

Continuous intravenous infusion anaesthesia with ketamine in medetomidine, midazolam, butorphanol premedicated and thiopental induced buffaloes

V MALIK¹, P KINJAVDEKAR², AMARPAL³, H P AITHAL⁴, A M PAWDE⁵ and SURBHI⁶

Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh 243 122 India

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ABSTRACT

The study was conducted with an objective to standardise and evaluate the continuous intravenous anaesthesia using ketamine in buffaloes and to compare it after 2 different preanaesthetic regimens. Continuous intravenous infusion (CII) anaesthesia in 6 male adult buffaloes was used in K-1 and K-2 groups. In K₁ medetomidine (2.5 µg / kg) + butorphanol (0.05 mg/kg) and in K₂ midazolam (0.25 mg/ kg) + butorphanol (0.05 mg/kg) intravenously were used. Induction by 5% thiopental sodium and maintenance by 1% ketamine was done. Clinicophysiological, haematobiochemical and haemodynamic parameters were recorded.

Group K-1 produced better sedation and analgesia. Muscular relaxation was excellent in both groups. Depression of palpebral reflex was better in K-2, depression of corneal reflex was comparable and depression of pedal and pinprick reflexes was higher in K-1. Lesser dose of thiopental was required in K-1 (2.87±0.44 mg/kg) than K₂ group (7.14±0.36 mg/kg). The infusion rates of ketamine were 0.13±0.01 and 0.16±0.01 mg/kg/min in K-1 and K-2. Weak time was comparable. Recovery time, resumption of sternal recumbency and standing time were higher in K-2. Bradycardia in K-1 and tachycardia in K-2 was recorded. Respiratory rate decreased in K-1. Rectal temperature decreased in both groups. MAP decreased in K-1 and increased in K-2. CVP increased after premedication, decreased after induction and maintenance in both groups.

Medetomidine - butorphanol provides better quality sedation, analgesia and muscle relaxation, has more dose sparing effect on induction and maintenance agents and maintains cardiopulmonary dynamics better than midazolam-ketamine in buffaloes. Additionally continuous intravenous infusion of ketamine (0.13–0.16 mg/kg/min) can be used safely and effectively for maintenance of anaesthesia in buffaloes premedicated with proposed drugs.

Key words: Buffaloes, Butorphanol, Continuous intravenous infusion, Ketamine, Medetomidine, Midazolam, Thiopental

Continuous intravenous infusion (CII) is a better alternative to intermittent bolus injection (IBI) and inhalant anaesthesia due to lesser side effects on cardio respiratory and adrenocortical systems (Ilkiw and Pascoe 2003). Most of these studies have been conducted in equine (Luna *et al.* 1996) and canine (Jacobson and Hartsfield 1993), and sporadic reports are available in small ruminants (Larenza *et al.* 2005) but use of these techniques in large ruminants especially buffaloes is lacking. The study was undertaken to test the suitability of CII with ketamine in buffaloes to compare the suitability of medetomidine/midazolam -

butorphanol combinations with thiopental, to standardize ketamine for maintenance of anaesthesia by CII and to compare the clinicophysiological and haemodynamic effects of ketamine in medetomidine/midazolam-butorphanol-thiopental premedicated buffaloes.

MATERIALS AND METHODS

The study was conducted in the Department of Surgery, Indian Veterinary Research Institute, Izatnagar and was approved by the Institutional Animal Ethics Committee.

Animals

Healthy male buffaloes (6) of 2 to 3 years of age, weighing 290 to 325 kg were used. The animals were stall-fed and had free access to feed and water. Uniform managerial conditions were maintained throughout the period of study. The animals were kept off feed for 48 h and off water for 24 h prior to each trial.

Present address: ¹Assistant Professor (e mail: vickeyvet@gmail.com), DUVASU, Mathura, Uttar Pradesh 281 001.

²Principal Scientist (e mail: pk@ivri.up.nic.in), ³⁻⁵Senior Scientist (e mail: amarpal@ivri.up.nic.in; aithal@ivri.up.nic.in; pawde@ivri.up.nic.in), ⁶PhD scholar (e mail: surbhiivri@gmail.com), Division of Surgery.

Design

The animals received 2 treatments (groups K-1 and K-2) randomly at weekly intervals. In K-1, medetomidine (2.5 µg/kg) + butorphanol (0.05 mg/kg), intravenously, while in K-2 midazolam (0.25 mg/kg) + butorphanol (0.05 mg/kg) were used intravenously. After premedication, the animals were restrained in right lateral recumbency and anaesthesia was induced by 5% thiopental sodium intravenously till the pinprick reflex over the ribs and coronary band was abolished. The anaesthesia was maintained with CII of 1% ketamine in both groups up to 120 min and the depth was determined by towel clamp method.

Clinical observations

Sedation: Sedation was evaluated by behavioural changes and graded on a 1–4 scoring scale where 1 (no sedation): Standing alert, keeping the head high, eyes open; 2 (mild): Standing tired, drooping of head and eyelids; 3 (moderate): Able to sit without support, drooping of head and eyelids; 4 (excellent): Unable to sit without support, drooping of head and eyelids

Analgesia: Analgesia was assessed by the animals' response at every 15 min interval by pinprick on the ribs, periosteum and at coronary band and was graded on a 1–4 scoring scale where 1 (no analgesia): Strong reaction to pin pricks; 2 (mild): Weak response to pin pricks 3 (moderate): Occasional response to pin pricks; 4 (excellent): No response to pin prick

Muscle relaxation: Muscles relaxation was observed by the ease with which the jaws of recumbent animals could be opened, their hind limbs could be bent without resistance, and the flaccid abdomen could be pressed and was graded on a 1–4 scoring scale where 1 (no relaxation): Tightly closed jaws and stiff limbs; 2 (mild): Moderate resistance to opening of jaws and bending of limbs; 3 (moderate): Mild resistance to opening of jaws and bending of limbs; 4 (excellent): No resistance to opening of jaws and bending of limbs and flaccid abdomen.

Reflexes: Degree of abolition of palpebral, corneal, pedal reflexes and pinprick were recorded at different intervals and was graded on a (-) to (+++++) scoring scale where (-): Completely abolished; (+): Mild response; (++) : Moderate response; (+++): Good response; (++++): Excellent response.

Position of eyeball: Position of eyeball was recorded at different intervals and was graded as C (central); or D (downward rotation).

Extent of salivation: The extent of salivation was recorded and was graded on a (-) to (+++++) scoring scale where (-): Absent; (+): Mild; (++) : Moderate; (+++): Good; (++++): Profuse.

Weak time (WT): The time elapsed from the time of injection of preanaesthetic agents to the time when the animals showed ptosis of head.

Recovery time (RT): The time from discontinuation of

intravenous drugs and the first spontaneous movement of any body part.

Sternal recumbency time (SRT): The time from discontinuation of intravenous drug to the spontaneous regaining of sternal recumbency.

Standing time (ST): The time from discontinuation of intravenous drug to spontaneous regaining of standing position.

Doses and infusion rates of drugs: The doses of thiopental sodium (mg/kg) and the infusion rate of ketamine (mg/kg/min) were calculated after completion of each trial.

Physiological observations

Heart rate (HR) (beats/min) by non-invasive blood pressure (NIBP) monitor, respiratory rate (RR) (breaths/min) by observing the thoracic excursion and rectal temperature (RT) (°C) was recorded by a digital thermometer before any drug (base line) and at 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 min of anaesthesia.

Haemodynamic observations

For recording central venous pressure (CVP), a preheparinized polythene catheter was introduced into the jugular vein through a 12-gauge hypodermic needle and passed up to the level of right atrium. It was attached to the saline manometer (CVP) (cm of H₂O) filled with heparinized saline, through a three-way stopcock. The cuff of the noninvasive blood pressure (NIBP) monitor was applied around the base of the tail for recording systolic (SBP), diastolic (DBP) and mean arterial blood pressure (MAP). The SpO₂ (%) was measured by applying the sensor of pulse oxymeter on tongue. The values of these parameters were recorded at time 0 (base line) and at 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 min of anaesthesia.

Analysis of variance (ANOVA) was used to compare the means at different time intervals between two groups. Paired “t” test was used to compare the mean at different intervals with their base values in both groups (Snedecor and Cochran 1980). For nonparametric observations Kruskal-Wallis one-way test (Siegel and Castellan 1988) was used to compare the means between groups.

RESULTS AND DISCUSSION

Clinical observations

Group K-1 produced better sedation than K-2. In K-1 group median sedation score was 3.5±0.816 whereas, in K-2 median sedation score was 2±0.894. In K-1 excellent sedation was evident after 2 to 3 min of premedication. Three animals in this group attained sternal recumbency, whereas, 2 animals bent on their knees and could stand up intermittently. All the animals remained calm and did not show any sign of excitement until anaesthesia was induced. Animals of K-2 group showed moderate sedation where 2 animals attained sternal recumbency immediately after premedication, but

they stood up after 5 to 8 min. Other animals remained in standing position with varying degree of ataxia. K-2 animals exhibited excitement with vigorous licking of muzzle, shaking of head and tail, tried to stand up, if recumbent within 5 min of drug administration. In this study an attempt was made to decrease these side effects by using a small dose of medetomidine with an opioid to get synergistic response. Synergistic sedative and analgesic activity between alpha-2 agonists and opioid agonist-antagonist has been reported in horses (Malik and Singh 2008) and in cattle (Levine *et al.* 1992). The doses of medetomidine (2.5 µg/kg) and butorphanol (0.05 mg/kg) were selected on the basis of pilot trials to get adequate sedation. Midazolam-butorphanol in the present study produced only moderate sedation and varying degrees of excitement in all the animals, which might be due to lower doses and probably lack of synergistic activity between the 2 drugs.

In K-1 the analgesia was excellent (median score 4±0.0). In K-2 the analgesia was good (median score 3±0.51) with 4 animals had score 3 and 2 animals had score 2. Group K-2 produced significantly lesser degree of analgesia than K-1. Butorphanol with medetomidine has a high affinity for μ receptors and decreases agonist activity of μ and κ receptors and produced good analgesia at lower doses owing to the synergistic action. Similar type of synergism between alpha-2 agonists and opioid analgesics was reported in goats (Carroll *et al.* 1998). Midazolam-butorphanol combination also provided adequate analgesia; however, opioids have not been used extensively in ruminants as they might cause excitement. Adequate analgesia was observed after midazolam-thiopental anaesthesia in buffaloes (Cheema 2002).

In both groups adequate and excellent muscle relaxation was observed with no significant difference between groups that might be attributable to combined effects of both drugs (Ko *et al.* 1996). Median muscle relaxation score was 4±0.51 in K-1 and K-2. In both groups 4 animals produced excellent (score 4) and 2 animals showed good muscle relaxation (score 3). The muscle relaxant property of midazolam is mediated through glycine receptors in the spinal cord (Richter 1981). Ketamine, however, do not possess muscle relaxation property.

During preanaesthetic period depression of palpebral reflex was higher in K-2, where 2 animals showed mild to moderate response at a few intervals, and lower in K-1, where most of the animals showed mild to moderate response. In both groups corneal reflex was depressed and showed good to moderate response after preanaesthetics, abolished completely after induction and remained mild or moderate up to the end and was comparable between K-1 and K-2. Moderate to complete abolition of these reflexes after medetomidine (10–30 µg/kg) and pentazocine (2–3 mg/kg) induced neuroleptanalgesia in goats (Amarpal *et al.* 1998) and midazolam (0.2 mg/kg, i/v) in bovine (Kaur and Singh

2004) were reported. During maintenance with ketamine in K-1, the palpebral and corneal reflexes remained moderately depressed. However, in K-2 the palpebral reflex was abolished except in two animals. Similar observations were reported during midazolam-ketamine anaesthesia in bovine (Kaur and Singh 2004).

The eyeball remained central in position during sedation in both groups. After induction, it rotated downward in K-1 whereas remained in centre in K-2. During maintenance, it remained in centre in both groups as the effect of thiopental had weaned off. Similar findings were reported after thiopental administration in bovine (Bishnoi 2001, Kaur and Singh 2004). Salivation during sedation, post-induction and maintenance period was higher in K-1 than K-2. Excessive salivation after alpha-2 agonists was reported even with prior atropinization due to their effects on salivary gland through alpha-1 adrenergic receptors (Ruskoaho 1986) and by decreased swallowing reflex (Kokkonen and Eriksson 1987).

The median values of weak time in K-1 and K-2 groups were 2.00±0.52 and 2.50±0.98 min, respectively. Almost similar values of weak time (112 sec) were reported after medetomidine (20 µg/kg) administration in buffalo calves (Kinjavdekar *et al.* 2003). Faster appearance of incoordination at lower dose of medetomidine (2.5 µg/kg) in the present study might be due to synergistic interaction between medetomidine and butorphanol.

The median values of recovery time in K-1 and K-2 were 10±3.39 and 35±15.95 min, respectively. The median values of SRT in K-1 and K-2 were 25±7.13 and 73±26.75 min respectively. The median values of ST in K-1 and K-2 were 35±11.29 and 204±74.4 min, respectively. K-2 took significantly ($P<0.05$) longer time to recover than K-1 due to the larger induction doses of thiopentone sodium.

Mean dose of thiopental sodium in K-1 was 2.87±0.44 mg/kg and in K-2 it was 7.14±0.36 mg/kg. K-1 required significantly ($P<0.05$) lesser dose of thiopental sodium. Medetomidine-midazolam has been reported to reduce the induction dose of thiopental greatly. However, midazolam-butorphanol combination moderately reduced the induction dose (Kojima *et al.* 2002). This supports the finding of the present study where significantly higher reduction in the induction dose of thiopental occurred in K-1 than K-2. A lower induction dose of thiopental (5.0±0.88 mg/kg) was reported after midazolam (0.2 mg/kg, i/v) administration in bovines (Kaur and Singh 2004) than used in the present study (7.14±0.36 mg/kg, in K-2). The difference in the induction dose might be attributed to the lower doses of midazolam used in the present study. Mean infusion rates of ketamine in K-1 and K-2 groups were 0.16±0.01 and 0.13±0.01 mg/kg/min, respectively. Higher infusion rate was required in K-1 group to maintain the adequate depth of anaesthesia which might be due to the higher induction dose of thiopental used in K-2 group.

Physiological observations

Heart rate significantly ($P < 0.05$) decreased after premedication in K-1 group up to 15 min (Fig.1). After 30 min, HR improved and returned around base value at the end. In K-2 group HR increased significantly ($P < 0.05$) after premedication and remained high up to 40 min. It decreased and fluctuated around the base line till the end. From 5 min to 50 min HR remained significantly higher in K-2 group. Inhibition of sympathetic tone from the CNS, vagal activity in response to medetomidine induced vasoconstriction and direct increase in the release of acetyl choline from sympathetic nerves in the heart have been reported as the possible mechanisms of bradycardia (MacDonald and Virtanen 1992). Similar effects have been reported after medetomidine administration in different species (Kuusela *et al.* 2000). On the other hand midazolam-butorphanol produced significant tachycardia, which is in accordance with the findings in goats after midazolam (1.2 mg/kg) administration (Stegmann and Bester 2001). Midazolam reportedly caused transient hypotension in man and the increase in HR may be a reflex response (Lebowitz *et al.* 1982). The heart rate in K-1 improved during maintenance due to the positive chronotropic effect of ketamine. Higher values of heart rate during ketamine infusion in comparison to post sedation values could be attributed to its sympathomimetic action mediated within the CNS, inhibition of catecholamine re-uptake by peripheral sympathetic nerve endings and the subsequent effects of catecholamines on the myocardium (Thurmon *et al.* 1996).

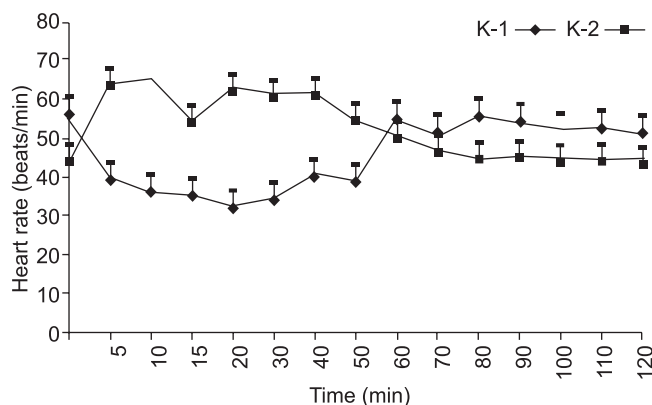


Fig. 1. Heart rate (beats/min) in the animals of groups K-1 and K-2.

In K-1, respiratory rate decreased nonsignificantly ($P < 0.05$) up to 30 min. RR increased significantly ($P < 0.01$) between 90 and 120 min (Fig. 2). K-2 showed significant ($P < 0.01$) bradypnoea 15 min after premedication up to 120 min. Significantly ($P < 0.05$) higher RR was recorded in K-1 up to 10 min and significantly ($P < 0.05$) lower RR was recorded in K-2 from 40 min till the end. Decrease in the frequency of respiration was observed in both groups during sedation period. Respiratory depression by medetomidine

might be secondary to the central nervous system depression produced by alpha-2 adrenoceptor stimulation (Sinclair 2003) or due to direct depression of the respiratory centers by preanaesthetics (Kumar and Thurmon 1979). A similar decrease in RR was also reported by Muge *et al.* (1994) after medetomidine in sheep. In contrast, a little effect on respiratory rate after intravenous medetomidine in goats (Pawde *et al.* 1996) was reported. Increase in respiratory rate during maintenance of anaesthesia in K-1 was due to some degree of hyperventilation induced by ketamine. Similar observations were reported in pigs (Sakaguchi *et al.* 1995). But respiratory rate remained decreased throughout the period of anaesthesia in K-2. However, comparatively lower infusion

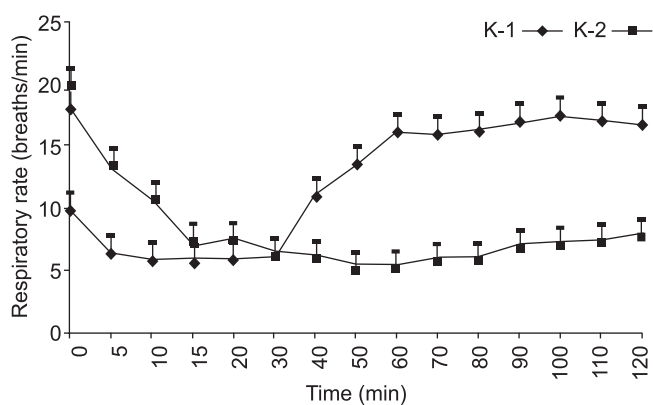


Fig. 2. Respiratory rate (breaths/min) in the animals of groups K-1 and K-2.

rate of ketamine was required in group K-2, which probably could not counterbalance the respiratory depression induced by midazolam-butorphanol and thiopental Sodium.

In K-1, rectal temperature decreased significantly ($P < 0.01$) from 40 min up to the end (Fig.3). In K-2, no

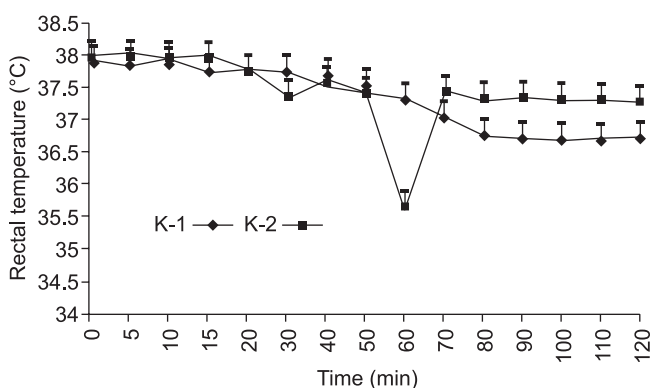


Fig. 3. Rectal temperature (°C) in the animals of groups K-1 and K-2.

significant difference in RT was recorded. Significant decrease in rectal temperature observed in both groups during post anaesthetic period might be attributed to a decrease in the skeletal muscle tone, reduced metabolic rate, depression

of thermoregulatory centres and vasodilation (Ponder and Clarke 1980). In K-1, hypothermia occurred earlier and was more pronounced than in K-2.

Haemodynamic observations

In K-1, a significant ($P < 0.05$) decrease in SBP was observed after premedication and induction, which improved but was lower than the base value. In K-2 SBP increased significantly ($P < 0.05$) after premedication. K-1 showed a significant ($P < 0.05$) decrease in DBP after premedication till the end. In K-2 a nonsignificant ($P > 0.05$) increase in DBP was noticed throughout the observation period. DBP remained significantly higher up to 70 min in K-2 group than K-1. K-1 showed significant ($P < 0.01$) decrease in MAP after premedication and induction till the end. In K-2 a nonsignificant ($P > 0.05$) increase in MAP was recorded after premedication and during induction and maintenance of anaesthesia (Fig. 4). It was significantly ($P < 0.05$) lower up to 70 min in K-1 than K-2 group. In contrast to our findings, a significant increase in systolic blood pressure was observed after xylazine-butorphanol in horses (Robertson and Muir 1983). Preservation of haemodynamic functions occurred with midazolam and this involves an intact sympathetic reflex as demonstrated by release of endogenous catecholamine (Glisson *et al.* 1982) and could be the possible reason for increase in MAP after midazolam-butorphanol administration. In K-1 group MAP remained on lower side throughout the period of observation but ketamine moderated the hypotensive effect of medetomidine. An increase in the arterial blood pressure after ketamine administration could be due to the selective positive inotropic influence on heart muscles or reflexogenic autonomic nervous system changes. Ketamine increased the blood pressure and heart rate in animals (Thurmon *et al.* 1996). On the contrary, hypotension was reported as intra-operative complications when midazolam-ketamine combination was used for induction of anaesthesia along with butorphanol as analgesic in a 2-month-old buffalo calf (Stegmann 2004). Midazolam on one hand depresses the parasympathetic system and ketamine

on the other hand stimulates the sympathetic system. Increased MAP during the entire observation period in K-2 group of the present study could be due to the combined effect of parasympathetic depression and sympathetic stimulation.

In K-1 a significant ($P < 0.01$) increase in CVP was noticed after premedication, which decreased after induction till the end. K-2 showed a significant ($P < 0.01$) increase after premedication and remained so up to the end (Fig. 5). It was significantly ($P < 0.05$) higher between 5 and 30 min in K-1. The combination of medetomidine and butorphanol produced a highly significant increase in CVP, which was a likely reflection of medetomidine induced bradycardia and possibly vasoconstriction resulting in to central shift of blood to the venous compartment (Klein and Sherman 1977), decrease in myocardial contractility and an increase in the after load (Serteyn *et al.* 1993). Significant increase in CVP was demonstrated after medetomidine-butorphanol administration in goats by Pawde *et al.* (1996). A highly significant increase in CVP recorded in the present study could be attributed to the combined action of medetomidine and butorphanol. A slight decrease in CVP was observed immediately after thiopentone administration in the present study. Similar findings were reported after thiopentone administration in buffaloes by Singh *et al.* (1980). In K-1 the CVP, however, showed a decline after the start of maintenance of anaesthesia but it remained significantly higher than the base values. Continued maintenance of CVP at higher level in this group might possibly be attributed to depressive influence of medetomidine-butorphanol on the heart that gradually subsided with the elimination of the drugs as reported by Kinjavdekar *et al.* (2005). In K-2, the CVP increased significantly after premedication but the increase was lesser in comparison to K-1 and this trend was recorded for the entire observation period. Lesser rise in CVP in this group might be attributed to increased HR and decreased systemic vascular resistance.

In both groups a significant ($P < 0.01$) decrease in SpO_2 was noticed from premedication till the end. However, the

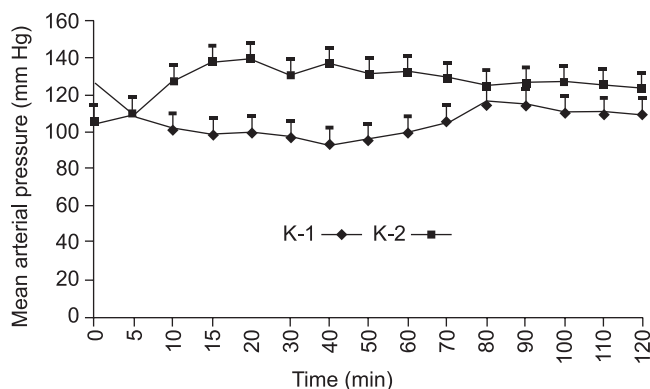


Fig. 4. Mean arterial pressure (mmHg) in the animals of groups K1 and K2.

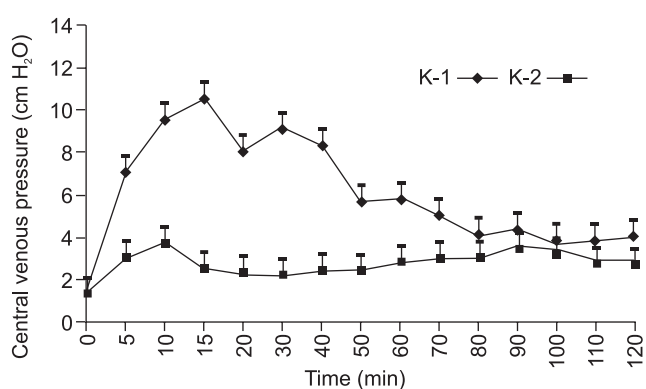


Fig. 5. Central venous pressure (cm H₂O) in the animals of groups K1 and K2.

values remained within normal physiological limits. Decrease in SpO₂ values were possibly due to certain degree of respiratory depression in both groups. Low SpO₂ values with medetomidine-ketamine anaesthesia were reported in rabbits (Grint and Murison 2008).

Our results suggested that medetomidine (2.5 µg/kg) - butorphanol (0.05 mg/kg) combination provides better quality sedation, analgesia and muscular relaxation with transient but slightly more cardiac depression than midazolam (0.25 mg/kg) - butorphanol (0.05 mg/kg) combination when used as preanaesthetics to thiopental sodium in buffaloes. Further, medetomidine-butorphanol combination provides more dose sparing effect on anaesthetics used for induction and maintenance than midazolam-butorphanol combination with shorter recovery times. Ketamine @ 0.13–0.16 mg/kg/min may be used safely for constant rate infusion anaesthesia of 2 h duration in buffaloes.

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