COMPARATIVE STUDY ON XYLAZINE, BUPIVACAINE AND BUPRENORPHINE WITH KETAMINE AS LUMBOSACRAL SPINAL ANALGESIA IN UREMIC BUFFALO CALVES

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ABSTRACT

36 male buffalo calves aged seven to eight months, weighing 60 to 75 kg were divided into three groups, A, B and C and were used to evaluate the efficacy and safety of lumbosacral spinal analgesia produced by bupivacaine, xylazine and buprenorphine in combination with ketamine respectively in the clinical cases of uremia in buffalo calves with urolithiasis. The onset of analgesia in the animals of group B took place in shortest time (1.75±0.47 min) followed by group C (3.5±0.6 min) and longest time (5.0±0.00 min) was taken by animals of group A . The longest (>180 min.) duration of complete analgesia was recorded in animals of group B. It was concluded that spinal bupivacaine and xylazine when given with ketamine combinations have similar analgesic potency on spinal administration in buffalo calves.

KEY WORDS: Spinal; Lumbosacral; Buffalo calves; Xylazine;, Bupivacaine; Buprenorphine; Ketamine; Uremia

INTRODUCTION

Uremia is a common clinical condition of almost all domestic animals (Blood and Radostits, 1989), with a higher incidence in bovine and caprine. Prolonged hypotensive anesthesia can cause a decrease in renal function and may cause pre-renal uremic and/or acute renal failure (Stone *et al.,* 1981). General anesthesia should thus be avoided in patients with increased blood urea nitrogen level (Lumb and Jones, 1984). Local and regional anesthesia would be a better choice in such patients. Regional anesthesia, like epidural/spinal anesthesia has been shown to have less cardiopulmonary and other systemic side effects than general anesthesia in ruminants (Hall *et al.,* 2001). When xylazine and ketamine combination was administered epidurally, both being acting at different sites, showed synergism thereby inducing more profound and prolonged analgesia with reduced cardiopulmonary depression in different animal species (Singh *et al.,* 2010). Epidural bupivacaine is successfully used as preemptive, post-traumatic analgesics and in laparotomy in goats (Pathak, 1999). Buprenorphine is a partial μ opioid and a weak kappa agonist. It has high affinity for the μ receptors, with slow dissociation resulting in a long duration of action. At higher doses, its agonist effects plateau and it begins to behave more like an antagonist, limiting the maximal analgesic effect. Thus, it has a very wide margin of safety. (Sporer, 2004).

Further, ketamine has been reported to have least cardiopulmonary effects when used epidurally. The present study therefore, was designed to evaluate effect of bupivacaine-ketamine, buprenorphine-ketamine and xylazine- ketamine combinations as spinal anesthesia and on the biochemical parameters in clinical cases of uremia in buffalo calves with urolithiasis.

MATERIALS AND METHODS

36 male buffalo calves with uriolithiasis of 7-8 months of age, weighing from 60-75 kg were equally divided into three groups of 12 animals each, designated as groups A, B and C. The study was approved by research, coordination and monitoring section of the institute. The animals were restrained in standing position with cotton rope halters in a cattle crush. The lumbosacral space

was palpated and the area of injection was clipped, shaved and painted with povidone iodine for aseptic spinal injection. An initial weal was produced with 2% lignocaine hydrochloride using a fine needle at the center of lumbosacral space. In group A ,Bupivacaine- ketamine (0.25mg/kg + 2.5mg/ kg), Group B ,Xylazine- ketamine (0.05mg/kg + 2.5mg/ kg) and Group C , Buprenorphine- Ketamine (20µg /kg + 2.5mg/ kg) was administered intraspinally at the lumbosacral space using an 18 gauge, 7.5 cm spinal needle under aseptic conditions. The correct position of the needle was ascertained by free outflow of CSF from the needle hub. The base line values (time 0) for physiological and clinical parameters were made before injection of the drug. Blood samples were also collected at zero hour before drug administration. Total quantity of injectable solution was made 6 ml by addition of normal saline solution in each group. After spinal injection of drugs, the animals were secured over the operation table for maximum 30 min for tube cystostomy to relieve the urinary bladder pressure.

The above three treatments were evaluated and compared on the basis of clinical and biochemical parameters. Onset of analgesia was determined by recording the response to skin pinpricks, made in the perineal region on either side of midline about 4–5 centimeters below the anus.

Duration of analgesia was considered as the time from the loss of sensation at the perineum to the time of return of full sensation at all the sites. Sedation and motor incoordination was also observed.

Blood was collected in separate vials of 2 ml each in heparin and 2 ml in sodium fluoride at 30, 60, 90, 120 180 minutes after administration of the drugs. Heparinized blood was centrifuged for separation of plasma . Estimation of blood urea nitrogen (Wybenga et al., 1971), creatinine (Bones et al., 1945), plasma cortisol (Carr et al., 1977) and gamma glutamyl transferase (GGT) (Szasz, 1969) at 30, 60, 120 minutes after the injection of drugs were carreid out . 2 ml of blood in sodium fluoride was used for the estimation of glucose by glucose oxidase peroxidase method (GOD/POD, Trinder, 1969). Analysis of variance and Duncan's multiple range tests were used to compare the data of parametric observations at different intervals between the groups. Paired t-test with Bonferroni correction was used for comparison of mean ± SE at different time intervals with the base values of the respective treatments as per the standard procedures (Snedecor and Cochran, 1967). Kruskal - Wallis's one way test was used to compare the means among the groups of non-parametric observations. The values were considered as significant at $P<0.05$.

RESULTS AND DISCUSSION

The onset time of analgesia was 5.0±0.00 min , 1.75±0.47 min and 3.5±0.6 min in group A,B and C respectively . xylzaine and ketamine (Gr.B) produced significantly ($P<0.05$) earliest onset as compared to all the groups , whereas bupivacaine and ketamine in the animals of group A produced significantly ($P<0.05$) the slowest onset as compared to all the groups. Group C animals, showed a significantly ($P<0.05$) earlier onset than group A and significantly ($P<0.05$) slower onset than group B. An early onset of xylazine-ketamine might have been due to the less absorption of drug from the site of injection as xylazine brings about bradycardia (Booth, 1988) and might be thought to aggravate the hypotension and might reduce the tissue perfusion further in uremic animals. Buprenorphine exerts an inhibitory control over the dorsal horn, where the primary sensory neurons involved in pain sensation by releasing predominantly substance P and glutamate (Nollet *et al.,* 2003). Late onset and comparatively less duration of action in group A (150 min)was observed in this study. The longest (>180 min.) duration of complete analgesia was recorded in animals of group B. The earliest recovery from anesthesia in the animals of group C might have been due to the less anaesthetic effect exerted by buprenorphine through its ceiling effect (Sporer, 2004). Group B animals showed prolonged recovery as compared to all the groups. It could be attributed to depression of cardiac functions (Kumar and Thurmon, 1979; Rings and Muir, 1982) by xylazine

and might have caused a reduced absorption of drugs from the site of injection and hence a prolonged recovery from regional anesthesia.

There was intense observable sedation and motor incoordination in group B than other groups. This was attributed to the fact that xylazine is a cardio depressant drug and causes aggravated bradycardia (Kumar and Thurmon, 1979; Rings and Muir, 1982) in the uremic animals, which are already in a state of dehydration, hypovolemia and hypotension (Guyton, 1991).

BIOCHEMICAL STUDIES

Mean±SE of plasma glucose, plasma urea, plasma creatinine, plasma cortisol and GGT in the animals of different groups are given in Table 1.

The decrease in glucose levels correspond with the decrease in plasma cortisol and the time intervals. The initial fall in plasma glucose in animals of group A and B could be attributed to temporary inhibition of stress response by regional analgesia by spinal bupivacaine and also partially due to haemodilution by fluid-therapy. The increase in glucose values thereafter might have been due to the post-operative stress after early recovery from anaesthesia and reduced analgesia scores (since the score of analgesia decreased after 120 min). Alpha-2 adrenoceptor stimulation induces hyperglycaemic responses through a peripheral effect that involves post-synaptic alpha-2 adrenoceptors in the pancreatic beta-cell which are linked to the inhibition of insulin release (Angel and Langer, 1988). Plasma glucose in the animals of group C suggested that the combination failed to produce the stress response in the uremic animals.

The initial decrease in plasma creatinine in animals of group A might have been due to the effect of evacuation of urine collected in the body cavity/organs and consequently decrease in uremia and also due to fluid therapy . The increase in plasma urea nitrogen did not go beyond the base levels, which ruled out the possible effect of anaesthetic on renal blood flow and instead reflects that animals required more time for stabilization. The reduction in plasma cortisol in group A at 30 min might have been due to reduction in the stress response of patients due to regional blockade and fluid therapy. Thereafter the increase might have been due to diminished effect of analgesia and concomitant surgical stress. Whereas animals of group B showed a significant increase in plasma cortisol at 120 min and the values at 180 min remained elevated than the base line. This might have been due to the increased anaesthetic stress in the animal after the surgery (Angel and Langer, 1988) . Plasma cortisol levels of group C animals showed a non-significant decrease up to 90 min. Thereafter the values started to increase and reached near the base line at the end of the observation period. It could be attributed to incomplete analgesia and only partial blockade pain stimuli in group C.

The plasma GGT values decreased non-significantly throughout the observation period in animals of group A and B but in the animals of group C, a significant increase was recorded from 120-180 min post-injection. This might be related to the drug induced metabolic disturbances of liver (Baxter and Miert, 1983). It was concluded that spinal bupivacaine and xylazine when given with ketamine combinations have similar analgesic potency on spinal administration in buffalo calves. Since xylazine-ketamine combination produced intense sedation, motor incoordination and alarming irreversible state of analgesia and further a higher and alarming plasma glucose and cortisol values in blood biochemical parameters directly reflects high amount of stress in these animals and hence not safe in urolithiasis.

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Table Mean±SE of (a) plasma glucose (mg/100ml) (b) plasma urea (g/l), (c) plasma creatinine (mg/100 ml), (d) plasma cortisol (n mol/L) and (e) GGT (U/L) in the animals of different groups

(mg/100 ml), (d) plasma cortisol (n mol/L) and (e) GGT (U/L) in the animals of different groups

Groups	Time Interval (min)					
	0	30	60	90	120	180
a. Plasma glucose (mg/100ml)						
A	40.58 ±11.86	27.94* ±8.8	70.12 ±15.9	71.55 ±17.6	102.53 ±36.2	109.76 ±34.8
B	122.53 ±55	90.78** ±53	86.17* ±47	108.17 ±40	128.97 ±33	128.90 ±33
C	48.85 ±13.7	43.40 ±17.4	51.05 ±14.8	45.43 ±10.5	56.28 ±9.7	66.12 ±12.2
b. Plasma urea (g/l)						
A	83.63 ±19.5	89.27 ±23.9	91.65 ±17.6	123.28 ±18.0	101.91 ±20.8	66.20 ±11.7
B	107.92 ±20.3	91.50* ±17.2	104.96 ±17.8	110.48 ±17.1	106.40 ±14.7	69.42* ±13.9
C	86.09 ±25.7	91.57 ±28.0	80.96 ±20.8	86.78 ±32.4	95.16 ±25.1	87.55 ±25.3
c. Plasma creatinine (mg/100 ml)						
A	24.75**a** ±4.1	19.03** ±3.4	18.26* ±2.7	19.12**a** ±2.0	19.33**a*** ±2.2	19.85 ±4.8
B	11.0**b** ±4.1	9.25 ±2.6	8.94 ±2.6	8.95**b** ±3.2	8.79**b** ±3.1	7.14 ±2.1
C	11.89**ab** ±2.2	11.52 ±2.5	13.45 ±2.8	13.43**ab** ±2.6	12.88**ab** ±2.7	14.48 ±2.9
d. Plasma cortisol (n mol/L)						
A	121.89 ±58.0	73.7 ±27.6	138.7**a** ±30.1	158.6** ±53	96.24 ±26.8	54.14 ±15.6
B	11.50 ±4.8	11.02 ±7.0	10.07**b** ±0.07	81.42 ±54.7	70.20* ±15.2	67.54 ±14.5
C	70.05 ±36.2	34.50 ±14.4	16.57**b** ±5.6	26.79 ±63	76.53 ±15.6	70.34 ±17.2
e. GGT (U/L)						
A	94.08a ±48.15	76.73a ±40.44	80.77a ±41.08	70.35a ±29.93	64.56a ±19.77	51.24a ±20.39
B	18.06b ±7.63	8.56b ±1.66	8.56b ±1.66	10.19b ±2.27	10.42b ±2.07	10.42b ±2.07
C	21.42a ±5.76	18.45a ±7.08	18.45a 7.08	47.06a 25.81	42.84a* 10.90	42.84a* 10.90

A: Bupivacaine + ketamine; B : Xylazine + Ketamine; C: Buprenorphine + Ketamine

* Significantly different from the base value within group (P<0.05)

** Significantly different from the base value within group (P<0.01)

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