

Evaluation of ketamine and bupivacaine with xylazine for epidural analgesia in buffalo calves

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ABSTRACT

The effects of epidural ketamine and bupivacaine with xylazine were evaluated and compared on the basis of analgesic, physiological and haemodynamic parameters in buffaloes. Xylazine (0.05 mg/kg) alone and combinations of xylazine and ketamine (0.05 mg/kg and 2.0 mg/kg), and xylazine and bupivacaine (0.05 mg/kg and 0.125 mg/kg) were administered epidurally in 4 animals each, randomly. Combination of xylazine with ketamine or bupivacaine produced complete analgesia of tail, perineum, inguinal region and upper parts of hind limbs. Xylazine/ketamine produced early onset and more depth of analgesia with less decrease in respiratory rate as compared to xylazine alone or xylazine/bupivacaine combination. Xylazine/bupivacaine produced significantly more depth and longer duration of analgesia than that produced by xylazine, but caused slightly more decrease in mean arterial pressure than xylazine/ketamine. The ECG changes were more obvious in xylazine/bupivacaine group than the animals of xylazine/ketamine group. It was concluded that both ketamine and bupivacaine can enhance the depth of analgesia produced by xylazine. Ketamine can also enhance the onset of analgesia and mitigate some of the side effects of xylazine in buffaloes.

Key words: Buffalo, Bupivacaine, Epidural analgesia, Ketamine, Xylazine

Bupivacaine is an amido-amine local anaesthetic of high potency, long duration, low degree of motor blockade, and minimal neurotoxicity (DeRossi *et al.* 2004). It has been used safely for epidural analgesia in buffaloes (Singh *et al.* 2009) and dogs (Gomez de Segura *et al.* 2009).

Ketamine in combination with xylazine has been used to induce spinal analgesia in dogs (Amarpal *et al.* 1999) and goats (Aithal *et al.* 1996). A synergistic interaction has been suggested between xylazine and ketamine when administered epidurally in goats (Aithal *et al.* 1996, Kinjavdekar *et al.* 2007). Xylazine can induce epidural analgesia with a prolonged duration and decreased disruption of motor function as compared to that induced by local anaesthetics (Grubb *et al.* 1993). These attributes of xylazine induced epidural analgesia are desirable, when surgical and obstetrical procedures are performed in standing cattle or buffaloes. However, sedation, cardiopulmonary depression, rumen hypomotility and delayed onset of analgesia are some of the known side effects of xylazine in ruminants (Singh *et al.* 2004). Further, higher doses of xylazine administered to

enhance the analgesia may not be safe as reported in horses (Doria *et al.* 2008).

Only little information is available about the use of ketamine or bupivacaine with xylazine for epidural analgesia in buffaloes. The present study was therefore, designed to evaluate and compare the effects of ketamine and bupivacaine on analgesic, physiological and haemodynamic actions of epidural xylazine in buffaloes.

MATERIALS AND METHODS

The study was conducted in 2 phases. Each animal was kept off feed for 24 h and water was withheld 12 h prior to the start of the experiment in each phase. In phase I, 12 buffalo calves were randomly divided in 3 groups of 4 animals each. The animals were restrained in standing position and area over first intercoccygeal space was clipped and prepared for aseptic injection. Xylazine (0.05 mg/kg), combination of xylazine/ketamine (0.05 mg/kg and 2.0 mg/kg), and combination of xylazine/bupivacaine (0.05 mg/kg and 0.125 mg/kg) were administered epidurally in groups 1, 2 and 3, respectively, using 4 cm long, 20-gauge hypodermic needle. The volume of the drug was made up to 4.0 ml by diluting the drugs with normal saline solution just before the injection in each animal. The animals were observed for the following parameters.

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Onset of analgesia: Response to pin pricks was recorded at the perineal region on either side of midline about 4–5 cm below the anus at every 5-min using 24 G, 2.5 cm long hypodermic needle. Time from injection to reduced response/loss of sensation was considered as the time of onset of analgesia.

Depth of analgesia: The depth of analgesia was observed at the tail, perineum, inguinal region, upper parts of hind limbs, digits, flank, thorax (ribs) and ventral abdomen. The depth of analgesia at these sites was subjectively graded as per Amarpal *et al.* (2007).

Motor in-coordination/ataxia: Motor in-coordination was evaluated by visually observing posture and gait of the animal. It was graded on a 0 to 3 scale using the methods of Amarpal *et al.* (2007).

Sedation: The depth of sedation was graded on a 0 to 3 scale as follows. 0-Animal standing alert; 1-Animal standing but appeared tired with slight ptosis of eyelids; 2-Animal standing with wide stance and extreme lowering of head; 3-Animal became recumbent.

Duration of analgesia: Time from loss of sensation from perineum to the time of full return of sensation at all the sites was considered as duration of analgesia.

Physiological observations: The heart rate (beats/min), respiratory rate (breaths/min) and rectal temperature (°C) were recorded as per the standard methods.

In phase II 8 buffalo calves were randomly divided in 2 equal groups. The animals were secured in right lateral recumbency for catheterization of common carotid artery and jugular vein using sterilized PVC catheters under local infiltration analgesia to record MAP and CVP (Lumb and Jones 1984). A lead II ECG was recorded at 1 mV and 25 mm/sec paper speed by placing negative electrode subcutaneously at caudal border of scapula and positive electrode at costo-chondral junction (base apex lead) using an ECG machine. All the animals were allowed a cooling time of 30 min before recording of base values. After recording the base values, combination of xylazine/ketamine (group 1) and xylazine/bupivacaine (group 2) were administered randomly in 4 animals each at first intercoccygeal epidural space. The doses and the concentrations of the drugs were kept same as in phase I of the study. Mean arterial pressure (MAP), central venous pressure (CVP) and ECG were recorded.

All the parameters, except for onset and duration of analgesia, were recorded before administration of the drugs (base values) and then at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min after injection of the drug(s).

Analysis of variance (ANOVA) and Duncan's multiple range test (DMRT) were used to compare the means at different intervals and with base values. Non-parametric data were compared at different intervals using Kruskal-Wallis rank test (Snedecor and Cochran 1967). In each analysis, a value of $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Onset of analgesia was evident within 5 min after administration of combination of xylazine/ketamine, whereas it was recorded in 15 min after the administration of xylazine, or combination of xylazine/bupivacaine. Xylazine/ketamine produced slightly longer duration of analgesia (135 ± 8 min) than that produced by xylazine (127 ± 7 min). Analgesia produced by xylazine/bupivacaine (206 ± 6 min) was significantly ($P < 0.05$) longer than that produced by xylazine alone or its combination with ketamine.

Xylazine produced mild to moderate analgesia up to 20 min interval and complete analgesia from 30–75 min interval at tail and perineum. Thereafter, moderate analgesia persisted until the end of observation period. Complete analgesia in inguinal region and upper parts of hind limbs was recorded from 45 to 75 min. Xylazine/ketamine produced complete analgesia from 15 to 60 min at tail and from 20 to 75 min at perineum. Mild to moderate analgesia persisted until the end of observation period. Complete analgesia was recorded from 15–60 min interval at inguinal region and upper parts of hind limbs from 45 to 75 min. Xylazine/bupivacaine produced complete analgesia at tail in 20 min and at perineum in 30 min, which persisted until the end of observation period. Complete analgesia was recorded from 30 min until the end of observation period at inguinal region and from 45 to 90 min at upper parts of hind limbs. No appreciable analgesia was recorded at flank, thorax and ventral abdominal area in any of the groups.

Two mechanisms are reported to be involved in epidural action of xylazine. Firstly, xylazine may bind to α -2 adrenergic receptors in the dorsal horn of spinal cord, inhibiting the release of substance P, which is involved in pain sensation (Grubb *et al.* 1993). Secondly, it may have a significant local anaesthetic action (Singh *et al.* 2004). Co-administration of xylazine and ketamine resulted in early onset and more depth of analgesia as compared to xylazine. The results were suggestive of a synergistic/additive interaction between ketamine and xylazine, which could be attributable to their ability to produce spinal analgesia through different mechanisms of action (Aithal *et al.* 1996). The inability of ketamine to increase the duration of analgesia produced by xylazine could be attributable to short distribution and elimination half-life of ketamine. Xylazine and lignocaine have been reported to act synergistically or additively (Grubb *et al.* 1993). Similarly, combination of xylazine and bupivacaine through different cellular mechanisms of action might have produced synergistic effect.

The animals of xylazine group showed mild in-coordination from 30 to 45 min, while animals of xylazine/ketamine group exhibited moderate in-coordination from 30 to 75 min and mild in-coordination up to the end of observation period. The animals of xylazine/bupivacaine group showed moderate in-coordination up to 75 min.

Animals of all the groups, however, remained in standing position throughout the observation period. The ataxia recorded after epidural administration of xylazine may be related to its postulated local anaesthetic properties (Singh *et al.* 2009). Butterworth and Strichartz (1993) reported that alpha-2 agonists tend to inhibit A delta and C fibers (responsible for pain perception) more potently than A alpha fibres (responsible for motor function and proprioception). The complete analgesia but only mild ataxia produced by xylazine may be attributable to this selective inhibition of nerve fibres by xylazine.

Complete motor in-coordination has been recorded after epidural/spinal administration of ketamine alone or in combination with xylazine in goats (Aithal *et al.* 1996) and cattle (Amarpal *et al.* 1997). Bupivacaine is the local anaesthetic with lowest degree of motor blockade and neurotoxicity (DeRossi *et al.* 2004). Further, the dose of bupivacaine used in the study was low, therefore, the animals of xylazine/bupivacaine group exhibited only mild to moderate ataxia.

All the animals of xylazine, xylazine/ketamine and xylazine/bupivacaine groups showed mild sedation between

20 and 30 min, and thereafter, moderate sedation until the end of observation period. Sedation recorded in animals given xylazine alone or in combination with ketamine or bupivacaine, in the present study, may be attributable to the supraspinal effect of xylazine following its systemic absorption from epidural space (Correa-sales *et al.* 1992).

Heart rate (HR) decreased 20 min after administration of xylazine and remained significantly ($P<0.05$) below the base line until the end of observation period. A significant decrease in HR after epidural administration of xylazine is considered as a classical response following administration of alpha-2 agonist in animals (Ruffolo *et al.* 1993). This bradycardia may be attributable to inhibition of sympathetic tone from CNS, inhibition of nor-epinephrine release from sympathetic nerve terminals, vagal stimulation in response to xylazine induced vasoconstriction and direct increase in the release of acetyl choline from parasympathetic nerve in the heart (Mac Donald and Virtanen 1992). Xylazine/ketamine caused a gradual and significant ($P<0.05$) decrease in HR from 5 to 90 min. The bradycardia in this group was less pronounced as compared to animals of xylazine group from 30 min onwards. Xylazine/bupivacaine also caused a significant

Table 1. Mean $\pm$ SE heart rate (HR), respiratory rate (RR), rectal temperature (RT), mean arterial pressure (MAP), and central venous pressure (CVP) after caudal epidural administration of xylazine (0.05 mg/kg), combinations of xylazine/ketamine (0.05 mg/kg and 2.0 mg/kg) and xylazine/bupivacaine (0.05 mg/kg and 0.125 mg/kg) in buffalo calves (n=4)

Parameters	Groups	Intervals (min)											
		0	5	10	15	20	30	45	60	75	90	105	120
HR (beats/ min)	Xylazine	59.00 ± 2.08	59.50 ± 2.63	59.50 ± 2.50	58.00 ± 2.94	55.00* ± 2.65	52.25* ± 2.01	49.50* ± 0.50	46.50** ± 1.70	45.00** ± 1.00	44.00** ± 0.82	42.00* ± 2.00	42.00* ± 2.63
	Xylazine/ Ketamine	57.50 ± 3.09	54.00* ± 2.16	52.00* ± 1.89	53.00* ± 1.00	55.50* ± 0.95	52.50* ± 2.50	52.50* ± 1.25	51.00* ± 0.57	52.00* ± 0.82	54.00* ± 0.81	56.00 ± 0.82	57.50 ± 1.25
	Xylazine/ Bupivacaine	70.50 ± 4.27	70.00 ± 4.69	68.00 ± 4.96	65.50 ± 4.71	63.50** ± 4.64	65.00** ± 4.43	63.00** ± 4.43	58.00** ± 4.99	60.50** ± 4.29	60.00** ± 4.27	65.00** ± 4.70	64.75** ± 4.67
	Xylazine/ Ketamine	16.00 ± 0.82	15.00 ± 0.58	15.25 ± 0.48	13.75 ± 0.85	13.50** ± 0.65	12.50** ± 0.65	12.00 ± 0.42	11.25** ± 0.45	11.00** ± 1.00	10.00** ± 0.82	10.25** ± 0.85	11.75** ± 0.85
	Xylazine/ Bupivacaine	14.50 ± 0.65	13.00 ± 0.40	13.50 ± 0.87	13.00 ± 1.00	12.00** ± 1.56	12.00** ± 1.80	14.00 ± 1.82	14.00 ± 0.80	14.00 ± 0.80	14.00 ± 0.80	15.00 ± 0.80	15.00 ± 0.58
RR (breath/ min)	Xylazine	15.75 ± 0.85	15.00 ± 0.58	14.75 ± 1.25	14.25 ± 1.18	10.00* ± 0.82	9.00** ± 0.58	9.00** ± 0.71	9.00** ± 1.08	11.50* ± 1.85	12.00* ± 1.63	12.00* ± 1.41	13.50* ± 1.25
	Xylazine/ Ketamine	37.60 ± 0.18	37.50 ± 0.30	37.40 ± 0.58	37.25 ± 0.44	37.25 ± 0.34	37.15 ± 0.42	37.05 ± 0.42	37.00 ± 0.35	36.96* ± 0.30	36.90** ± 0.13	36.70** ± 0.17	36.50** ± 0.28
	Xylazine/ Bupivacaine	37.45 ± 0.56	37.40 ± 0.38	37.06 ± 0.27	36.92 ± 0.20	36.96 ± 0.24	36.90 ± 0.29	36.80* ± 0.30	36.74* ± 0.29	36.74* ± 0.32	36.64** ± 0.36	36.52** ± 0.16	36.70** ± 0.34
	Xylazine/ Ketamine	37.40 ± 0.11	37.45 ± 0.32	37.40 ± 0.16	37.35 ± 0.16	37.25 ± 0.28	37.20 ± 0.16	36.85* ± 0.21	36.90* ± 0.27	36.70* ± 0.36	36.70** ± 0.13	36.65** ± 0.22	36.60** ± 0.16
	Xylazine/ Bupivacaine	135.50 ± 3.30	125.25 ± 2.50	126.50 ± 3.30	120.00 ± 8.18	111.00* ± 5.01	110.50* ± 4.19	109.50** ± 4.11	106.00** ± 0.81	106.50** ± 2.50	104.00** ± 2.82	104.50** ± 2.87	108.00** ± 0.82
MAP (mmHg)	Xylazine	134.00 ± 4.54	122.00 ± 1.63	110.25 ± 1.43	106.50* ± 2.25	97.75** ± 0.85	95.75** ± 2.09	89.75** ± 2.89	97.00** ± 3.69	87.50** ± 2.36	90.75** ± 2.05	87.00** ± 2.88	86.25** ± 4.13
	Xylazine/ Ketamine	06.50 ± 0.19	07.39 ± 0.15	08.48* ± 0.18	11.00** ± 0.20	11.55** ± 0.32	12.00** ± 0.11	14.03** ± 0.13	12.03** ± 0.08	11.73** ± 0.19	11.00** ± 0.18	11.00** ± 0.18	10.75** ± 0.16
	Xylazine/ Bupivacaine	05.02 ± 0.16	07.02* ± 0.12	07.97** ± 0.26	08.75** ± 0.27	10.99** ± 0.15	11.75** ± 0.16	12.53** ± 0.20	12.90** ± 0.52	13.25** ± 0.47	09.40** ± 0.37	08.33** ± 0.64	08.88** ± 0.42
	Xylazine/ Ketamine	05.02 ± 0.16	07.02* ± 0.12	07.97** ± 0.26	08.75** ± 0.27	10.99** ± 0.15	11.75** ± 0.16	12.53** ± 0.20	12.90** ± 0.52	13.25** ± 0.47	09.40** ± 0.37	08.33** ± 0.64	08.88** ± 0.42
	Xylazine/ Bupivacaine	05.02 ± 0.16	07.02* ± 0.12	07.97** ± 0.26	08.75** ± 0.27	10.99** ± 0.15	11.75** ± 0.16	12.53** ± 0.20	12.90** ± 0.52	13.25** ± 0.47	09.40** ± 0.37	08.33** ± 0.64	08.88** ± 0.42

* $P<0.05$; ** $P<0.05$.

($P < 0.05$) decrease in HR. Bradycardia in this group was of similar extent as that produced by xylazine (Table 1). The lesser extent of bradycardia in xylazine/ketamine group may be attributable to the opposite systemic action of ketamine over xylazine on the heart rate.

Epidural administration of xylazine induced a significant ($P < 0.01$) decrease in respiratory rate (RR) from 20 min to the end of observation period. This decrease in RR may be attributable to depression of respiratory centre by xylazine after systemic absorption (Aminkov and Hubenov 1995). A significant depression of respiratory frequency has been reported after epidural/subarachnoid administration of xylazine in cattle (DeRossi *et al.* 2003) and goats (Aithal *et al.* 1996). The administration of ketamine with xylazine resulted in less pronounced and short-lived decrease in RR as compared to xylazine group (Table 1), suggesting that ketamine is useful in counteracting some of the depressant action of xylazine on respiratory rates. More pronounced depression of RR recorded in xylazine/bupivacaine group as compared to that recorded after epidural administration of xylazine or xylazine/ketamine might be due to decrease in sympathetic tone and depression of respiratory centre caused by the combination of xylazine and bupivacaine (Lumb and Jones 1984).

Rectal temperature (RT) decreased in all the groups especially towards the end of observation period. In animals of xylazine group, significant ($P < 0.05$) decrease in RT was observed from 75 min up to the end of observation period. Xylazine/ketamine and xylazine/bupivacaine also induced significant ($P < 0.05$) decrease in RT. The difference in RT between the combination groups was not significant (Table 1). Generalized sedation, reduced metabolism, muscle relaxation and depression of the CNS may have caused a reduction in RT. Bupivacaine may also cause decrease in RT through vasodilatation (DeRossi *et al.* 2003).

A gradual decrease in mean arterial pressure (MAP) was recorded in animals of both combination groups. MAP reached significantly ($P < 0.05$) below the baseline at 20 min interval in xylazine/ketamine group and at 15 min interval in xylazine/bupivacaine group. MAP remained significantly ($P < 0.01$) lesser than base line values until the end of observation period in both the groups (Table 1). The decrease in MAP was more striking in xylazine/bupivacaine group, but the difference between the groups was not significant at most of the intervals. After epidural administration, xylazine may cause hypotension by supraspinal mechanism and also by spinal hypotensive mechanism by activation of α -2 adrenergic receptors, resulting in reduction of activity of efferent sympathetic nerves (DeRossi *et al.* 2003). Ketamine, upon systemic absorption from the epidural space, may have counter-balanced some hypotensive effect of xylazine in the animals of xylazine/ketamine group by increasing arterial pressure (Reich and Silvay 1989). On the other hand, bupivacaine probably could not check the hypotension caused

by xylazine in xylazine/bupivacaine group, resulting in more hypotension in this group as compared to xylazine/ketamine group.

A significant increase ($P < 0.05$) in central venous pressure (CVP) was recorded up to 45 min in xylazine/ketamine and 60 min in xylazine/bupivacaine group (Table 1). CVP started to decrease thereafter, in both combination groups. The difference between the 2 groups was not significant. Central shift of blood to the venous compartment might be associated with increase in CVP. Alteration in myocardial contractility and an increase in the afterload may also have contributed to increase in CVP (Serateyn *et al.* 1993).

Sinus arrhythmia and increase in duration of QRS complex were recorded in one animal 5 min after administration of xylazine/ketamine. QS pattern of QRS complex was observed in all the animals of xylazine/bupivacaine group up to 75 min. Two animals of this group showed a tall 'T' wave at 60 min. ST elevation was also recorded at 75 min interval in 1 animal. Second degree heart block was seen in 1 animal of xylazine/bupivacaine group at 90 and 105 min intervals. A tall positive T wave and elevation of ST segment predominantly observed in the animals of xylazine/bupivacaine group might be due to myocardial hypoxia (Tilley 1985). Sinus arrhythmia and second degree AV heart block observed in 1 animal of xylazine/bupivacaine group may be due to increased vagal activity caused by vasopressor effects of xylazine.

On the basis of above observations it was concluded that epidural ketamine and bupivacaine can enhance the depth of epidural analgesia induced by xylazine and ketamine, and can also mitigate some of the side effects of xylazine.

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