EVALUATION OF DEXMEDETOMIDINE ALONE AND ITS COMBINATION WITH KETAMINE AND ROPIVACAINE FOR TUBE CYSTOSTOMY IN UROLITHIC BUFFALO CALVES

Deepesh Gautam*, P. Kinjavdekar, Amarpal, H.P. Aithal, A.M. Pawde, Rohit Kumar, Sivanarayan T.B., Divya Mohan and Ravinder Singh

ABSTRACT

The present study was conducted to evaluate clinicophysiological and biochemical effects of dexmedetomidine and its combination with ketamine and ropivacaine for tube cystostomy in urolithic buffalo calves. The study was conducted on 15 male buffalo calves of 3 to 4 months of age having the body weight of 40 to 50 kg which were suffering from urinary obstruction for 2 to 4 days. The animals were divided into three groups *viz*. D, DK and RDK on the basis of anesthetic agent(s) used. In group D- dexmedetomidine 7.5 µg/kg, in group DK- dexmedetomidine and ketamine 3.75 µg/kg and 2 mg/kg, respectively, and in group RDK- ropivacaine, dexmedetomidine and ketamine 0.15 mg/kg, 2.5 µg/kg and 2 mg/kg, respectively, were administered subarachnoidally at lumbosacral space. In all the groups the onset of analgesia, extent and depth of analgesia at tail, perineum, inguinal region, thigh, digits, anterior flank, posterior flank, lower abdomen and thorax were recorded up to 90 minutes. The clinical examination revealed earliest onset of analgesia in group DK followed by group RDK and Group D. However, duration of analgesia was similar in all the groups. Motor incoordination was recorded earlier in DK and RDK groups. Recovery time was shortest in dexmedetomidine (128.80±5.11 minutes) alone. Heart rate and respiratory rate decreased in all the groups. Rectal temperature decreased significantly in all the groups. Plasma glucose increased significantly in all the groups. However, plasma urea nitrogen and plasma creatinine values did not change significantly. It was concluded that RDK Group provides better extent and depth of subarachnoid analgesia than D and DK with only transient and minor changes in physiological and biochemical parameters and therefore, could be used safely for tube cystostomy in urolithic buffalo calves.

Keywords: buffalo calves, dexmedetomidine, ketamine, subarachnoid, tube cystostomy, urolithiasis

INTRODUCTION

Obstruction induced by urethroliths causes urine retention and leads to bladder distention, abdominal pain and eventual urethral perforation or bladder rupture with death from uremia or septicemia. Urolithiasis is a common clinical condition of almost all domestic animals, but higher incidence has been recorded in bovine and caprine most often during winter or during severe weather conditions with limited water intake, especially when the water has a high mineral content (Radostits *et al*., 1994). Urinary calculi are believed to be formed as a result of abnormally

Division of Surgery, Indian Veterinary Research Institute, Uttar Pradesh, India, *E-mail: gautamdeepesh87@gmail.com

high concentration of insoluble complexes in the urine or mineralization of a nidus (Smith, 1989). Complete urethral obstruction requires immediate surgical intervention and such patients are graded as poor surgical risk patients requiring great care in anesthetic management.

Several anesthetic techniques with different drugs have been used for the purpose in different species of animals. But, local and regional anesthesia may be a better choice. 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). Spinal anesthesia involves injection of local anesthetic and/or other appropriate drug(s) into the spinal canal at the lumbosacral space in order to produce analgesia. Dexmedetomidine, a newer alpha$_2$-agonist, shows the highest affinity for alpha$_2$-adrenergic receptors compared to other drugs such as xylazine and medetomidine and has gained interest in veterinary anesthesiology over medetomidine (Kuusela *et al*., 2000). Epidural ropivacaine (Singh *et al.,* 2005) and epidural xylazine and ketamine (Singh *et al.,* 2007a), have been used for anesthetic management of goats suffering from urolithiasis. Combination of xylazine and ketamine has been used with intraspinal and intramuscular route in uremic buffalo calves (Pathak *et al.*, 2009).

Dexmedetomidine has also been studied in goats, and its clinical effects are presumed to be comparable with those of racemic medetomidine (Hayashi *et al.,* 1991). When ketamine was used with dexmedetomidine, it opposed the bradycardic effects of dexmedetomidine in human patients (Shukry and Miller, 2010). Ketamine along with xylazine for safe epidural analgesia has been studied in uremic goats (Singh *et al*., 2007) and buffalo calves (Pathak *et al*., 2009). The present study was designed to compare the effects of dexmedetomidine alone and its combination with ketamine and/or ropivacaine on the clinical, physiological and biochemical parameters for tube cystostomy in urolithic buffalo calves.

MATERIALS AND METHODS

The study was conducted on 15 male buffalo calves reported with the complain of urinary obstruction at the Division of Surgery, Indian Veterinary Research Institute, Izatnagar, Bareilly (U.P.) and selected for tube cystostomy. Only those cases of urethral obstruction, which had obstruction for 2 to 4 days were included in the study. The clinical status of the animal was assessed by recording heart rate, respiratory rate and rectal temperature and by conducting hematological examination.

Experimental design

The animals were randomly distributed to 3 equal groups *viz*. D, DK and RDK based on the anesthetic agent(s) used. The dose of different anesthetics were standardized after conducting pilot trials in a few buffalo calves before start of the study. In Group D- dexmedetomidine 7.5 µg/kg, in Group DK- dexmedetomidine and ketamine 3.75 µg/kg and 2 mg/kg, respectively, and in Group RDK- ropivacaine, dexmedetomidine and ketamine 0.15 mg/kg, 2.5 µg/kg and 2 mg/kg, respectively, were administered subarachnoidally at lumbosacral space. Onset of analgesia was recorded by observing response to pin pricks at the perineal region at every 10 seconds till no response was shown by the animal. The time from injection of drug to the loss of pin prick response was considered as the time of onset of analgesia

(in seconds). The extent of analgesia was recorded by making pin pricks at tail, perineum, inguinal region, upper part of hind limbs, digits, posterior flank, anterior flank, thorax and lower abdomen at 0, 5, 10, 15, 20, 30, 45, 60, 75 and 90 minutes after injection of drug(s). The depth of analgesia was assessed by assigning by a sense to pin prick response as shown in PF- posterior flank,

1. Relaxation of the jaw was taken as a measure of muscle relaxation. It was evaluated by observing the resistance to opening of the jaw on applying the pressure on lower and upper jaws. Time (in minutes) from loss of sensation to return of sensation at perineal region was considered as duration of analgesia. Time of standing recovery was recorded as the time when animals started walking without support.

Heart rate (beats/min) by non-invasive blood pressure (NIBP) monitor, respiratory rate (breaths/min) by counting the movement of thorax and rectal temperature (^{o}C) by a digital thermometer were recorded before at 0 minute and at 5, 10, 15, 20, 30, 45, 60, 75, and 90 minutes after administration of drugs. Blood samples (4 ml in heparin and 1 ml in sodium fluoride) were collected from the jugular vein at 0 minute (base line), 30, 60 and 90 minutes after administration of drugs. The blood samples were centrifuged at 3000 rpm for 15 minutes and plasma was separated and stored at -20^{o}C until assayed. The plasma was used for estimation of urea nitrogen by diacetyl monoxide (DAM) method (Wybenga *et al*., 1971), plasma glucose by GOD/POD method (Trinder, 1969) and plasma creatinine by alkaline picrate method (Toro and Ackerman, 1975).

One way ANOVA (analysis of variance) was used to compare the values of recovery time, sternal recumbency time and duration of anesthesia between groups. Two-way ANOVA was used to compare the means at different time intervals among different groups as well as at different time intervals using Proc. GLM of SAS 9.2. The subjective data generated from the scoring of various parameters was analyzed using Kruskal Wallis test. A value of $P<0.05$ was considered significant.

RESULTS

Time of onset of analgesia was significantly ($P<0.05$) higher in Group D than other groups. Analgesia of tail in animals of Group RDK and DK was complete after 5 minutes and remained so until the end of observation period. It was complete after 15 minutes in Group D. Analgesia of perineum was complete after 5 minutes in DK and RDK while after 30 minutes in Group D. Analgesia at inguinal region was complete after 5 minutes in Group DK, after 10 minutes in Group RDK and after 30 minutes in Group D. Analgesia at digit was complete after 5 minutes in Group DK and RDK while after 20 minutes in Group D. Analgesia at posterior flank was complete after 10 minutes in Group DK and RDK while after 30 minutes in Group D. Complete analgesia at anterior flank in Group DK and RDK was recorded from 15 to 75 minutes, while in Group D it is recorded from 30 to 75 minutes interval. Analgesia at thorax was complete in Group D with score of 2 from 30 to 75 minutes interval. In Group DK, it almost remained 2 throughout the observation. In Group RDK, the score reached maximum at 60 and 75 minutes interval. Analgesia at thigh was complete from 10 minutes in Group DK and RDK, while it is after 20 minutes in Group D throughout the observation. Analgesia at lower abdomen was complete in Groups DK and RDK from 10 to 90 minutes interval while it was after 30 minutes in Group D.

Table 1. Numeric scoring system used for recording of various reflexes and response.

Parameter	Score				
	0	1	2	3	4
Extent and depth of analgesia	No analgesia (strong response)	Mild analgesia (weak response)	Moderate analgesia (occasional response)	Complete analgesia (no response)	
Motor incoordination	Walking without staggering	Walking with staggering (little in-coordination)	Walking with extreme in-coordination.	Unable to walk or sternal recumbency	Lateral recumbency
Salivation	No salivation	Mild salivation	Moderate salivation	Excessive salivation	
Sedation	Standing alert	Standing but tired with slight ptosis of eyelids	Standing with wide stance and extreme lowering of head	Animal attain recumbency but can sit without support	Animal is unable to sit without support and attain lateral recumbency
Jaw relaxation	Not allowing to the open the jaws.	Resistant to opening the jaws and closed quickly	Less resistance to opening of jaws and closed slowly	No resistance and jaws remain open	

Table 2. Mean±SE values for onset of analgesia, duration of analgesia and recovery time in different groups at different intervals.

Groups	Onset of analgesia	Duration of analgesia	Recovery time
D	19.00±2.61^{b}	100.80±5.42^{a}	128.80±5.11^{a}
DK	1.15±0.11^{a}	135.20±3.22^{b}	142.00±4.64^{a}
RDK	2.37±0.22^{a}	124.60±6.45^{b}	134.20±6.01^{a}

Values with different superscript among groups differ significantly (P<0.05) at corresponding intervals.

Table 3. Duration of complete analgesia at different sites of the body (in minute).

Group	Parameters								
	Tail	Perineum	Inguinal	Thigh	Digit	PF	AF	LA	Thorax
D	15-90	30-90	30-90	30-90	20-90	30-90	30-75	30-90	-
DK	5-90	5-90	5-90	5-90	5-90	10-90	15-75	10-90	-
RDK	5-90	5-90	10-90	10-90	5-90	10-90	15-75	10-90	-

PF- posterior flank, AF- anterior flank, LA- lower abdomen

Table 4. Mean±SE of biochemical parameters in buffalo calves of different groups.

Parameter	Group	Interval (minute)			
		0	30	60	90
Plasma glucose (mmol/L)	D	6.00±0.34	7.10±0.63*	6.71±0.66	7.41±0.67^{*c}
	DK	5.98±0.20	6.57±0.50	7.03±0.39	7.04±0.19^{*bc}
	RDK	5.74±0.41	5.62±0.37	5.92±0.56	5.47±0.50^{a}
Plasma urea nitrogen (mmol/L)	D	9.72±1.10	9.63±1.10^{ab}	9.91±1.14	10.04±0.84
	DK	10.64±1.21	11.82±1.28^{ab}	10.40±0.61	11.20±0.63
	RDK	9.22±1.76	8.41±1.44^{a}	9.49±1.87	9.12±1.84
Plasma creatinine (µmol/L)	D	166.37±50.00	199.97±36.66	183.17±57.24	193.71±68.13
	DK	144.73±18.00	134.41±40.64	214.14±37.05	197.66±34.70
	RDK	381.27±177.49	398.62±199.11	300.34±160.55	362.36±143.79

^{a,b,c} Values with different superscript among groups differ significantly (P<0.05) at corresponding intervals.

*Significantly different from base value (P<0.05).

interval while it was after 30 minutes in Group D. Duration of analgesia of Group D, was significantly (P<0.05) lower than other Groups. In Group DK and RDK the score of 4 (lateral recumbency) was recorded from 10 minutes interval up to the end of observation period. While in Group D, a score of 4 was recorded from 45 minutes after drug administration, till the end of observation period. In Group D, the sedation score remained 0 up to 30 minutes interval. Thereafter, it reached 2 from 45 to 90 minutes. In Group DK, the sedation score remained 1 from 15 to 90 minutes interval, barring 75 minutes where score of 2 was recorded. In Group RDK, no sedation was recorded up to 30 minutes. Thereafter, the score of 1 was recorded from 45 to 90 minutes interval. No significant salivation was recorded in any group. Non significant (P>0.05) jaw relaxation was recorded in all the groups. The recovery time did not differ significantly among the groups. Significantly (P<0.05) higher sedation score was recorded in Group DK than other groups. No significant salivation and jaw relaxation was recorded among the groups. Heart rate decreased gradually and remained significantly (P<0.05) lower than the baseline value until the end of observation period in all the groups. No significant (P>0.05) difference was recorded in respiratory rate among D, DK and RDK Group. A non significant (P>0.05) differences in rectal temperature was recorded among all the groups. PUN remained around the baseline value without any significant (P>0.05) change in Group D and RDK. However in Group DK, a non-significant increase (P>0.05) was recorded up to the end. In Group D, creatinine values increased non-significantly (P>0.05) as compared to baseline value till the end of observation period. In Group DK, creatinine decreased non-significantly (P>0.05) at 30 minutes interval. Thereafter, it increased non-significantly (P>0.05) at 60 and 90 minutes interval as compared to the baseline value. In Group RDK, a non-significant increase (P>0.05) was recorded at 30 minutes interval after drug administration. Thereafter, the value decreased non-significantly (P>0.05) at 60 and 90 minutes interval as compared to the baseline value. Plasma glucose among different groups, revealed a significantly (P<0.05) lower values of plasma glucose at 90 minutes intervals in Group RDK than Group D and DK. There was no significant (P>0.05) difference in plasma glucose values among other groups at all intervals (Figure 1, 2 and 3).

DISCUSSION

In our study dexmedetomidine alone produced delayed onset than dexmedetomidine with ketamine or dexmedetomidine with ropivacaine and ketamine. This might be attributed to the fact that the analgesia induced by alpha$_2$-adrenergic agonists are spinal cord mediated whereas it is spinal nerve mediated in local anesthetics (LeBlanc *et al*., 1988). In the present study, subarachnoid administration of D, resulted in longer duration of analgesia than DK or RDK. A longer duration of analgesia probably occurred as a synergistic effect of the three drugs. Xylazine with ketamine and medetomidine with ketamine produced analgesia of non-significantly longer duration as compared to ketamine alone in goats (Kinjavdekar *et al*., 2007). The extent and depth of analgesia was better in Group RDK followed by DK and then D. Better extent and depth of analgesia in combination groups could be attributed to the additive or synergistic effect of the drugs. Ketamine in combination with xylazine/medetomidine, produced moderate to complete analgesia of hindquarter in goats

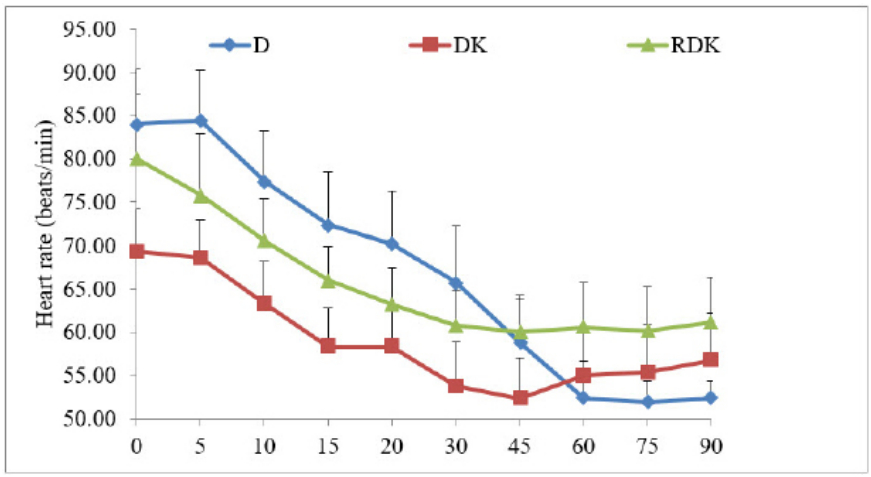

Figure 1. Mean ±SE values of heart (beats/min) rate in different groups at different intervals.

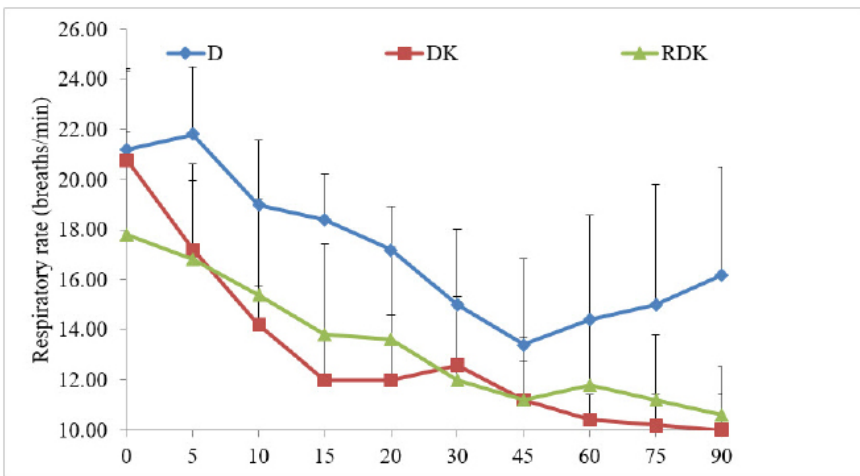

Figure 2. Mean ±SE values of respiratory rate (breaths/min) in different groups at different intervals.

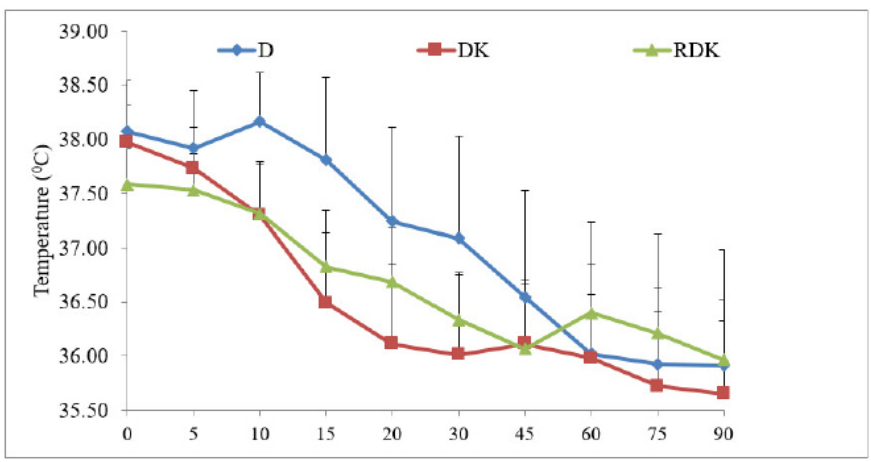

Figure 3. Mean ±SE values of rectal temperature (°C) in different groups at different intervals.

(Kinjavdekar *et al*., 2000). Complete analgesia for maximum duration recorded at the tail, perineum, inguinal region, thigh, digit and posterior flank in the present study could be attributed to the highest concentration of the drug being in the lumbosacral space, as the drug was injected at this space. The lower degree of analgesia of anterior flank, thorax and lower abdomen, might be due to the decreased concentrations of anesthetic solution away from the site of injection (Kuusela *et al*., 2000). Lower extent and depth of analgesia in dexmedetomidine alone may be due to low dose used in the present study. Kinjavdekar *et al*. (2000) reported good spinal analgesia after administration of medetomidine (10 µg/kg) in normal goats. Motor incoordination was recorded earlier in DK and RDK than dexmedetomidine alone, which might be due to local anesthetic action of ketamine/ropivacaine. In the present study, lesser motor incoordination in D Group might be due to poor motor blockade by dexmedetomidine. In goats, severe motor incoordination with xylazine and ketamine was reported by Kinjavdekar (1998) in goats. Mild to moderate sedation was recorded in all the groups. The sedative effects of alpha$_2$-agonists are associated with the activation of central alpha adrenoceptors, which causes decrease in the release and turnover of nor-epinephrine in the CNS. This indicates that the drug after absorption from the subarachnoid space was distributed to the brain (Skarda *et al*., 1992). The alpha$_2$-adrenoceptor agonist drugs give analgesia through both spinal and central actions even in subsedative doses (Vainio *et al*., 1986). It was also observed that 10 µg/kg of dexmedetomidine intravenously induced maximum sedation; increasing the dose only increased duration of sedation not intensity (Kuusela *et al*., 2000). Sedation was recorded after spinal administration of medetomidine (Kinjavdekar, 1998) and romifidine (Amarpal *et al*., 2002) in goats and epidural xylazine in goats (Singh *et al*., 2005) and in buffalo calves (Pathak *et al*., 2009). Mild degree of salivation was recorded in Group DK only. Khattri *et al*. (2013) also recorded mild salivation by dexmedetomidine, in urolithic buffalo calves. Ketamine has also been reported to stimulates salivation in most species (Haskins *et al*., 1975; Muir *et al*., 1977). Jaw relaxation signifies the extent of sedation and muscle relaxation up to head region. Alpha$_2$-agonists have been reported to produce profound muscle relaxation when used alone or in combination with opioid agonist-antagonists (Pratap *et al*., 2000; Ahmad *et al*., 2011). Moderate muscle relaxation has been recorded in all groups in the present study. Ketamine does not have musle relaxant property and the relaxation of jaw in Groups DK and RDK might be attributed to the action of dexmedetomidine. Early recovery in Group D, might be attributed to the subsedative dose taken. In all the groups, there was gradual decrease in heart rate, which might be due to decrease in sympathetic tone. A significant decrease in heart rate is considered a classical response following administration of alpha$_2$-agonist (Ruffolo *et al*., 1993). Ketamine alone and along with medetomidine cause increase in heart rate for few minutes and then again comes to normal (Amarpal *et al*., 2005). Decrease in respiratory rate was recorded in all groups. However, decrease in respiratory rate was more pronounced in groups containing ketamine *viz*. DK and RDK. In contrast to the present study the combination of alpha$_2$-agonist with ketamine first increased the respiratory rate up to 45 to 60 minutes (Kinjavdekar *et al*., 2000). Alpha$_2$-agonists have been reported to cause some degree of respiratory depression. This could be due to depression of respiratory centres through stimulation of supraspinal adrenoceptors following

systemic absorption of the drug, as suggested by Lin *et al*. (1998); Prado *et al*. (1999).

Amarpal *et al*. (2007) observed dose dependent decrease in respiratory rate after lumbosacral administration of ropivacaine in buffaloes. Decreased respiratory rate might result from their depressing action on respiratory center in central nervous system (Hall *et al*., 2001). Decrease in rectal temperature was recorded in all groups. However, more pronounced decrease was recorded in Groups DK and RDK contained ketamine. In the present study decrease in RT might be due to the additive depressant effect of ketamine on thermoregulatory centres in CNS. Kinjavdekar (1998) also recorded significant decrease in RT after administration of alpha$_2$-agonost with ketamine in goats. The decrease in rectal temperature by dexmedetomidine may be due to generalized sedation, decrease in metabolic rate, muscle relaxation and CNS depression produced by sedative and analgesic effect. Alpha$_2$-agonists have been reported to induce prolonged depression of thermoregulation (Ponder and Clarke, 1980) Simlarly, decrease in RT has been reported after medetomidine administration in goats (Kinjavdekar *et al*., 2000), dexmedetomidine in uremic goats (Kumar *et al*., 2013) and buffalo calves (Khattri *et al*., 2013) and after ropivacaine administration in buffaloes (Amarpal *et al*., 2007). The plasma urea nitrogen (PUN) showed only non-significant changes in the values throughout the observation period, suggesting that the groups are safe and rule out the possibility of renal damage. Kinjavdekar *et al*. (2000) found non-significant increase in serum urea nitrogen in lignocaine, medetomidine and their combination group with ketamine in goats. Khattri *et al*. (2013) in buffalo calves and Kumar *et al*. (2013) in goats found non-significant increase in PUN in dexmedetomidine treated animals. Plasma glucose increased significantly in all groups. Plasma creatinine did not change significantly in any group in the present study. Contrary to the present study Kumar *et al*. (2013); Khattri *et al*. (2013) reported decrease in plasma creatinine values after IV dexmedetomidine in goats and in buffalo calves, respectively. Hyperglycemia may be attributed to alpha$_2$-adrenergic mediated inhibition of insulin release by stimulation of alpha$_2$-adrenoceptors in the pancreatic beta cells (Angel and Langer, 1988). Hyperglycemic effect after medetomidine and medetomidine-ketamine administration had been reported in goats (Hugar *et al*., 1998).

CONCLUSION

It was concluded that, dexmedetomidine produces delayed onset and short duration of analgesia on subarachnoid administration at lumbosacral space. Combination of ropivacaine, dexmedetomidine and ketamine provides better extent and depth of analgesia without alarming changes in biochemical and physiological parameters and thus, may be considered safe for tube cystostomy in urolithic buffalo calves.

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