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Studies to Evaluate the Safety of Constant Rate Infusions of Dexmedetomidine, Ketamine and Lidocaine Alone or in Combination during Isoflurane Anesthesia in Horses

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ABSTRACT

Background: Horses mount a huge stress response to anesthesia when compared to other animals, hence are risky candidates for anesthesia. Inhalant anesthetic agents offer more control to anesthetic depth and facilitate rapid recovery, hence are considered to be safer than intravenous agents for surgical procedures requiring more than an hour, however, newer drug combinations are being explored to minimize the undesired consequences and dose rate of inhalant agents. The present study explored the safety of dexmedetomidine, ketamine and lidocaine constant rate infusion alone or as a combination along with Isoflurane for safer anesthesia in horses.

Methods: The study was conducted on 28 horses divided into S, D, DK and DKL groups having 7 animals in each. Xylazine (1 mg/kg) and butorphanol (0.05 mg/kg) were given intravenously for premedication. Ketamine (2 mg/kg) and midazolam (0.2 mg/kg) were used for induction and anesthesia was maintained with isoflurane. Normal saline (1000 ml/hour), Dexmedetomidine (2 µg/kg/hr), Dexmedetomidine and ketamine (2 µg/kg/hr and 2 mg/kg/hr) and Dexmedetomidine, ketamine and lidocaine (2 µg/kg/hr, 2 mg/kg/hr and 2 mg/kg/h) were given as CRI in groups S, D, DK and DKL, respectively. Thiopentone sodium (250 mg bolus, 5%) was given as a fast intravenous bolus whenever required. Anesthetic efficacy was evaluated based on clinical, haemato-biochemical, hemodynamic, and endocrine variables.

Result: A significant decline in mean arterial pressure was noticed in group DKL but changes in CVP and SpO2 in different groups were non-significant. Higher Blood glucose and low Insulin levels were seen in group DK during 45-60 min. Constant rate infusions of Dexmedetomidine, Ketamine and Lidocaine alone or in combination produced a significant sparing effect on Isoflurane and thiopentone while they improved peri-operative quality of anesthesia in horses.

Key words: CRI, Dexmedetomidine, Horses, Ketamine lidocaine.

INTRODUCTION

Horses mount a huge stress response to anesthesia compared to humans and other companion animals and hence are risky candidates for anesthesia (Taylor, 1989, Wagner *et al*., 2008). Day-to-day equine clinics handle surgical diseases that require both short and long-term anesthetic procedures. Though TIVA is considered safer in horses for short-term surgery, inhalant agents are unavoidable for long-term procedures (Wagner, 2008). Newer sedatives and drug combinations are employed to reduce the side effects and dose rate of inhalant agents (Bettschart-Wolfensberger and Larenza, 2007). The continuous rate infusion of Alpha 2 agonists helped to abolish many of the side effects apprehended when they were used as bolus infusions (Marcilla *et al*., 2012). A newer alpha 2 agonist like Dexmedetomidine was found to reduce the MAC value of isoflurane significantly when used as continuous rate infusions in horses (Schauvliege *et al*., 2011). Gastrointestinal surgery, particularly colic case is a big challenge to both the surgeon and anesthetist. Safer anesthetic protocols can give hope to handle risky surgeries like colic in horses while avoiding economic loss to the owner. The present study explored the safety of balanced anesthetic protocols employing Dexmedetomidine, Ketamine and Lidocaine constant rate infusion alone or in combination with Isoflurane anesthesia for elective and gastrointestinal surgery in horses.

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MATERIALS AND METHODS

Animals

The client owned horses of either sex, with an average body weight of 253.75 (160 kg to 410 kg) and an age of 4 to 9-year-old referred for elective surgery, soft tissue surgery, tumor removal, ESF, castration (ASA scale 1 and 2) and requiring approximately 1 hour of surgical procedures presented at the Referral Veterinary Polyclinic, IVRI from March 2013 to December 2015 were considered for this study. Permission to perform the study was sought from Institute Animal Ethics Committee (IVRI/SURG/12-15/012). Informed consent was taken from the owner for the collection of blood samples at required intervals.

Experimental design

The study was conducted on 28 apparently healthy adult horses with the approved consent of the owner. Animals were assigned to groups S, D, DK and DKL having seven animals in each. Individual horses of the assigned group were treated with CRI of the following drugs along with inhalant agent Isoflurane 2% in Oxygen (10 ml/kg/min) as shown in (Table 1).

Technique of drug administration

The food was withheld 10-12 hours before anesthesia with limited access to water. A 14 gauge catheter was aseptically inserted into the jugular vein for IV administration of anesthetics and blood sample collection. Pre-anesthetics were administered after proper restraining of the horses. Xylazine[1] (Xylaxin®, Indian Immunological Limited, Hyderabad, India) @ 1 mg/kg body weight and Butorphanol[2] (Butodol-2®, Neon Laboratories Limited, Mumbai) @ 0.05mg/kg body weight were injected intravenously. After 10 minutes, anesthetic induction was done with Ketamine[3] (Ketamax- 50®, Troikaa Pharmaceuticals Ltd. Uttarakhand, India) (2 mg/kg) and Midazolam[4] (Mezolam®, Uttarakhand, India) (0.2 mg/kg) intravenously. All the drugs were injected using separate syringes. Immediately after induction, an endotracheal tube was inserted and the CRI was started as mentioned in (Table1). Thiopentone sodium[5] (Thiosol* sodium, Neon Laboratories Limited, Mumbai (250 mg, 5%) bolus was administered whenever deeper anesthesia was required.

Table 1: Anaesthetic drug combination used in animals of different group.

Group	No of animals	Treatment
Group S	7	Saline (1000 ml/hr)
Group D	7	Dexmedetomidine[6] @ 2 µg/kg/hr (Dextomid®. Neon Laboratories Limited, Mumbai)
Group D K	7	Dexmedetomidine @ 2 µg/kg/hr and Ketamine @ 2 mg/kg/hr
Group D K L	7	Dexmedetomidine @ 2 µg/kg/hr, Ketamine @ 2 mg/kg/hr and Lidocaine @ 2 mg/kg/hr

Physiological parameters

Heart rate (beats/min), respiratory rate (breaths/min) and rectal temperature (°F) were recorded before administration of the drug (s) and at 0 (after induction), 15, 30, 45 and 60 min after administration of the drugs.

Biochemical observations

Blood samples (8 ml) were collected from the jugular vein in a disposable syringe before anesthesia (baseline) and at 0 (start of CRI), 15, 30, 45 and 60 min after injection of the anesthetic(s). The blood samples were centrifuged at 3000 rpm for 5 min and the serum was collected and stored at -20°C until assayed. The serum samples were subjected to the following estimations: Triglycerides: Triglycerides were estimated by using commercial kits supplied by Span Diagnostics Ltd., Surat, India. The values were expressed in mg/dl, Cholesterol: Cholesterol was estimated by using commercial kits supplied by Span Diagnostics Ltd., Surat, India. The values were expressed in mg/dl, Blood glucose: The blood glucose was estimated by using Blood Glucose Meter (Romo check insta, Acon Loboratiries, Inc. U.S.A). The values are expressed in mg/dl. Insulin, Cortisol, Adrenocorticotropic hormone (ACTH) were estimated through the RIA kit.

Cardiovascular study

Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP) and Central venous pressure (CVP) were recorded during pre, peri and post-operative periods. CVP was measured with the help of a water column manometer (cm of H2O) (C.V.P. Manometer®, Romsons Scientific and Surgical Industries Pvt. Ltd., Agra, India) before and 0 (after induction), 15, 30, 45 and 60 minutes of anesthesia. Pulse rate and SPO_2 were measured using a pulse oximeter (Model: MD300C26, pulse oximeter; Beijing Choice Electronic Tech. Co.Ltd. SN: 122526304335). The probe of the instrument was applied to the tongue of the animal. The recordings were made at the same intervals as for CVP and Oxygen saturation of hemoglobin (SpO_2).

Clinical observations

The quality of sedation, induction, muscle relaxation, analgesia and recovery from anesthesia were recorded. Sedation was recorded after pre-anesthetic administration as 0: No sedation, 1: Mild sedation with slightly lowered head, 2: Moderate sedation with the head lowered below manubrium, but respond to audible stimuli and 3: Intense sedation with head lowered below manubrium, but no response to audible stimuli. Ataxia score was evaluated before and after premedication. It was graded on 0 to 3 scales as; 0- No ataxia, 1- Animal was stable but slightly swaying, 2- Animal was swaying and leaning against the stock and 3- Animal was leaning against the stock and swaying with its hind limbs crossed and forelimbs buckling at the carpal joint. Relaxation of the trunk and limb muscles was taken as a measure of muscle relaxation during the study. It was evaluated by observing the muscular activity

of the trunk and limbs. The subjective observation was graded 0 to 3 scale as follows; 0: Muscle relaxation present in trunk and limbs, 1: Muscle twitching present in some regions of trunk and limbs, 2: Muscle twitching present over the majority portions of trunk and limbs and 3: Muscle rigidity present over the majority portions of trunk and limbs. Muscle relaxation was recorded at 0 (after induction), 15, 30, 45, and 60 min intervals. The quality of intubation was recorded as the ease and attempts to intubate by the same observer throughout the anesthetic trials. Anesthetic depth was assessed by physical signs, including movement, the position of the eyeball, depression of the protective reflexes of the eye, loss of the swallowing reflex, rate and depth of breathing, and the horse's response to surgical stimulation. The total dose of thiopentone (mg)/isoflurane (ml) required during the entire surgical procedure and the duration of the anesthesia for the surgical procedure were also recorded. Quality of recovery was scored as 1: One attempt to stand, no ataxia, 2: One or two attempts to stand, some ataxia, 3: >2 attempts to stand, but quiet recovery, 4: > 2 attempts to stand, excitation and 5: Severe excitation (Clark-Prince, 2013).

Statistical analysis

Continuous data of parametric variables within and between groups at different time intervals were analyzed using repeated measures ANOVA and that of non-parameric variables (scores) at different intervals were compared using Kruskal-Wallis test. The data were analyzed by using SAS 9.3 software.

RESULTS AND DISCUSSION

The cardiovascular and biochemical changes of the individual as well as the combination of short-acting anesthetic adjuvants as constant rate infusion during total intravenous and inhalant anesthetic (isoflurane) have been explored for anesthesia of horse. Though TIVA is considered safer in this species, inhalant agents are unavoidable for long-term procedures. Newer sedatives and drug combinations are being tested by various workers to reduce the side effects and dose rate of inhalant agents (Bettschart-Wolfensberger *et al.,* 2011). The present study was designed to derive a safer anesthetic protocol with Dexmedetomidine, Ketamine and Lidocaine as constant rate infusion along with Isoflurane anesthesia for elective surgery in horses. Different surgical procedures performed during the study are mentioned in (Table 2).

Xylazine and butorphanol brought about sedation while induction of anesthesia with midazolam- Ketamine provided adequate muscle relaxation and the horses attained recumbency easily with little assistance. Pharyngeal and laryngeal reflexes were abolished in most of the cases and freehand intubation was achieved easily. Lack of adequate laryngeal relaxation could also be due to pre-existing chronic inflammation of the larynx and trachea. Whenever freehand intubation was found difficult, a single fast bolus of 250 mg thiopentone sodium (5% solution) provided adequate muscle relaxation for intubation. Anaesthetic protocols in horses using xylaxine and ketamine alone as sedative and induction agent often required larger doses of Thiopentone sodium (1.5-2 g, 5% solution as bolus) for facilitating intubation. In our study we have observed that the pre-anesthetic and induction protocols employed in our study spared the use of thiopentone, or if at all required, a very small amount of thiopentone aided in laryngeal relaxation. Manually assisted ventilation was provided whenever apnoea spanning for more than a few minutes was observed.

There was a significant decline in rectal temperature in all the groups till the completion of the observations (45 to 60 min) (Fig 1). The decrease in RT as recorded in groups might be due to a decrease in the skeletal muscle tone, reduced metabolic rate, and muscle relaxation along with depression of the thermoregulatory center of the brain. Alpha-2 adrenergic agonists have been reported to induce prolonged depression of thermoregulation (Ponder and Clarke, 1980). These agents have also been found to depress hypothalamic noradrenergic α-2 receptors to cause hypothermia (MacDonald *et al*., 1988). Heart rate fluctuated near the baseline values during these intervals in all the groups. A decreased heart rate in groups DK and DKL might be due to the overriding effect of dexmedetomidine over ketamine (Fig 1). The incidence of postoperative bradycardia has been reported as high as 40% in healthy surgical patients who received dexmedetomidine, especially in high doses (Aho *et al*., 1993). Respiration rate also showed a significant decline from baseline values in groups DK and DKL (Fig 1). Suppression of hypothalamic center by dexmedetomidine and profound relaxation of intercostal muscles might have influenced in lowering respiration rate in these groups. Thiopentone administration can also cause depression in the respiratory center of the brain (Rawling and Kolata, 1983). At clinically effective doses, dexmedetomidine has been shown to cause much less respiratory depression than other sedatives (Belleville *et al*., 1992). However, co-administration of dexmedetomidine with anesthetic agents is likely to cause additive effects (Aantaa *et al*., 1990).

Cardiovascular parameters showed a significant decline in mean arterial pressure in groups DKL as compared to other groups (Fig 2). CRI administration of lidocaine might have reduced the MAP in DKL group animals. Similarly, a lower MAP was observed after CRI administration of Lidocaine in horses (Feary *et al*., 2005). Fielding *et al*. (2006)

Table 2: Different surgical techniques performed under the anaesthetic protocols.

Surgery performed under Inhalant anaesthesia	No. of Animals
Hernioplasty	4
Soft tissue repair	5
Elective castration	6
Rupture of orbit	3
Fracture	7
Tumour removal	3

also reported significant bradycardia and decreased mean arterial blood pressure six hours after CRI of ketamine in horses. Contrary to the present study findings, CRI of ketamine used for short- to medium-term infusion did not show significant cardiovascular depressing effects in horses (Sharma *et al*., 2019).

The changes were non-significant in Central Venous Pressure and Capillary Oxygen Saturation (SpO_2) in different groups (Fig 3). The variation in CVP in the present study may probably be attributed to the pooling of blood in the venous circulation because of the low heart rate caused by the administration of multiple drugs in this study. High levels of plasma dexmedetomidine stimulate Alpha-2B adrenoceptors in smooth muscles of blood vessels producing vasoconstriction and consequently hypertension (MacMillan *et al*., 1996). A non-significant decrease in SpO2 has been reported following administration of butorphanol–dexmedetomidine in propofol anesthetized dogs (Surbhi *et al*., 2010) which is quite similar to results obtained in this study.

Blood glucose was significantly higher in group DK as compared to base value during 45-60 min and the Insulin levels showed a decline from base values during these

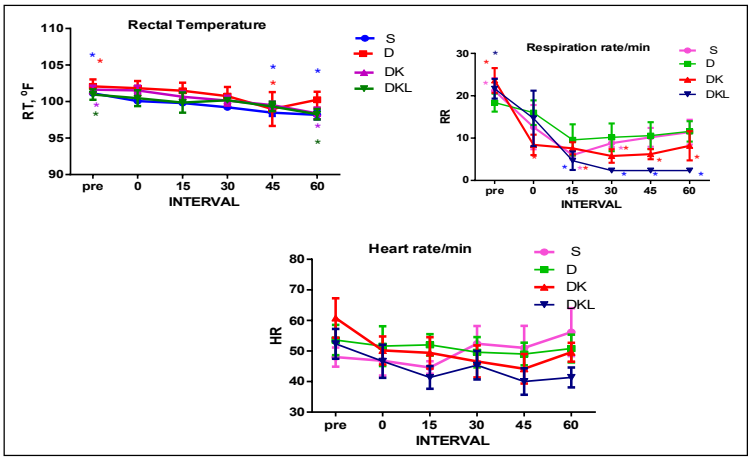

Fig 1: Mean±SD values of heart rate, respiratory rate and rectal temperature in different clinical parameters.

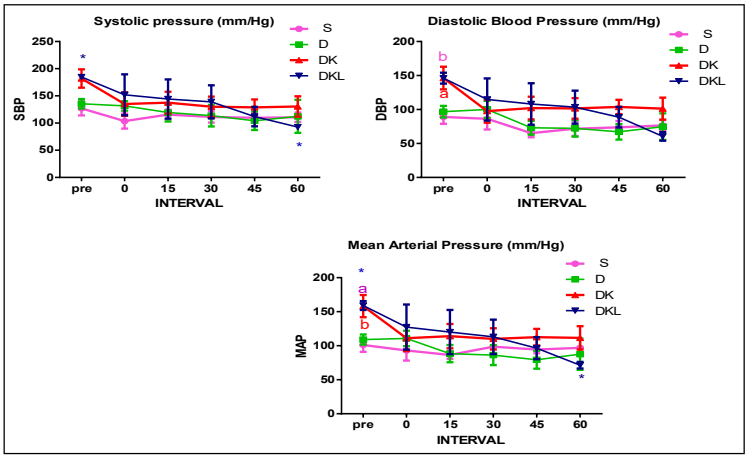

Fig 2: Mean±SD values of SBP, DBP, MAP in mm of Hg in different groups at different time intervals .

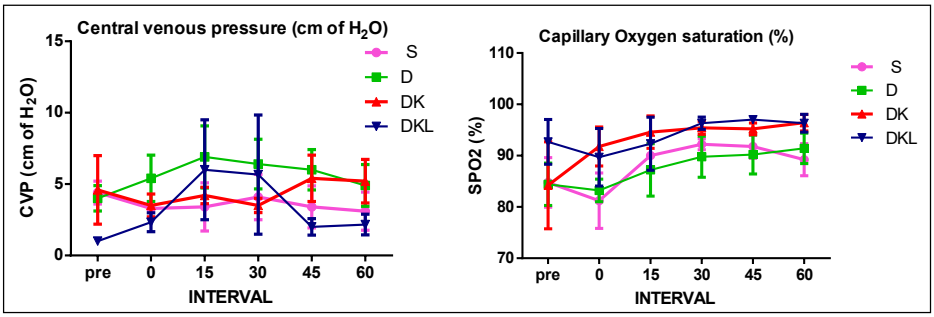

Fig 3: Mean±SD values of CVP and SPO_2 in different groups at different time intervals.

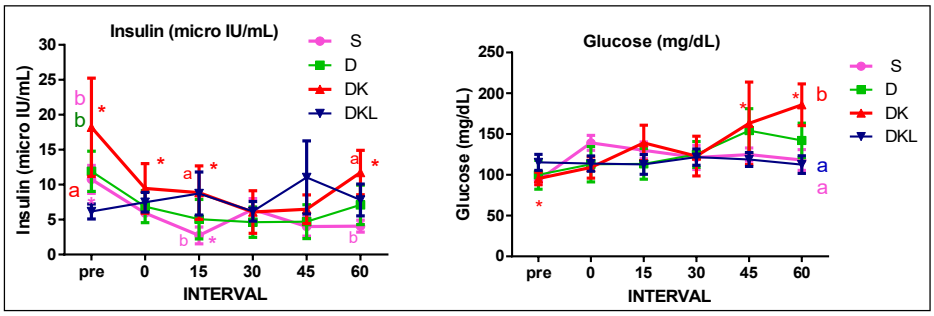

Fig 4: Mean±SD values of insulin and glucose in different groups at different time intervals.

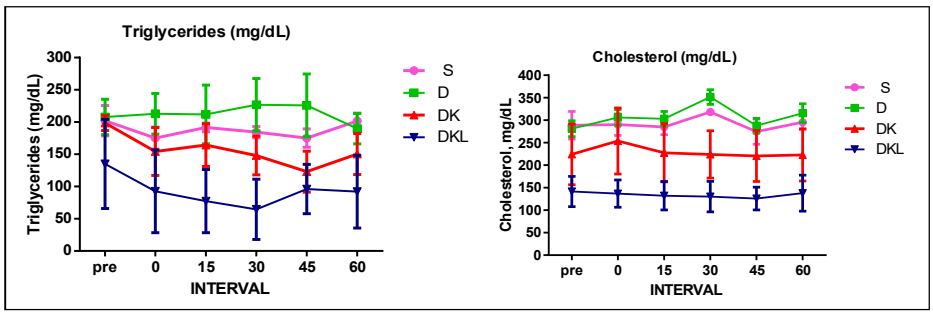

Fig 5: Mean±SD values of triglycerides and cholesterol in different groups at different time intervals.

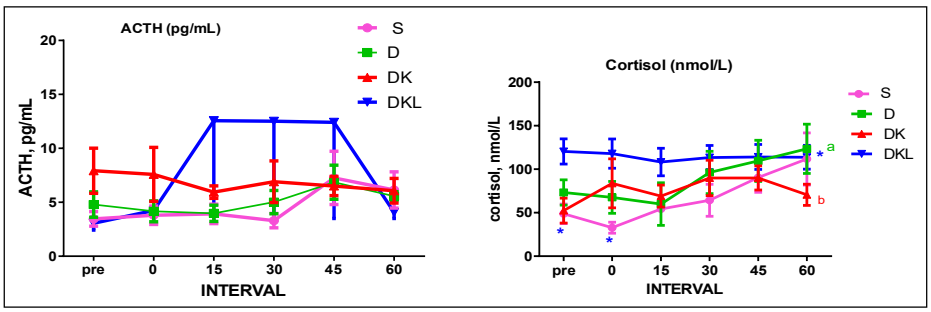

Fig 6: Mean±SD values of ACTH and Cortisol in different groups at different time intervals.

Table 3: Mean±SD values of scores sedation, ataxia, quality of induction, muscle relaxation, response to stimulus and quality of recovery in different groups.

Groups	Sedation	Ataxia	Quality of induction	Muscle Relaxation	Response to stimulus	Quality of recovery
S	2.00±0.447	2.00±0.894b	2.00±0.837	2.00±1.095	3.00±0.894	3.00±1.14
D	3.00±0.447	3.00±0.548a	2.00±0.707	1.00±1.034	3.00±0.548 a	2.00±0.548
DK	2.00±0.00	2.00±0.548b	2.00±0.548	1.00±0.548	2.00±0.447	2.00±0.548
DKL	2.00±0.00	2.00±0.548 b	1.00±0.548	1.00±0.548	1.00±0.447 b	1.00±0.548

Table 4: Mean±SD values of Induction/down time, Duration of anesthesia, Time for head lift, sternal recumbency, standing time, Total isoflurane requirement (ml), Total thiopentone requirement (mg) and attempt of intubation (number) in different groups.

Groups	Induction /down time(min)	Duration of anesthesia (min)	Head lift time(min)	Sternal recumbency (min)	Standing time (min)	Isofluranerequire-ment (ml)	Thiopentone requirement (mg)	Quality of intubation
S	13.00±4.35	60.00±00	13.00±4.63	21.00±60	32.00±4.3	26.2±8.80^{b}	700.00±124.2^{b}	2±0.316
D	12.40±2.29	60.00±00	6.00±1.703	4.00±12.91	22.00±4.006	14.00±1.87^{a}	200.00±122.47^{a}	1.8±0.49
DK	15.00±3.87	53.00±7.000	25.00±10.12	37.00±9.16	38.00±9.002	16.00±2.44^{a}	200.00±122.47^{a}	1.60±0.400
DKL	10.00±0.00	66.00±7.48	27.00±8.6	42.00±12.5	43.00±12.10	18.60±3.64^{a}	224.00±29.59^{a}	1±0.00

periods (Fig 4). The changes in biochemical parameters indicating stress like total cholesterol and triglycerides differed non-significantly in different groups (Fig 5). There was a significant increase in cortisol in group S at 60 min intervals compared to the base value. ACTH values increased in Group DKL at 15, 30 and 45 minutes intervals compared to baseline (Fig 6). Overall sedation and muscle relaxation score did not show any significant difference in all the groups. Quality of induction, recovery, and response to the stimulus was better ($p \leq 0.05$) in the DKL group as compared to groups D, S and DK. Muscle relaxation was better in groups D, DK and DKL, when compared with group S. Ataxia, was significantly more in group D compared to groups DK and DKL (Table 3). There was no significant change in downtime and duration of anesthesia among groups. Time for first head lift, sternal recumbency time and standing time was more in group DK and DKL. Isoflurane and thiopentone requirement were significantly less in groups D, DK and DKL than in group S. Attempts of intubations were non-significantly less in group DK than in other groups (Table 4).

Response to surgical stimuli was significantly low in group DKL as compared to Group D. Ataxia score was more in group D as compared to DKL ($p \leq 0.05$). Attempts for intubation and standing time did not have any significant change in different groups. Isoflurane and thiopentone requirement during the observation period was found significantly high in group S as compared to groups D, DK, and DKL. Results of our study showed that constant rate infusion of multiple anesthetic adjuvants reduced the stress response to anesthesia, facilitated adequate muscle relaxation for smooth performance of surgery with lower response to surgical stimuli with a significant reduction in Isoflurane and thiopentone requirement. However, a drastic reduction in rectal temperature and respiration rate needs to be addressed with amenities for maintaining body temperature along with manual or machine-assisted ventilation.

CONCLUSION

Constant rate infusion of short-acting anaesthetic adjuvants facilitated peri-operative muscle relaxation, reduced response to surgical stimuli, aided smooth recovery from anaesthesia while reducing the requirement for Isoflurane and thiopentone. Careful monitoring of vital parameters like rectal temperature, respiration rate and adequate external support to manage these parameters is warranted.

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Conflict of interest

Authors report no conflict of interests.

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