	2.7 ± 0.1	2.5 ± 0.1	2.9 ± 0.3
	III	2.2 ± 0.3	2.4 ± 0.1	2.7 ± 0.2
Globulin (g dL^{-1})	I	5.5 ± 0.3	5.0 ± 0.3	4.9 ± 0.2
	II	5.6 ± 0.3	4.8 ± 0.4	5.2 ± 0.2
	III	4.8 ± 0.6	5.1 ± 0.3	5.7 ± 0.3
Creatinine (mg dL^{-1})	I	0.8 ± 0.3	0.9 ± 0.2	0.9 ± 0.3
	II	1.0 ± 0.4	1.1 ± 0.5	0.9 ± 0.4
	III	0.2 ± 0.0	0.5 ± 0.1	0.4 ± 0.1
Aspartate amino transferase	I	280.4 ± 34.2	291.4 ± 21.2	288.3 ± 31.5
(IU L^{-1})	II	317.2 ± 22.3	290.9 ± 27.7	297.6 ± 34.6
	III	271.8 ± 57.4	273.1 ± 39.2	277.5 ± 32.8
Alanine amino transferase	I	57.1 ± 12.4	59.2 ± 15.1	66.1 ± 17.3
(IU L^{-1})	II	69.9 ± 10.7	53.9 ± 11.8	50.3 ± 11.3
	III	37.5 ± 6.8	33.2 ± 1.2	33.5 ± 1.7

group (I; AXPI) was 65.6 ±8.8 mL. However, the volume of isoflurane utilized by group II was 38.5 ± 5.7 mL and by group III was 41.0 ± 4.8 mL. The percentage reduction from control group was 41.2% for AXBPI and 37.5% AXPPI group. There was significant reduction in the amount of isoflurane used in group II and Group III in comparison to group I. However, there was no significant variation in any of the haematological variables (packed cell volume, total lecucocyte count and haemoglobin) and biochemical variables (cortisol, blood glucose, urea, total proteins, albumin, globulin, aspartate amino transferase, alanine amino transferase, creatinine) as well as electrolytes (sodium and potassium) among the three groups (Table 1 and Table 2). Weight and duration of anaesthesia of female buffaloes under study is given in Table 3.

The results of study supports the results of previous workers that opioid analgesics are reported to have inhalant sparing effect in different species (Tranqulii *et al*. 2007; Ko *et al*. 2000; Senthilkumar *et al*. 2013). Based on a search of literature, this is the first report evaluating the isoflurane sparing effect of butorphanol and pentazocine in buffaloes. There was significant reduction in the percentage utilization of isoflurane in both the groups from control group but there was no significant difference between group II and group III. It is possible that change in nociceptive stimuli, surgeon variation and anesthetist variation may affect inhalant anaesthesia requirement (Torske *et al*. 1998). This clinical study used same nociceptive stimuli (DH), surgeries were performed by the same surgeons, and depth of anesthesia was controlled by the same anesthetist, which reduced variability regarding isoflurane requirement for maintenance. Senthilkumar *et al*. (2013) observed 18.7% and 14.63% reduction in MAC of isoflurane when cattle calves were premedicated with opioids like butorphanol tartrate (0.02 mg/kg) and buprenorphine hydrochloride (0.006 mg/kg) respectively. Ilkiw *et al*. (2002) reported a 19% reduction in isoflurane requirement in cats premedicated with butorphanol. Ramakrishnan *et al*. (2019) reported that both buprenorphine and butorphanol had sparing effect on isoflurane in cattle anaesthetized with midazolam (0.3 mg/kg) - ketamine (11 mg/kg) mixture and among that butorphanol (0.4 mg/kg) had higher isoflurane sparing effect than buprenorphine (0.01 mg/kg). However, Butorphanol did not affect the halothane MAC in ponies (Matthews and Lindsay 1990; Doherty *et al*. 1997) or dogs (Quandt *et al*. 1994), but it decreased the isoflurane MAC in dogs (Ko *et al*., 2000). In rabbits butorphanol pretreated with saline reduced MACiso by 7.63% where as pretreatment with meloxicam (0.3 and 1.5 mg/kg) caused significant reduction of 11.3% and 12.41% respectively (Patricia *et al*. 2006). Doherty *et al*. (2004) concluded that the MAC of isoflurane decreased by 29.7% following IV administration of morphine (2 mg/kg) and 29.4% following that of morphine plus flunixine (1.5 mg/kg). Isoflurane sparing effect of pentazocine was evaluated for the first time and it caused significant reduction in isoflurane required in buffaloes than in control group but no parallel studies are available in any species in the literature.

Table 3: Weight and duration of anaesthesia of female buffaloes under study.

Animal	Group I	Group II	Group III
A	305	315	498
B	355	337	305
C	327	235	365
D	332	315	275
E	296	273	340

There are limitations in this study as numbers of animals were less in the study and research study on more number of animals might help in standardization of the isoflurane sparing effect of analgesics in buffaloes and other animals. Other analgesics might also helpful in reducing isoflurane utilization during surgery. Therefore, more research is needed in the upcoming future in this field.

CONCLUSION

Inclusion of opioid analgesic (butorphanol/pentazocine) significantly reduced the quantity of isoflurane required for maintenance of anaesthesia in buffaloes undergoing diaphragmatic herniorraphy anaesthetized by atropine-xylazine-propofol combination. Butorphanol has the highest sparing effect (41.2%) on isoflurane followed by pentazocine (37.5%).

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Conflict of interest

Authors declare no conflict of interest.

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