The Haryana Veterinarian (March, 2024) **63(SI),** 49-52 ISSN 0033-4359 (P) **Research Article**

ANALGESIC EFFICACY OF BUPRENORPHINE HYDROCHLORIDE AND FENTANYL CITRATE FOR THE POSTOPERATIVE PAIN MANAGEMENT IN BUFFALOES

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Received: 06.06.2023; Accepted: 22.07.2023

ABSTRACT

The objective of the present study was to evaluate the analgesic efficacy of buprenorphine hydrochloride and fentanyl citrate for the postoperative pain management in buffaloes undergoing diaphragmatic herniorrhaphy. The study was conducted in 12 buffaloes undergoing diaphragmatic herniorrhaphy under general anesthesia. The buffaloes were randomly divided into two groups of six each. The analgesic efficacy was evaluated based on; the clinical examination, haemato-biochemical assessment and the pain score. No significant change was recorded in the clinical as well as haemato-biochemical parameters of buffaloes. The pain score were found significantly lower in buffaloes administered fentanyl citrate than buprenorphine hydrochloride. The study concluded fentanyl citrate to be superior analgesic than buprenorphine hydrochloride in buffaloes undergoing diaphragmatic herniorrhaphy.

Keywords: Buffaloes, Buprenorphine Hydrochloride, Fentanyl Citrate, Pain

How to cite: Deepanshu, Chaudhary, R.N., Kumar, S., Tiwari, D.K. and Dinesh (2024). Analgesic efficacy of buprenorphine hydrochloride and fentanyl citrate for the postoperative pain management in buffaloes. *The Haryana Veterinarian* **63(SI)**: 49-52.

Pain is an important animal welfare issue, not least in bovines (Huxley and Whay, 2006). Klinck and Troncy (2016) stated that the physiology involved in the processing of pain is similar amongst vertebrate animals including humans. One reason for the inconsistence in understanding of pain relief for cattle is the inadequate ability to assess pain (Flecknell, 2008). Pain assessment based on physiological parameters has proven to be inapplicable as these are often unspecific and sensitive to stress as well as being difficult to measure on-farm (Hansen, 1997). Therefore, pain assessment based on behavior has received increasing attention (Gleerup *et al.*, 2015).

Diaphragmatic herniorrhaphy in buffaloes is a surgical procedure done under general anesthesia and involves separation of adhesions and retracting hernial contents into the abdominal cavity. The surgery induces severe pain and may leads to shock if not managed properly. Opioids have been found to be better in management of visceral pain than NSAIDs. There has been no study in buffaloes evaluating fentanyl citrate and buprenorphine hydrochloride on the basis of cow pain scale and Botucatu pain scale to assign objective score. Many opioids analgesics like butorphanol, pentazocine, fentanyl citrate, buprenorphine hydrochloride and NSAIDs like meloxicam have been tried in management of pain in buffaloes undergoing diaphragmatic herniorraphy. None has been assessed objectively on pain scales for large animals. So, it was decided to evaluate fentanyl citrate and buprenorphine hydrochloride on the basis of cow pain scale and Botucatu pain scale along with their systemic effects in buffaloes.

Fentanyl is a synthetic μ-opioid receptor agonist that has been used clinically in several pharmaceutical formulations as an analgesic and tranquilizer in buffaloes (Singh *et al.*, 2013) and dogs (KuKanich and Clark, 2012). It binds to opioid receptors raising the pain threshold or decreasing perception of pain by acting at the dorsal horn of the spinal cord and mesolimbic system (Yaksh, 1997), resulting in subsequent reduction in the release of transmitter substances, such as substance P, dopamine and norepinephrine thereby inhibiting synaptic transmission of nociceptive input (Inturrisi, 2002).

Buprenorphine is a partial μ-opioid agonist-antagonist derived from thebaine. Its agonistic properties are approximately 30 times more than that of morphine. Onset of action is relatively slow, requiring 20-30 minutes to reach its full effect. Its analgesic action may last as long as 8 to 12 hrs. It causes minor respiratory depression that can be reversed with naloxone or naltrexone. Dose of buprenorphine in cattle varies from 0.005 mg to 0.001 mg per kg body wt. IM (Lumb and Jones, 1996).

MATERIALS AND METHODS

The study was conducted in 12 buffaloes undergoing diaphragmatic herniorrhaphy. The buffaloes were randomly divided into two groups (Group B: n=6, administered buprenorphine hydrochloride and Group F: n=6, administered fentanyl citrate).

The condition of diaphragmatic hernia was diagnosed by radiography and confirmed on rumenotomy. The ruminal contents were evacuated completely and the

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foreign body, if any was removed through left flank rumenotomy. The buffaloes were kept off feed and off water after rumenotomy. The diaphragmatic herniorrhaphy was done on the next day of rumenotomy.

After pre-anaesthetic medication with atropine (0.04 mg/kg body weight, IM), (Khan *et al.*, 2007) and xylazine (0.05 mg/kg body weight, IM), the buffaloes were restrained in lateral recumbency for induction of anesthesia. All the buffaloes were administered normal saline throughout the period of surgery.

Fifteen minutes after xylazine administration buprenorphine hydrochloride (6 µg/kg body weight) or fentanyl citrate (2 µg/kg body weight) was administered intravenously, in group B and group F, respectively. Induction of anesthesia was achieved using propofol (1.3 mg/kg body weight, IV). The intubation was done with cuffed endotracheal tube of size 20-22 and was connected to *Vetland*® large animal inhalant anesthetic machine. For maintenance of anaesthesia, isoflurane was used through agent specific vaporizer along with 100% oxygen through a semi-closed rebreathing system. The oxygen flow rate and vaporizer setting were initially kept on higher side (i.e. 10 litres/min, 5%, respectively) which were gradually reduced after 10-15 minutes (6 litres/ min, 1.2%, respectively) to maintain uniform surgical plane of anesthesia for every buffalo.

The buffaloes were made in dorsal recumbency for herniorrhaphy through post-xiphoid trans-abdominal linea alba approach. Post-operatively; all the buffaloes received strepto-penicillin twice a day for five days. Group B and Group F animals were administered buprenorphine hydrochloride (BID) and fentanyl citrate (QID) at designated intervals for 24 hours and then meloxicam @ 0.3 mg/kg for the next two days.

To judge the efficacy of the analgesic drug regimens pain evaluation and clinical examination was done; preoperatively, 1 hr, 1½ hrs, 2 hrs, 6 hrs, 12 hrs and 24 hrs after surgery. Respiration rate (per minute), heart rate (per minute) and rectal temperature (ºF) were recorded. The pain scoring system was done as per Cow pain scale given by Gleerup *et al.* (2015) and Botucatu uni-dimensional pain scale given by Oliveira *et al.* (2014). The cow pain scale and Botucatu pain scale was based on the behaviour signs which reflect pain sensation. Six behaviours were included in the cow pain scale: 'attention towards surroundings', 'head position', 'ears position', facial expressions', 'response to approach' and 'back position'. Botucatu pain scale was based on behavior parameters: 'locomotion', 'interactive behavior', 'activity', 'appetite' and miscellaneous behaviors (wagging of tail abruptly, kicking/foot stamping, licking the surgical wound, hind limb extend caudally when in standing posture etc.). Score 0 to 2 was given for pain scoring in both the pain scale. Blood samples were collected aseptically from jugular venipuncture at pre-operatively i.e before diaphragmatic herniorraphy and 1 hr, 2 hrs, 6 hrs, 12 hrs and 24 hrs after surgery. Hematological parameters like hemoglobin, packed cell volume, total leucocyte count, differential leucocyte count and total erythrocyte count were estimated in automatic analyzer MS4 after collecting blood in vials containing EDTA. Blood samples for analysis of biochemical parameters were collected in two sets of test tubes. One set of test tube were containing 3.8% sodium fluoride solution (10 mg/ml of blood) for estimation of glucose and the other containing heparin (10 IU/ml) for estimation of aspartate amino transferase (AST), blood urea nitrogen, serum creatinine and serum cortisol. Biochemical parameters were analyzed with EM 200™ analyzer using commercially available Transasia XL system pack kits. Cortisol level was assessed by using calbioteck (a life science company) serum ELISA kit.

The statistical analysis of data was done by one way -ANOVA with linear repeated measure by SPSS software. All the data values were expressed as Mean± Standard error of mean (Mean±S.E). P-value less than 0.05 considered as statistically significant.

RESULTS AND DISCUSSION

The buffaloes survived after surgery was included for results interpretation. Between the groups, no significant difference was observed in heart rate, respiratory rate and rectal temperature at different time intervals and the observations remained within normal range throughout the study (Table 1). In haematological parameters, no significant difference was observed in haemoglobin, packed cell volume, total leucocyte count, total erythrocyte count and differential leucocyte count, when compared between the groups. However, in group B, total leucocyte count increased significantly at 2 hrs and 6 hrs postoperatively in comparison to preoperatively (Table 2).

There was no significant difference in the level of blood glucose (mg%) when compared between the groups (Table 3). Blood glucose increased significantly at 1 hr post-operatively in both the groups from preoperative level. It might be due to increased sympathetic stimulation caused during the restraint of buffaloes resulting in increased secretion of adrenocortical hormone (Mirakhur *et al.*, 1984). Hyperglycaemia might also be attributed to alpha2-adrenergic inhibition of insulin from beta-pancreatic cells and to increased glucose production in liver (Gasthuys *et al.*, 1987). The increase in plasma glucose

Table 1. Effects of different analgesics in similar anaesthetic combinations on physiological parameters in buffaloes undergoing diaphragmatic herniorrhaphy (Mean± S.E.)

Groups	Parameters	Preop	1 Hr	1.5 Hrs	2 Hrs	6 Hrs	12 Hrs	24 Hrs
Group B	HR[1](per minute)	67.50^{bc}±1.06	63.17^{a}±1.30	63.83^{ab}±1.22	65.00^{abc}±0.93	66.33^{abc}±1.15	66.67^{abc}±1.20	68.00^{c}±1.37
	RR[2] (per minute)	17.00±0.58	14.67±0.56	15.17±0.54	15.33±0.61	15.83±0.65	16.33±0.61	16.83±0.70
	RT[3] (F°)	100.55±0.43	100.12±0.61	100.13±0.59	100.13±0.58	100.3±0.50	100.37±0.50	100.47±0.46
Group F	HR (per minute)	66.67^{c}±0.42	60.00^{a}±0.42	61.67^{a}±0.52	62.67^{ab}±0.42	65.33^{bc}±0.34	66.17^{c}±0.36	66.83^{c}±0.29
	RR (per minute)	17.17^{d}±0.32	12.33^{a}±0.31	13.83^{ab}±0.25	14.50^{abc}±0.31	15.67^{bcd}±0.34	16.33^{cd}±0.27	16.83^{d}±0.31
	RT (F°)	100.62±0.10	100.32±0.07	100.25±0.07	100.35±0.07	100.43±0.06	100.65±0.09	100.58±0.08

Mean with different superscripts (a,b,c,d) in a row show significant differences within group (P<0.05).
1. Heart rate, 2. Respiratory rate, 3. Rectal temperature

Table 2. Effects of different analgesics in similar anaesthetic combinations on haematological parameters in buffaloes undergoing diaphragmatic herniorrhaphy (Mean± S.E.)

Groups	parameters	Preop	1 Hr	2 Hrs	6 Hrs	12 Hrs	24 Hrs
Group B	Hb[1] (g%)	10.33±0.38	9.70±0.36	9.85±0.38	10.02±0.39	10.13±0.38	10.28±0.38
	PCV[2] (%)	33.60±1.33	29.82±0.95	31.02±1.21	31.58±1.22	32.52±1.46	33.2±1.53
	TLC[3] (10^3/cumm)	7.43^{a}±0.60	8.88^{ab}±0.87	10.05^{b}±0.99	11.00^{b}±1.09	8.77^{ab}±0.65	7.08^{a}±0.34
	TEC[4] (10^6/cumm)	5.78±0.36	5.47±0.34	5.45±0.38	5.60±0.38	5.79±0.35	5.82±0.35
Group F	Hb (g%)	10.30±0.15	9.37±0.21	9.48±0.21	9.65±0.21	10.05±0.17	10.18±0.17
	PCV (%)	30.80±0.51	27.55±0.53	28.30±0.58	29.00±0.60	30.07±0.55	30.55±0.58
	TLC (10^3/cumm)	8.31±0.94	9.13±0.94	8.40±0.72	8.66±0.80	7.72±0.50	7.30±0.50
	TEC (10^6/cumm)	5.30±0.12	4.72±0.11	4.88±0.11	5.02±0.17	5.16±0.11	5.01±0.13

Mean with different superscripts (a,b) in a row show significant differences within group (P<0.05).
1. Haemoglobin, 2. Packed cell volume, 3. Total leucocyte count, 4. Total erythrocyte count

Table 3. Effects of different analgesics in similar anaesthetic combinations on biochemical parameters in buffaloes undergoing diaphragmatic herniorrhaphy (Mean±S.E.)

Groups	parameters	Preop	1 Hr	2 Hrs	6 Hrs	12 Hrs	24 Hrs
Group B	Glucose (mg%)	105.33^{a}±3.86	115.50^{b}±3.02	108.50^{a}±3.21	106.67^{a}±3.04	106.83^{a}±4.22	106.50^{a}±3.06
	BUN[1] (mg%)	19.60±2.01	19.77±1.99	19.75±1.97	19.77±1.97	19.67±1.99	20.62±1.98
	Creatinine (mg%)	1.87^{a}±0.23	2.03^{ab}±0.24	2.17^{bc}±0.23	2.28^{cd}±0.23	2.42^{cd}±0.22	2.59^{d}±0.21
	AST[2] (IU/L)	191.65±21.28	197.78±23.82	203.88±23.16	201.18±22.66	201.73±22.99	197.78±22.18
	Cortisol (µg/dl)	25.67^{Bb}±2.13	32.28^{Cc}±2.26	30.53^{Cc}±1.27	25.40^{Cb}±1.55	22.43C^{ab}±0.7	19.03^{Ba}±0.74
Group F	Glucose (mg%)	104.83^{a}±1.85	113.67^{b}±1.78	107.83^{ab}±1.47	105.67^{a}±1.29	105.83^{a}±1.71	108.83^{ab}±1.88
	BUN (mg%)	19.08±0.71	19.55±0.70	19.78±0.92	20.03±0.91	20.28±0.87	20.15±0.85
	Creatinine (mg%)	1.76^{a}±0.04	1.94^{ab}±0.04	2.13^{abc}±0.04	2.25^{cd}±0.04	2.40^{cd}±0.04	2.52^{d}±0.05
	AST (IU/L)	203.78±8.67	217.03±10.06	223.55±9.73	223.53±9.75	216.23±9.35	210.9±9.02
	Cortisol (µg/dl)	23.77^{Bbc}±0.79	26.05^{Bc}±0.61	21.78^{Bbc}±0.61	15.65^{Aa}±0.91	13.33^{Aa}±0.93	18.08^{Bab}±0.99

Mean with different superscripts (a,b,c,d) in a row show significant differences within group (P<0.05).
Mean with different superscripts (A,B,C) in a column show significant differences between groups (P<0.05)
1. Blood urea nitrogen, 2. Aspartate amino transferase

Table 4. Effects of different analgesics in similar anaesthetic combinations on pain score as per cow pain scale and Botucatu pain scale in buffaloes undergoing diaphragmatic herniorrhaphy (Mean± S.E.)

Groups	Pain scales	Preop	1Hr	1.5 Hrs	2Hrs	6Hrs	12 Hrs	24 Hrs
Group B	Cow pain scale	4.50^{Bb}±0.43	7.00^{Cd}±0.37	6.17^{Cc}±0.31	5.67^{Cc}±0.21	4.33^{Cb}±0.21	3.83^{Bab}±0.17	3.33^{Ba}±0.21
	Botucatu pain scale	3.67^{Bb}±0.33	7.00^{Cd}±0.37	5.67^{Cc}±0.33	5.33^{Cc}±0.21	3.67^{Cb}±0.33	2.67^{Bab}±0.33	2.50^{Ba}±0.43
Group F	Cow pain scale	4.50^{Bd}±0.43	4.83^{Bd}±0.48	4.00^{Bcd}±0.26	3.67^{Bbcd}±0.33	2.50^{Bab}±0.34	2.00^{Aa}±0.52	2.83^{Babc}±0.60
	Botucatu pain scale	3.83^{Bb}±0.31	4.83^{Bc}±0.48	3.50^{Bb}±0.34	3.00^{Bb}±.29	2.00^{Aa}±.30	1.17^{Aa}±0.17	1.83^{Ba}±0.31

Mean with different superscripts (a,b,c) in a row show significant differences within group(P<0.05).
Mean with different superscripts (A,B,C) in a column show significant differences between groups(P<0.05)

after xylazine administration has also been reported in cattle (Thurmon *et al.*, 1996).

There was no significant difference observed in the values of blood urea nitrogen (mg%) when compared within and between the groups. There was no significant difference observed in the values of serum creatinine (mg%) when compared between the groups, however it increased significantly at 6 hrs, 12 hrs and 24 hrs post-operatively in both the groups (Table 3).

Stoelting (1999) described that present day volatile inhalant anaesthetics produced mild, reversible, dose related decrease in renal blood flow and glomerular filtration rate (GFR) due to decrease in cardiac output. The renal function parameters are highly influenced by an animal's state of hydration and hemodynamics during anesthesia (Nunez *et al.*, 2004). An increase in creatinine has been observed during prolonged anaesthesia (Steffy *et al.*, 1979).

No significant variation was observed in the aspartate amino transferase (IU/L) when values were compared within and between the groups at different time intervals.

Between the groups, the cortisol values differed significantly at different time intervals except at pre-operatively and at 24 hrs post-operatively between group B and group F. The cortisol level was significantly lower in group F than group B indicating less stress in buffaloes administered fentanyl citrate. In group B, the cortisol level was significantly increased at 1 hr, 2 hrs post-operatively and decreased at 24 hrs post-operatively from pre-operative level. In group F, the cortisol level was significantly decreased at 6 hrs and 12 hrs post-operatively from pre-operative and immediately (1 hr) after surgery.

In both the pain scales (Table 4); between the groups, pain score varied significantly at different intervals except that there was no significant difference observed at pre-operatively and at 24 hrs post-operatively between group B and group F. The pain score was significantly lower pain in group F than group B since 1 hr post-operatively to 12 hrs after surgery in both the pain scales. However, within the group pain was also better managed in group F than group B.

So, it was concluded that fentanyl citrate administered IV, QID is superior analgesic than buprenorphine hydrochloride in management of pain in buffaloes undergoing diaphragmatic herniorrhaphy.

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