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Comparison of Lidocaine and Lidocaine–Neostigmine for Epidural Analgesia in Water Buffalo Calves (Bubalus Bubalis)

Alaa Ghazy,[1*] Ayman Atiba,[1] Mustafa Shukry,[2] Tarek Kamal[3]
[1]Department of Surgery, Anesthesiology and Radiology, [2]Department of Physiology, [3]Department of Biochemistry, Faculty of Veterinary Medicine, Kafrelsheikh University, Kafrelsheikh, 33516, Egypt.

Key words
Buffalo calves; epidural analgesia; lidocaine; neostigmine

ABSTRACT:

The objective of this study was to evaluate and compare the effectiveness of epidural injection of lidocaine alone and lidocaine plus neostigmine for perineal analgesia in buffalo. Caudal epidural analgesia was performed in ten water buffalo calves at the sacrococcygeal extradural space. It was produced in all calves by 2% lidocaine alone (LA) (0.22 mg/kg) and with 2 weeks intervals, repeated by a combination of lidocaine–neostigmine (LN) (0.22 mg/kg and 10 µg/kg respectively). Analgesia was tested using deep pin prick stimuli. The time of onset and duration of analgesia, ataxia, heart rate (HR), respiratory rate (RR), and rectal temperature (RT) were compared among the two treatments. These parameters were determined before drug administration (baseline 0), at 10 minute intervals thereafter. haemato-biochemical parameters such as haemoglobin (Hb), packed cell volume (PCV%), total leukocyte count (TLC), total erythrocytes count (TEC), alanine aminotrans-ferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN) and blood glucose were determined. Both treatments resulted in complete analgesia of the tail, perineum, and the upper parts of the hind limbs. The onset of analgesia was faster, but not significant in LN group compared with LA group. The duration of epidural analgesia was significantly longer in LN group than in the LA group. Both treatments produced mild or moderate motor block. There was no significant alteration in HR, RR, and RT in both treatments. The haematological parameters decreased in all the groups. The biochemical parameters like ALT, ALP, BUN and glucose increased in all the animals. All haemato-biochemical parameters return to baseline levels at 24h. No adverse effects were observed in any of the buffaloe calves. In conclusion, the combination of LN produced analgesia of longer duration than LA. This combination would appear to be recommended for single-dose epidural administration in buffalo calves undergoing long surgical procedures in the perineal region.

*Corresponding Author : Alaa Ghazy; aladdinkfs@gmail.com

1. INTRODUCTION

Caudal epidural analgesia is simple, inexpensive, and requires no sophisticated equipment (Thurmon et al. 1996). It is routinely used in ruminants for obstetric manipulations, caudal surgical procedures, and as an adjunct treatment for control of rectal tenesmus (Muir et al., 2000). Lidocaine is undoubtedly the most widely used local anesthetic agents for epidural analgesia (Hall, et al., 2001). Lidocaine has excellent diffusing and penetration properties as well as rapid onset of action, but has a relatively short duration of analgesia (Day and Skarda 1991; Hall et al., 2001). Therefore, many of drugs have been co-administered with caudal lidocaine to maximize and extend the duration of analgesia (Harjai, et al., 2010).

Neostigmine, a cholinesterase inhibitor that inhibits the breakdown of endogenous acetylcholine and thus indirectly stimulates both muscarinic and nicotinic receptors, induces spinal analgesia (Bouaziz et. al., 1995; Lauretti et al., 1999). Caudal epidural neostigmine with or without local anesthetics has been used in many studies to extend the duration of analgesia in human (Lauretti et al., 1999; Alkan and Kaya, 2014; Cossu et al., 2015). Neostigmine is more recent additives to the list of epidural anesthetic for epidural analgesia (Alkan and Kaya, 2014). Only a few studies have described its use of epidural analgesia in animals. It prolongs the duration of epidural analgesia in dogs (Marucio et al. 2008; Marucio et al., 2014) and cattle (Bigham et al., 2010) compared with lidocaine alone. In equine, neostigmine co-administered with lidocaine improved and extended the duration of analgesia in the perineal region (Derossi et al., 2013). The epidural administration of neostigmine combined with lidocaine has not been investigated in buffalo. Therefore, we designed this study to determine if the addition of neostigmine to lidocaine in caudal epidural anesthesia may prolong the duration of analgesia in buffalo calves.

2. MATERIALS AND METHODS

Ten healthy male water buffalo calves (Bubalus bubalis), aged 7–10 months, weight 80–115 kg were used in this study.

Calves received each of the two treatments, with a two week interval between them. Treatment 1 was 2% lidocaine alone 0.2 mg/kg without vasoconstrictor (*Debocaine 2% Al-Debeiky Pharmaceutical Industeries Co. Egypt*) (LA), and Treatment 2 was 2% lidocaine 0.2 mg/kg combined with neostigmine 10 µg/kg (*Neostigmine, Amriya Pharm. Ind. Alex. Egypt*) (LN). The volume of the drug was expanded to 4.0 ml by adding 0.9 % normal saline solution. The animals were restrained in the standing position. The skin over the sacrococcygeal (S5 -Co1) space was clipped and prepared aseptically. About 1 ml of 2% lidocaine was injected subcutaneously in order to perform insensitive skin area. Epidural injection was made using a 20-G, 4-cm long hypodermic needle. Epidural space was recognized by the standard technique of loss of resistance to injection and the hanging drop technique. All drugs were administrated slowly over a period of about 30 seconds.

Time to the onset, duration, and anatomical distribution of the anesthesia were recorded. Time to the onset was considered as the time from the injection to loss of sensation in the perineal region. The duration time of analgesia was considered as the period between loss and reappearance of pain response in the perineal region. Loss of sensation was tested by a pin prick test (using a 22-gauge needle inserted through the skin into the underlying tissues) and by pressure from a haemostat clamp (closed to the first ratchet) applied at the tail base, anus, perineum and upper hind limb area. The response was measured each minute until no reaction occurred, and then at 10-min intervals until a response reoccurred or every 10 min until a response reoccurred. The observer assessing anesthesia was blind to the treatments.

The motor block or the presence of ataxia was examined by walking calves out of the stanchions at 10 minute intervals until 60 min, and at 15 min intervals thereafter until the end of the experiment. The ataxia was graded according to Grubb *et al.*, 2002 (Table 1).

Heart rate (HR), respiratory rate (RR), and rectal temperature (RT) were recorded before (baseline, 0) and at 10 minute intervals for 2 hours after the administration of each treatment protocol.

Blood samples were collected from the jugular vein for haemato-biochemical parameters before (0 minutes) and at 30, 60, 90 and 120 minutes, and 24 hours intervals after administration of drugs. For haematology, 3 ml venous blood was collected in test tubes containing EDTA. Haematological parameters including, haemoglobin (Hb), packed cell volume (PCV), total erythrocytes count (RBCs) and total leukocyte count (TLC). For biochemical parameters; 7 ml venous blood was collected in test tubes and serum was separated. Biochemical parameters including, alanine aminotrans-ferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN) and blood glucose.

The results were expressed as mean ± SD. Graphpad Prism version 5 software programs was used for all analyses. Changes in HR, RR, RT, time of onset and duration of analgesia were analyzed by a one-way analysis of variance and Duncan's test as a post hoc. A value of $P< 0.05$ was considered significant.

3. RESULTS

In all calves, the needle inserted into the epidural space without difficulty. All treatments were effective in producing analgesia in the tail, perineum and upper hind limb regions in all calves but at different times.

Onset times of analgesia were shorter after LN than after LA (Table 2). Duration of analgesia was significantly prolonged with LN than LA ($P<0.05$) (Table 2). Mild to moderate ataxia was observed in all animals after both LA and LN.

The HR, RR, and RT did not change significantly ($P>0.05$) from baseline values following epidural administration of LA and LN treatments (Table 3). None of the two epidural treatments produced adverse behavioral changes in these calves.

Haemato-biochemical parameters have been shown in Table 4. Hb, PCV%, RBCs and TLC decreased from 30 min to 120 min in LA and LN groups. But all those parameters returned to baseline level at 24 h in both groups. A significant increase in ALT and ALP levels at different times was observed in LA and LN groups. BUN levels were significantly increased in all animals after different treatment. A significant increase in glucose levels was observed in all animals after LA and LN treatments. At 24h, ALT, ALP, BUN and blood glucose levels return to basal levels in all groups.

Table 1: Grades of ataxia

Grade	Symptoms
Normal	Quietly standing, no change in limb position or any other signs
Mild	Slight stumbling, easily able to continue walking
Moderate	Marked stumbling, walking but very ataxic
Severe	Falling

Table 2: Anesthetic indices of epidurally administered lidocaine alone (0.2 mg/kg) (LA) and lidocaine-neostigmine (0.2 mg/kg and 10 ug/kg respectively) (LN) in buffalo calves (mean ± SD; n= 10 calves).

Indices	LA	LN
Onset of analgesia	4 ± 1	3 ± 1
Duration of analgesia	68 ± 9	134 ± 11 *

* Significant differences between duration of LA and LN.

Table 3: Effects of caudal epidural administration of lidocaine alone (LA) and lidocaine-neostigmine (LN) on heart rate (HR,) respiratory rate (RR) and rectal temperature (RT) (°C) in buffalo calves (mean ±SD, n= 10)

Time	HR		RR		RT	
(min)	**LA**	**LN**	**LA**	**LN**	**LA**	**LN**
0	62.2 ± 3.0	58.0 ± 4.4	20.2 ± 4.4	22.3 ± 2.1	38.0 ± 0.4	38.5 ± 0.3
10	60.3 ± 6.2	56.5 ± 3.1	19.3 ± 1.2	20.4 ± 4.5	38.1 ± 0.1	38.3 ± 0.4
20	61.6 ± 2.3	57.2 ± 2.5	19.3 ± 3.2	21.2 ± 2.7	38.4 ± 0.5	38.1 ± 0.3
30	60.3 ± 2.1	58.2 ± 3.0	20.2 ± 2.5	19.4 ± 2.5	38.0 ± 0.2	38.3 ± 0.2
40	59.5 ± 3.5	60.1 ± 2.5	19.3 ± 4.1	20.7 ± 2.0	38.3 ± 0.3	38.4 ± 0.2
50	61.6 ± 2.4	58.3 ± 3.1	20.2 ± 3.5	21.3 ± 2.2	38.2 ± 0.2	38.4 ± 0.5
60	59.0 ±2.2	60.4 ± 3.2	20.5 ± 6.7	21.2 ± 3.6	38.4 ± 0.1	38.3 ± 0.2
70	58.2 ± 2.3	58.1 ± 3.3	22.3 ± 3.1	20.9 ± 2.4	38.2 ± 0.3	38.4 ± 0.3
80	60.3 ± 4.0	59.6 ± 2.5	23.1 ± 5.5	20.2± 5.1	38.3 ± 0.1	38.1 ± 0.5
90	61.0 ± 2.4	60.2 ± 3.4	20.6 ± 7.4	22.4 ± 3.0	38.2 ± 0.4	38.2 ± 0.5
100	58.2 ± 3.7	58.3 ± 2.7	21.2 ± 5.1	21.5 ± 2.2	38.3 ± 0.2	38.3 ± 0.4
110	58.5 ± 3.6	58.2 ± 4.6	21.0 ± 6.5	20.7 ± 5.2	38.0 ± 0.5	38.4 ± 0.2
120	60.0 ± 2.3	58.4 ± 3.2	23.2 ± 4.8	20.4± 2.3	38.1± 0.3	38.2 ± 0.5

Table 4: Hematology and biochemical parameters after caudal epidural administration of lidocaine alone (LA) and lidocaine-neostigmine (LN) in buffalo calves (mean ±SD, n= 10)

		Time interval					
Parameter	Group	**0 min**	**30 min**	**60 min**	**90 min**	**120 min**	**24 h**
Hb (gm/dl)	**LA**	9.6 ± 1.2^{ab}	7.61 ± 1.0^{b}	7.10 ± 1.2^{b}	7.01 ± 0.2^{b}	6.88 ± 0.2^{bc}	9.8 ± 0.2^{ab}
	LN	10.3 ± 2.0^{a}	7.62 ± 1.0^{b}	7.02 ± 1.3^{b}	6.96 ± 0.3^{b}	6.79 ± 1.0^{bc}	10.0 ± 0.1^{a}
PCV%	**LA**	27.9 ± 1.2^{ab}	24.04 ± 1.6^{c}	22.61 ± 1.2^{cd}	21.30 ± 1.0^{d}	20.2 ± 1.2^{de}	28.01 ± 1.0^{a}
	LN	29.0 ± 1.1^{a}	24.30 ± 1.1^{c}	22.56 ± 1.1^{cd}	21.6 ± 0.1^{d}	20.2 ± 1.3^{de}	28.2 ± 0.2^{a}
RBCs	**LA**	5.9 ± 0.2^{a}	4.9 ± 0.2^{b}	4.3 ± 0.1^{b}	4.0 ± 0.3^{b}	3.99 ± 0.3^{bc}	6.01 ± 0.1^{a}
(10^6/mm^3)	**LN**	5.8 ± 0.1^{a}	4.8 ± 0.1^{b}	4.6 ± 0.2^{b}	4.0 ± 0.1^{b}	3.89 ± 0.2^{bc}	5.9 ± 0.1^{a}
TLC	**LA**	9.15 ± 0.17^{a}	8.2 ± 0.11^{b}	7.21 ± 0.22^{bc}	6.41 ± 0.12^{c}	6.0 ± 0.01^{c}	9.35 ± 0.17^{a}
(10^3/mm)	**LN**	9.18 ± 0.92^{a}	8.3 ± 0.12^{b}	7.15 ± 0.13^{bc}	6.25 ± 0.15^{c}	6.1 ± 0.02^{c}	9.45 ± 0.92^{a}
ALT	**LA**	25.4 ± 0.7^{c}	26.1 ± 1.1^{b}	28.6 ± 0.2^{a}	28.3 ± 0.1^{a}	26.91 ± 0.1^{ab}	25.1 ± 0.6^{c}
(Unit/ml)	**LN**	24.2 ± 0.2^{c}	27.2 ± 0.2^{ab}	28.89 ± 0.2^{a}	27.99 ± 0.2^{a}	26.1 ± 0.2^{b}	23.2 ± 0.1^{c}
ALP	**LA**	82.14 ± 1.7^{c}	85.1 ± 3.0^{a}	85.6 ± 1.1^{a}	84.5 ± 1.0^{a}	84.1 ± 3.0^{ab}	81.12 ± 1.0^{c}
(Unit/ml)	**LN**	82.4 ± 2.2^{c}	84.2 ± 2.21^{a}	84.9 ± 1.1^{a}	85.6 ± 0.1^{a}	84.0 ± 2.01^{ab}	81.4 ± 1.0^{c}
BUN (mg/dl)	**LA**	22.4 ± 2.2^{d}	25.1 ± 1.3^{bc}	26.6 ± 0.1^{ab}	30.3 ± 0.2^{a}	27.3 ± 1.0^{b}	22.4 ± 2.2^{a}
	LN	22.2 ± 2.3^{d}	24.2 ± 1.2^{bc}	26.8 ± 0.2^{ab}	29.7 ± 0.1^{a}	28.1 ± 1.0^{b}	21.2 ± 2.3^{ab}
Blood glucose	**LA**	70.54 ± 1.7^{ab}	55.1 ± 1.5^{d}	70.1 ± 0.1^{ab}	70.2 ± 0.1^{ab}	54.1 ± 1.5^{d}	69.54 ± 1.0^{ab}
(mg/dl)	**LN**	69.2 ± 1.2^{ab}	66.2 ± 1.3^{c}	64.3 ± 2.1^{c}	65.3 ± 2.1^{c}	65.2 ± 1.0^{c}	69.4 ± 1.2^{ab}

Values with different letters differ significantly ($P < 0.05$) among groups

4. DISCUSSION

Epidural administration of neostigmine has been used in animals and man **(**Lauretti et al., 1999; Natalini, and Robinson, 2000; Demiraran et al., 2005; Marucio et al., 2008; Almeida et al., 2010; and Bigham et al., 2010), without any adverse effects. All previous studies were designed to evaluate the effects of adding neostigmine to lidocaine for epidural analgesia reported extension of the duration of analgesia (Bigham et al., 2010; Marucio et al., 2014; and Cossu et al., 2015). Similarly, our results have proven that, adding of 10 μg/kg nesostigmine as an adjuvant to lidocaine in caudal epidural block significantly extended the duration of analgesia (134 ± 11 min) than lidocaine alone (68 ± 9 min) in buffalo calves ($P < 0.05$).

No study to date has evaluated the pharmacokinetics of epidural neostigmine. The analgesia resulting from epidural administration of neostigmine may be due to inhibition the breakdown of endogenous acetylcholine (AchL) and sequentially increasing Achl levels to act on both muscarinic and nicotinic receptors in the dorsal horn of the spinal cord provides analgesia (Lauretti et al., 1999; Memis et al., 2003; and Kumar et al., 2005).

Motor block is expected after administration of local anaesthetics such as lidocaine because these drugs not only induce analgesia but also block the motor fibers (Day and Skarda, 1991). A certain degree of motor weakness can result from intrathecal administration of cholinesterase inhibitors (Hood et al., 1995); it is related to an acetylcholine effect on the motor neuron that can potentiate the axonal conduction block caused by local anesthetics. However, in our results there is no difference in the degree of motor block or ataxia between LA and LN treatments.

HR, RR and RT were not significantly different compared with baseline values with all 2 treatments throughout the experiment. Similar results were obtained after epidural administration of epidural neostigmine in man (Lauretti et al.1999).

Haematological parameters like Hb, PCV, RBCs and TLC decreased in all animals after epidural injection of LA and LN. But those values returned to baseline levels at 24 h in all animals. Pooling of the circulating blood cells in the spleen or other reservoirs secondary to decreased sympathetic activity could be the reason for the decrease of those parameters (Sharda et al., 2008). It might be also due to shifting of fluids from the extravascular compartment to the intravascular compartment in order to maintain normal cardiac output during the period of anesthesia (Wagner et al., 1991). Similar observations were also recorded after administration of lignocaine alone or in combination with xylazine for epidural analgesia in cow calves (Moulvi et al., 2011), in buffalo calves (Singh et al., 2005).

A significant increase in ALT and ALP levels at different time points was recorded in all animals. This increase might be related to some alteration in cell membrane permeability, which may permit these enzymes to leak from the cells with intact membranes (Koichev et al., 1988). As the values returned to baseline levels at 24 h of observation, the possibility of pathological changes in the liver could therefore be ruled out. Similar findings were reported after xylazine, lignocaine and their combination for lumbar epidural analgesia in water buffalo calves (Singh et al., 2005). The increase in BUN in all animals after both treatments may be as a result of increased hepatic urea production from amino acid degradation could account for the observed increase in BUN as has been reported earlier (Singh et al., 2005). Similar changes in BUN have also been reported after administration of medetomidine in goats (Hugar et al., 2000).

A significant increase in glucose levels was observed at different time points in all the animals. But at 24h, the values for glucose returned to basal levels. The exact mechanism of lidocaine alone or Lidocaine-neostigmine induced hyperglycaemia was not investigated in the present study. However, it has been suggested that hyperglycaemia may be due to a rise in adrenocortical hormones during stress (Mirakhur et al., 1984).

Adverse side effects with epidural neostigmine in human patients include nausea, vomiting and diarrhea; the most serious is early or delayed respiratory depression after administration of epidural opioids (Wilder-Smith, 1998; and Lauretti, et al.1999), such adverse effects were not observed in this study.

5. Conclusion

In conclusion, neostigmine, as an adjuvant to epidural lidocaine, prolongs the duration of analgesia compared with lidocaine alone. Therefore, a single-dose epidural administration of neostigmine with lidocaine could be a safe and cheap drug in buffalo calves undergoing long surgical procedures in the perineal region.

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