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Effect of Constant Rate Infusion of Different Anaesthetic Adjuvants Undergoing Thiopentone Sodium Total Intravenous Anaesthesia in Horses

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ABSTRACT

Background: Co-administration of anesthetic adjuvants as continuous rate infusion (CRI) can be controlled and hence is considered safer, as it can reduce the cardiopulmonary alterations in horses and is also adaptable in field conditions. Hence this study was planned to evaluate the effect of CRI of dexmedetomidine, ketamine, butorphanol and midazolam during thiopentone TIVA in horses.

Methods: Thirty horses were randomly divided into five groups S, D, K, B and M having six animals in each. Premedication was done with Xylazine (1 mg/kg) and butorphanol (0.05 mg/kg) intravenously. Ketamine (2 mg/kg) and midazolam (0.2 mg/kg) were used IV for induction. CRI of normal saline alone, dexmedetomidine @ 2µg/kg/hr., butorphanol @ 0.2 mg/kg/hr., midazolam @ 0.2 mg/kg/hr. and ketamine @ 2 mg/kg/hr. were administered in groups S, D, B, M and K, respectively. Thiopentone sodium (5%) was given as a fast intravenous bolus whenever required to provide adequate anesthesia. Depth of anesthesia was evaluated on the based on clinical, haemato-biochemical, hemodynamic and endocrine variables.

Result: First head lift, sternal recumbency time, standing time and quality of recovery showed no significant difference between the groups. Heart rate, RR, RT, SBP, DBP, CVP and MAP, BUN, creatinine, ALT, AST, cortisol, ACTH and ghrelin did not show significant variation among groups. Hb, PCV, TLC, TEC and neutrophil found significantly decreased and blood glucose remained significantly higher than the baseline value in all groups post induction. CRI of ketamine produced a better quality of recovery and thiopentone sparing effect and was found suitable for moderating stress response to anesthesia, inflammation and metabolic changes in horses administered with TIVA.

Key words: Butorphanol, CRI, Dexmedetomidine, Horses, Ketamine, Midazolam.

INTRODUCTION

Total intravenous anesthesia in horses poses a lesser risk to death (0.31%) (Bidwell *et al.,* 2007) which is quite high with inhalant agents (0.99%) (McMurphy *et al.,* 2002). Cardiovascular function is least disturbed in intravenous anesthesia. The delivery of anesthetics can be safer and controlled through constant rate infusions (CRI) (Gopinathan *et al.*, 2021). It is also quite adaptable with protocols of intravenous anesthesia. Alpha-2 agonists, opioids, NMDA receptor agonists, benzodiazepines and lidocaine are some of the agents used as CRI in equine practice. The short duration of action and the pharmacokinetic profile of dexmedetomidine make it suitable for prolonged infusion without cardiopulmonary side effects (Bettschart-Wolfensberger *et al.,* 2005). Butorphanol is a kappa-opioid receptor agonist and competitive agonist-antagonist at mu and sigma opioid receptors, thus exerting its analgesic effect (Commiskey *et al.,* 2005). Midazolam, a benzodiazepine, produces muscle relaxation through agonism of inhibitory neurotransmitter GABA (Muir, 2009). Sub-anesthetic doses of ketamine produce an analgesic effect without causing any side effects of dissociative anesthesia (Valverde, 2013). The primary objective of this study was to find the safety of short-acting anesthetic adjuvants as a constant rate infusion during intravenous anesthesia in horses that undergo shorter duration surgeries.

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MATERIALS AND METHODS

Animals

Thirty client-owned horses of either sex, with a mean body weight 263.92±14.94 kg and mean age of 3.78±0.43 years referred for surgeries like castration, tumor removal, repair of extensive lacerated wounds, repair of corneal laceration *etc.* (ASA scale 1 and 2) were considered for this study. The surgeries were performed in the Referral Veterinary Polyclinic, IVRI, Izatnagar, Bareilly, UP during the period of January 2015 to December 2015. Permission to perform the study was taken from the Institute Animal Ethics Committee (IVRI/SURG/12-15/012).

Experimental design

Animals were randomly divided into five groups S, D, K, B and M having 6 animals in each. Animals were treated with CRI of drugs as mentioned in Table 1.

Technique of drug administration

The food was withheld for 10-12 hours before anesthesia with limited access to water. A 14-gauge catheter was inserted aseptically into the jugular vein for IV administration of drugs and for blood sample collection. The animals were restrained and xylazine and butorphanol were injected intravenously @ 1 mg/kg and 0.05 mg/kg body weight, respectively. Ten minutes later, anesthetic induction was done with ketamine @ 2 mg/kg and midazolam @ 0.2 mg/kg IV. After induction an endotracheal tube was placed and CRI of the concerned group was started (Table 1). Thiopentone sodium (5% solution) as bolus was administered whenever deeper anesthesia was required.

Clinical observations

All horses underwent scoring for sedation (0-3), Ataxia (0-3), muscle relaxation (0-3) and quality of analgesia (0-3) (Gopinathan *et al.,* 2021). The palpebral reflex (1-4) and Corneal reflex (1-4) were graded. Sedation, ataxia, muscle relaxation, analgesia, palpebral and corneal reflexes were recorded at 0 (after induction), 15-, 30-, 45- and 60-min intervals. Quality of intubation was recorded by the same observer throughout the anaesthetic trials.

The anaesthetic depth and the horse's response to surgical stimulation were recorded. The dose of thiopentone required during the surgical procedure was recorded (5% solution in ml). Duration of anaesthesia (min), the first head lift (the time from discontinuation of anaesthesia till the first lifting of the head) (min) and the time taken by animal to reach sternal recumbency after anaesthesia (min) were recorded. Time taken by animal to stand after anaesthesia was recorded as standing time (min). Quality of recovery was scored 1-4 (Clark-Prince, 2013).

Physiological observations

Heart rate, respiratory rate and rectal temperature (°F) were recorded before and at 0 (immediately), 15, 30, 45 and 60 minutes after administration of the drugs.

Hematological and biochemical observations

Blood samples were collected from each animal, before induction (baseline) and at 0 (start of CRI), 15, 30, 45 and 60 min after the administration of the drugs. Hemoglobin (g/dl), packed cell volume (PCV %), total leucocyte count (TLC), total erythrocyte count (TEC) and differential leukocyte count (DLC) were analyzed from whole blood. The serum samples were used to measure urea nitrogen, creatinine, alanine amino transferase (ALT), aspartate aminotransferase (AST), triglycerides, cholesterol and blood glucose, using span diagnostic kits. Serum insulin (nIU/ml) and Interleukin-6 (pg/ml) were estimated by ELISA (Cusabio Biotech Co., Ltd Wuhan Hi-tech Medical Devices Park, Wuhan). Serum cortisol (ng/ml), ACTH (pg/ml), Ghrelin (pg/ml) and Leptin (ng/ml) were estimated using ELISA kits (Blue Gene Biotech, Shanghai, China).

Table 1: Anaesthetic drug combination used as CRI in animals of different groups.

Groups	Number of animals	CRI protocol
S	6	Saline alone
D	6	Dexmedetomidine (2 μg/kg/h)
K	6	Ketamine (2 mg/kg/h)
B	6	Butorphanol (0.2 mg/kg/h)
M	6	Midazolam (0.2 mg/kg/h)

Hemodynamic study

Systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), mean arterial pressure (mmHg) were recorded by NIBP monitor (BPX™, Romsons®, Rennex medical) before anesthesia, at 0 (after induction) and 15, 30, 45 and 60 min, after administration of the drug. Central venous pressure (cm of H_2O) was measured with the help of a water column manometer (C.V.P. Manometer®, Romsons Scientific and Surgical Industries Pvt Ltd., Agra, India) at all the above-mentioned intervals. Pulse rate and oxygen saturation of hemoglobin (SpO_2) were measured using a pulse oximeter (Model: MD300C26, pulse oximeter; Beijing Choice Electronic Tech. Co., Ltd.). The recordings were made at the same intervals as for CVP.

Statistical analysis

The parametric data at different time intervals were compared by repeated-measures ANOVA whereas the non-parametric data were compared with Kruskal-Wallis test. The data were analysed by using SAS 9.3 software.

RESULTS AND DISCUSSION

The duration of surgery was relatively longer in group B (95±12.89 min), followed by (in decreasing order) groups K (66±12.89 min), D (60±12.89 min), M (51±0.96 min) and S (46±12.89min). First head lift (min), sternal recumbency time (min), standing time (min) and quality of recovery showed no significant difference between groups. The longest duration of sternal recumbency was recorded in group B, followed by groups D, S, K and M. Mean standing time in groups K, D, S, B and M were 161.8±42.4 min, 132±42.4 min, 118±42.4 min, 104±42.4 and M 102±42.4 min, respectively. Horses of group K took a longer time for standing followed by groups, D, S and B. The shortest standing time was recorded in group M (Fig 1).

Premedication with xylazine and butorphanol significantly improved sedation in horses within a minute, as evidenced by drooping of the lower lip and upper eyelid, head-down posture and reluctance to move (Muir *et al.,*1977). Overall ataxia remained mild to moderate. Adequate muscle relaxation was found in all the groups except group K, wherein a high level of muscle hypertonicity was observed. Excellent muscle relaxation was found in the midazolam

group (Hellyer *et al.,* 1991). Analgesia was excellent in groups K, D and B as compared to group S and M (England and Clarke, 1996). Alpha 2 adrenoceptor agonists as infusion have been reported to produce excellent analgesia in horses (Kamerling *et al.,* 1988).

Lacrimation and spontaneous blinking remained active during TIVA, particularly in ketamine group. Palpebral and corneal reflexes were abolished completely in group D after induction (Yamashita *et al*.,1999). The quality of intubation was good to excellent in all groups. Laryngeal and pharyngeal reflexes were well maintained with ketamine (Haskins *et al.,* 1975), although the co-administration of alpha-2 agonists, benzodiazepine and opioids greatly obtund this effect (Ko *et al.,* 2000). In group S and group B, shivering and muscle twitching were observed during the perioperative period. It could be due to persistent cutaneous vasodilatation or hypothermia. (Hall and Clarke,1991).

The average dose of thiopentone in groups S, D, K B and M were 6.38±3.03 10.66±3.03, 8.55±3.03, 16.2±3.03 and 13.22±3.03 mg/Kg respectively. In groups B and M, more thiopental was injected (mg/Kg), which could be due to an increase in surgical time in these groups (Fig 1). Delayed first head left time in group M could be attributed to the synergistic action of alpha-2 agonist, midazolam, opioids and ketamine, resulting in deeper anaesthesia (Ko *et al.,* 2000). Sternal recumbency time in group B was longer; this might be either due to the longer surgical time or because of synergistic action with pre-anaesthetics. The quality of recovery ranged from excellent to good with no significant difference between groups. In group M there was severe paddling on recumbency and the animals were ataxic during standing which could be attributed to prolonged muscle relaxation (Yamashita *et al.,* 2007).

There was a significant (P<0.05) decrease in haemoglobin in group M (Fig 2). The decrease in haemoglobin in groups S D, K and M and lower PCV in groups S and D might be due to shifting of fluids from the extravascular compartment to the intravascular compartment (Wagner *et al.,* 1991, Skarda, 1994). There was a significant (P<0.05) decrease in the total leucocytic count in group S. TEC values were significantly higher in group K (Fig 2).

A decreased heart rate was observed in all groups which could be due to baroreceptor activation, as reported by Kerr *et al*. (1996). Similarly, the reduction in blood pressure may be caused by a decreased sympathetic tone resulting from the activation of central and pre-synaptic sympathetic neuronal alpha-2 adrenoceptors (Moens, 2000). Respiratory depression was greater in group S as compared to other groups although the difference was not significant. A decrease in RR in group S might be due to thiopental which causes transient apnoea due to direct depression of the respiratory centre in the medulla. In all groups, the rectal temperature decreased during anaesthesia (Fig 2) (Carmona *et al.,* 2007).

The fluctuation in BUN and creatinine values was non-significant among the groups (Fig 3). There was no significant change in serum ALT and AST among different groups (Fig 3), however, there was a significant increase in triglycerides within-group D at 15, 30, 60 min and at 30 min in group M. IL-6, a major liver protein responsible for several endocrine and metabolic changes seen during surgical stress response (Garcia *et al*., 2002) was slightly elevated in all groups. Lipolytic activity was stimulated by cortisol, catecholamines and growth hormones, which was inhibited in the presence of insulin, resulting in increased mobilization of triglycerides.

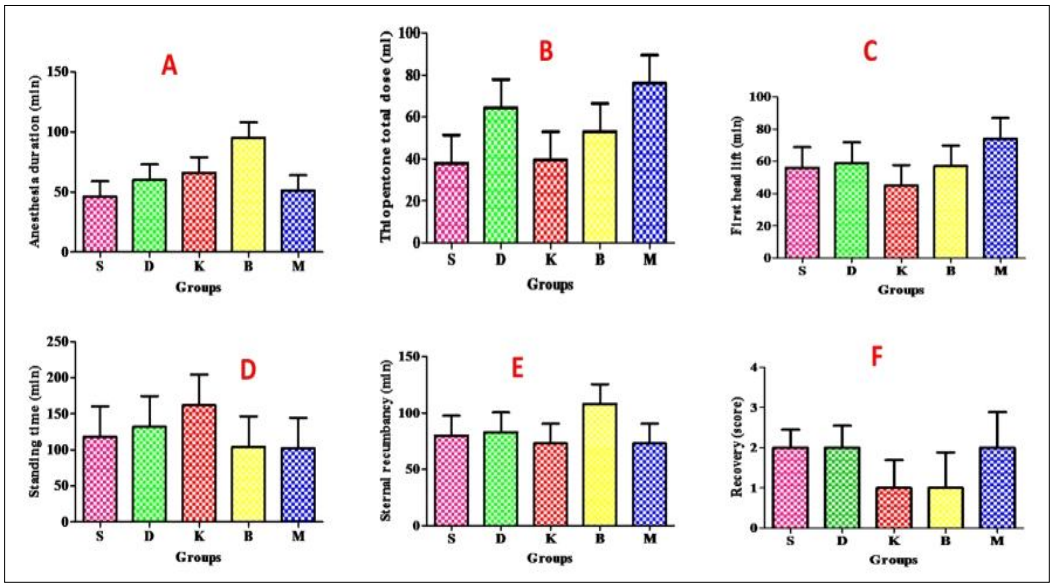

Fig 1: Mean ± SD values of A) Duration of surgery, B) Thiopentone dose, C) First head lift, standing time, D) Sternal recumbency and F) Quality of recovery in different groups.

Insulin, cortisol and ghrelin did not vary significantly between groups, but ACTH showed a gradual increase from 30 to 60 minutes. Leptin increased significantly ($P<0.05$) at 60 min, compared to post-induction value in the group S (Fig 4). Increased cortisol might be due to anaesthetic and surgical stress during surgery (Jena *et al.,* 2014). Increase in ACTH post-surgery was observed in all the groups because surgery was a potent activator of ACTH (Desborough, 2000). The non-significant increase in leptin might be due to the stimulatory effect of cortisol, which was produced in response to surgical and anaesthetic stress. The secretion of ghrelin could be stimulated by fasting and its concentrations elevated in response to surgical stress (Kontoravdis *et al.,* 2012). The significant increase in the glucose value at 45 and 60 min compared to baseline value and a non-significant decrease in the insulin level at 60 min in group D might (Fig 4) be due to the suppression of insulin release by dexmedetomidine by its action on β cells of the pancreas (Kumar *et al.,* 2013).

The increased SBP values in group K at 30 min might be due to the desensitization of arterial baroreceptors and vagal blockade, which reduces the negative feedback mechanism on the vasomotor centre, resulting in arterial hypertension and tachycardia (Kinjavdekar *et al.,* 2000).

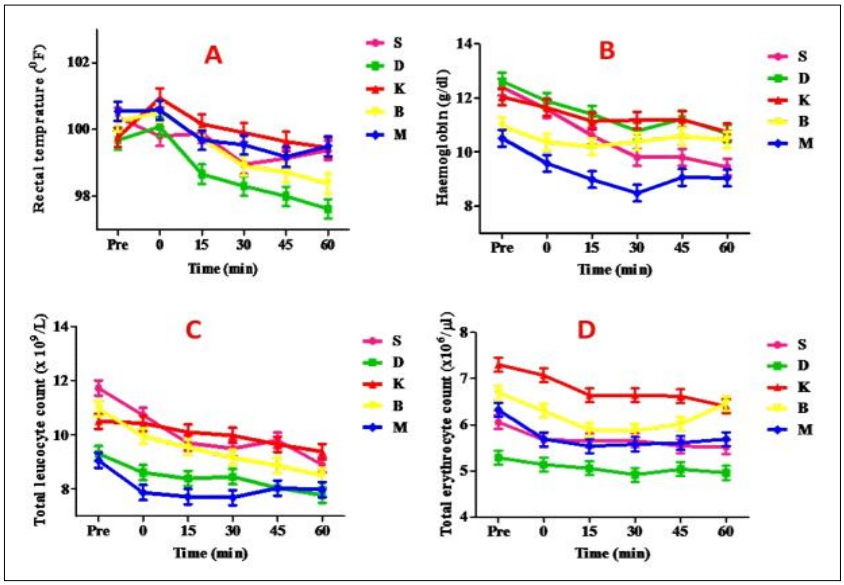

Fig 2: Mean ± SD values of A) Rectal temperature, B) Haemoglobin, C) Total leucocyte count (TLC) and D) Total erythrocyte count (TEC) in different groups at different time intervals.

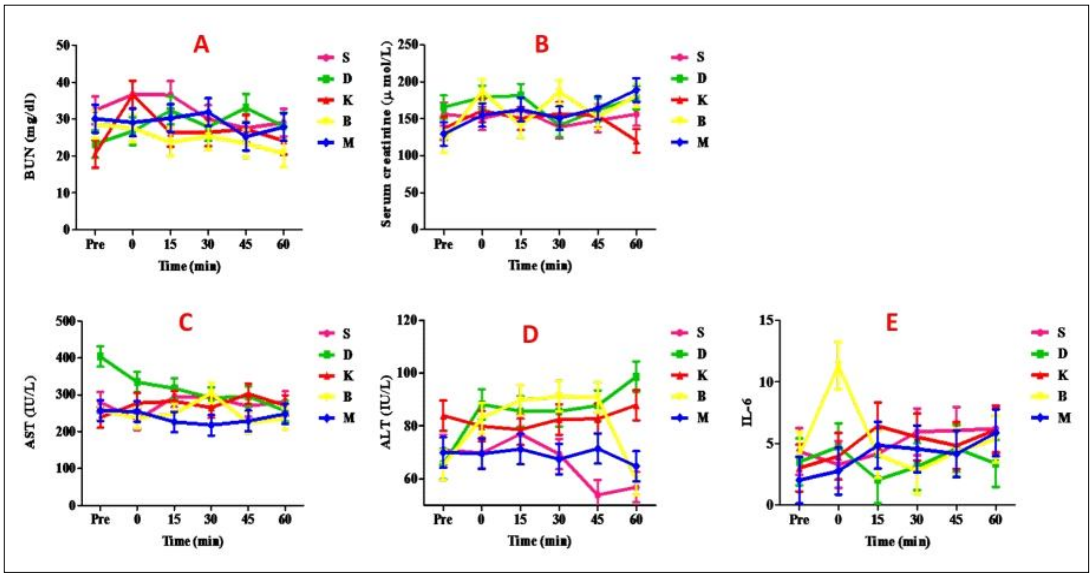

Fig 3: Mean ± SD values of A) Serum urea nitrogen, B) Creatinine, C) AST, D) ALT and E) IL-6 in different groups at different time intervals.

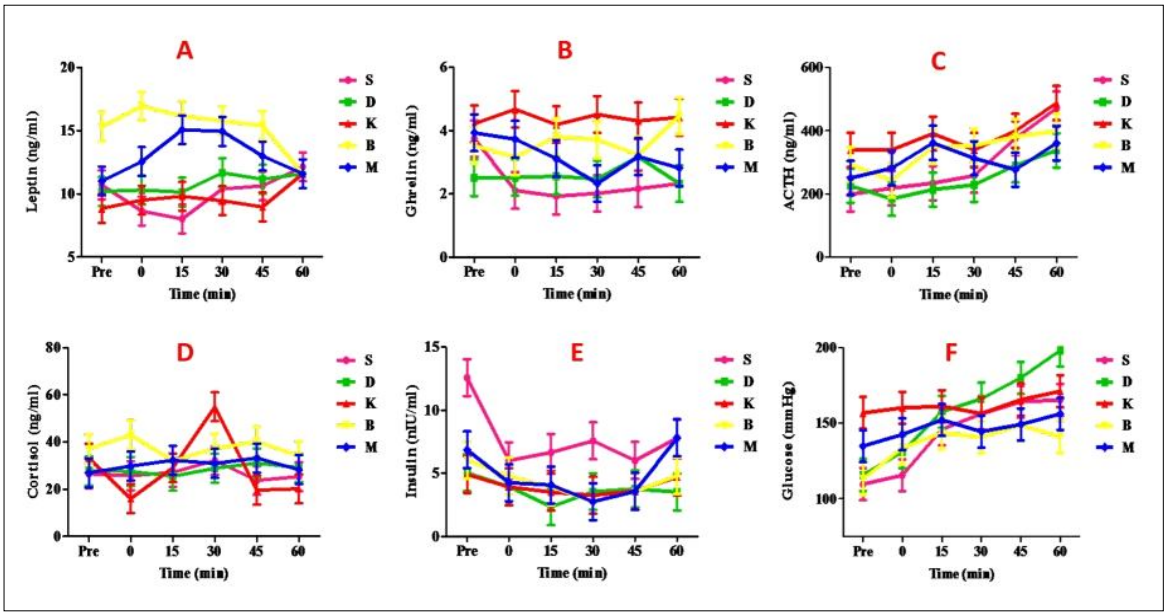

Fig 4: Mean ± SD values of A) Leptin, B) Ghrelin, C) ACTH, D) Cortisol, E) Insulin and F) Glucose in different groups at different time intervals.

There were no significant variations in diastolic blood pressure in different groups. During this study BP fluctuated near the baseline and an expected fall in the BP could be due to the action of dexmedetomidine, midazolam and butorphanol, which was abrogated by the administration of ketamine. The increase in the CVP in groups S and D could be partly attributed to post-synaptic peripheral alpha 2- receptor stimulation, leading to vasoconstriction (Venugopalan *et al.,* 1994). Decrease in SpO_2 in animals of group D might be attributed to an initial vasoconstriction caused by dexmedetomidine (Kuusela *et al.,* 2000). or it could be due to the depression of respiration caused by butorphanol (Muir *et al.,* 1999) and midazolam (Butola and Singh, 2007).

CONCLUSION

Constant rate infusion of midazolam, produced complete muscle relaxation throughout the surgical procedures, whereas that of ketamine and butorphanol produced a better quality of recovery and thiopentone sparing effects. CRI of Ketamine and that of midazolam was helpful in moderating stress response to anaesthesia, inflammation and metabolic changes during TIVA in horses.

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Conflict of interests

Authors report no conflict of interests in the present study.

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