Analgesic and adjunct actions of nalbuphine hydrochloride in xylazine or xylazine and acepromazine premedicated horses

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ABSTRACT
The study was conducted in eighteen clinical cases of horses for diagnostic and surgical procedures requiring general anaesthesia were randomly divided into three groups, group I, group II and group III, each consisting of six cases. All the horses were premedicated with glycopyrrolate at the dose rate of 0.02 mg/kg body weight, intravenously. Horses in Group I and Group II were administered xylazine hydrochloride at the dose rate of 1.10 mg/kg body weight intravenously whereas in Group III at the dose rate of 0.50 mg/kg body weight intravenously. In Group III, acepromazine was injected after xylazine administration, at the dose rate of 0.02mg/kg body weight, intravenously. Before induction of anaesthesia, nalbuphine hydrochloride was administered for Group II and Group III at the dose rate of 0.75 mg/kg body weight intravenously. Ketamine hydrochloride was administered intravenously to induce anaesthesia at the dose rate of 2.20 mg/kg body weight and maintained with 0.50 mg/kg body weight in required cases to maintain for duration of 15 ± 1.04 minutes. The mean time for induction in group I, group II and group III were 1.78 ± 0.27, 1.73 ± 0.10 and 1.85 ± 0.28 minutes respectively. The mean total number of additional doses of ketamine for standard duration of 15 ± 1.04 minutes surgery required in group I, group II and group III were 5.00 ± 0.36, 1.66 ± 0.33 and 2.00 ± 0.36 respectively. The quality of induction was 100 per cent smooth in group III, 83.33 per cent smooth and 16.67 per cent rough in group II and 66.66 per cent smooth and 33.34 per cent rough in group I. The quality of analgesia in group I, group II and group III were 2.83 ± 0.47, 1.83 ± 0.30 and 1.33 ± 0.21 respectively. The quality of muscle relaxation in group I, group II and group III were 3.16 ± 0.30, 1.50 ± 0.22 and 1.33 ± 0.21 respectively. The mean time for recovery in group I, group II and group III were 23.00 ± 1.52, 33.00 ± 0.93 and 41.98 ± 1.32 minutes respectively. The mean number of attempts for unassisted standing in group I, group II and group III were 6.66 ± 0.71, 5.00 ± 0.57 and 5.00 ± 0.36 respectively. The quality of recovery was 83.33 per cent smooth and 16.67 per cent rough in group III, 66.66 per cent smooth and 33.34 per cent rough in group II and 50.00 per cent smooth and 50.00 per cent rough in group I. None of the animals in any groups showed any intra and post operative complication.

Key words: Analgesia, Nalbuphine, Adjunct Action, Horse.

INTRODUCTION
Pain is very intense and debilitating in the horse than any other farm animals and may be primarily responsible for decreased performance, high morbidity and mortality. The pharmacological approach towards the control of pain that has evolved in the history for the past few decades stresses the need for selection and need of appropriate analgesic agent. The use of a good analgesic agent in horses during intra and post-operative surgical procedures will inevitably be a greater contribution in the field of equine anaesthesia and analgesia.

The popular alpha – 2 adrenergic agonist, xylazine, offers intraoperative analgesia only for a short duration of 15 to 20 minutes, which may not be sufficient to protect the surgical patients during the post-operative period as surgical pain exists for about 18 hours. Newer non-steroidal cox-2 analgesics cannot be included in the anaesthetic procedures because as analgesics they depress the vital functions and paradoxically increase the post anaesthetic morbidity and mortality rate through cox-1 and cox-2 mediated actions (Clarke et al., 1970). In recent years, synthetic opiates have been developed with mixed agonist – antagonist actions. Development of drugs that have selective opiate receptor activity has resulted in superior analgesia with minimal respiratory depression and excitatory effects.

Nalbuphine ([−]-17-[cyclobutylmethyl]-4, 5 alpha-epoxymorphinan-3, 6alpha, 14- triol) is a semi-synthetic narcotic agonist-antagonist analgesic of the phenanthrene series. It has agonistic activity at kappa receptors and is
antagonistic at mu receptors. It is chemically related to the widely used narcotic antagonist, naloxone and the potent narcotic analgesic, oxymorphone. Its analgesic potency is equivalent to morphine. Opioids when included in equine anaesthetic regimen offer the benefit of adjunct action (Brunson and Majors, 1987).

The present study was conducted to identify the analgesic and adjunct action of nalbuphine hydrochloride with widely used anaesthetic agent ketamine in order to achieve better intraoperative and postoperative analgesia with minimal changes in vital parameters and reduced dose of principal anaesthetic agent for major and minor surgical and diagnostic procedures and a desired regimen for field equine practice can be evolved.

MATERIALS AND METHODS

The clinical study was conducted on 18 horses of either sex brought to the Large Animal Surgery Unit, Madras Veterinary College Teaching Hospital, Chennai-7 for castration (7 Kathiawari horses, 4 Marwari horses and 2 ponies), traumatic lacerated wound (4 Kathiawari horses) and tumor excision (one Indian Thorough breed). The selected horses were randomly allotted to Group I, Group II or Group III, each consisting of 6 horses. Feed and water were withheld for 18 hours and 6 hours respectively prior to anaesthesia. On the day of surgery all the horses were groomed thoroughly and mouth was washed with plain water to remove any food particles. All the trials were conducted in the forenoon to avoid diurnal variations.

All the horses were premedicated with glycopyrrolate, 15 minutes before administration of xylazine at the dose rate of 0.02mg/kg body weight, intravenously. Horses in Group I and Group II were administered xylazine hydrochloride at the dose rate of 1.10 mg/kg body weight intravenously, whereas in Group III at the dose rate of 0.5mg/kg body weight intravenously. In Group III, acepromazine was injected after xylazine administration, at the dose rate of 0.02mg/kg body weight, intravenously. Before induction of anaesthesia, nalbuphine hydrochloride was administered in Group II and Group III horses at the dose rate of 0.75mg/kg body weight intravenously. Ketamine hydrochloride was administered intravenously to induce anaesthesia at the dose rate of 2.20 mg/kg body weight and maintained with 0.5 mg/kg body weight in required cases to maintain for a period of 15 ± 1.04 minutes.

The anaesthetic parameters studied were mean time for induction (in minutes), quality of induction was recorded in terms of smooth or rough and expressed in percentage, mean total number of additional doses of ketamine quality of muscle relaxation was scored (1 – 4) as described by Muir et al. (2000). reflex status (0-2), mean duration of anaesthesia (in minutes), quality of analgesia was scored as described by Muir et al. (2000) as 1 (no responses to surgical stimulation), 2 (brief contraction of abdominal and limb muscles, temporary twitching and spasms), 3 (movements of fore limb or hind limbs) and 4 (repeated movements of fore limbs or hind legs requiring additional doses of drug administration), mean time for recovery (in minutes), the quality of recovery was assessed as rough or smooth and expressed in percentage, mean number of attempts for unassisted standing and post anaesthetic complications (if any). The obtained data were statistically analysed using completely randomized block design as statistical tool (Ott and Longneker 2001).

RESULTS AND DISCUSSION

The mean time for induction in group I, group II and group III were 1.78 ± 0.27, 1.73 ± 0.10 and 1.85 ± 0.28 minutes respectively. Statistical analysis revealed no significant difference between the groups but the values of group III was more as compared to group II and Group I which could be due to slower onset of action of acepromazine and results concurred with Gaikwad et al. (2006). Hubbel (2009) observed onset of action occurred within 15 – 30 minutes, but peak effects seen after 45 minutes and duration of action was dose dependent and last for 6-10 hours following intravenous administration of acepromazine at the dose rate of 0.02 to 0.05mg/kg body weight in horses. Combination of alpha 2 adrenergic agonists and phenothiazine derivatives were reduced the time taken to produce ataxia in horses attributed to their synergistic activity (Sankar et al., 2010 and Hofmeister et al., 2010). The tranquilizing effects of acepromazine was due to the blocking of the central post synaptic dopamine D2 receptor in the fore brain, basal ganglia, chemoreceptor trigger zone, hypothalamus and peripherally blocks cholinergic, histaminergic and adrenergic receptors as well (Baldessarini, 1996 and Gross, 2001). Xylazine is popularly used as a preanaesthetic agent produced safe, reliable, sedation within three to eight minutes following intravenous administration at the dose rate of 1.1mg/kg body weight (Carastro, 2004 and Sankar et al., 2010) and mean duration of sedation lasted up to 36 minutes (Hofman, 1974). The sedation was characterised by lowering the head and drooping of eyelids and lips (Hewes et al., 2007). Xylazine produced sedation was mainly attributed to a dose related depression of the central and peripheral nervous system with decreased motor activity due to central and peripheral presynaptic alpha 2 receptor agonistic activity (Gleed, 1987 and Maze and Tranquilli, 1991). Opioids and alpha 2 adrenergic agonists combination have shown to produce profound sedation and analgesia in horses and it can be
attributed to their synergistic activity (Clarke and Paton, 1988 and Daunt and Steffey, 2002), Matthews and Van Dijk (2004) reported that nalbuphine could be combined with xylazine to provide safe and better sedation. Lester et al. (2003) concluded that combination of nalbuphine and xylazine is a useful premedicant which provided greater sedation than acepromazine and reduced anxiety behaviours more than did xylazine alone.

The rapid onset of induction following the administration of ketamine could be attributed to the ability of ketamine to cross the blood-brain barrier in one – arm – brain circulation (Bovil et al., 1971) and the antagonistic action at the N-methyl D-aspartate receptors in the cortical area of the brain and spinal cord (Kawamata et al., 2000 and Mazar et al., 2005). The mean total number of additional doses of ketamine used in group I, group II and group III were 5.00 ± 0.36, 1.66 ± 0.33 and 2.00 ± 0.36 respectively for a mean duration of 15 ± 1.04 minutes. Statistical analysis revealed significant increase in number of additional doses of ketamine in group I as compared to group II and group III. The quality of induction was 100 per cent smooth in group III, 83.33 per cent smooth and 16.67 per cent rough in group II and 66.66 per cent smooth and 33.34 per cent rough in group I.

The quality of muscle relaxation in group I, group II and group III were 3.16 ± 0.30, 1.50 ± 0.22 and 1.33 ± 0.21 respectively. Statistical analysis revealed that the quality of muscle relaxation was significantly higher in group II and group III than group I. The reflex status in group I, group II and group III were 1.10 ± 0.24, 1.04 ± 0.14 and 1.07 ± 0.31 respectively. Statistical analysis revealed no significant difference between the groups.

Ketamine due to its extrapyramidal activation, increased electrical activity at the basal ganglia, brain stem and limbic system produced muscle tremors, limb stretching and tonic clonic convulsion (Mazar et al., 2005 and Visser and Schug, 2006). The muscle relaxation observed during xylazine – acepromazine premedication could be attributed to decrease intraneuronal transmission of impulses from the muscles to the central nervous system (Haskins et al., 1975) and decreased motor activity (Gleed, 1987). The vital reflexes were also sluggish during xylazine – acepromazine – ketamine anaesthesia due to decreased motor activity (Ogidiben and Potter, 1991 and Robertson, 2004).

The mean time for recovery in group I, group II and group III were 23.00 ± 1.52, 33.00 ± 0.93 and 41.98 ± 1.32 minutes respectively. Statistical analysis revealed a significant increase in recovery time in group II and highest in Group III as compared to group I (P < 0.05). The mean number of attempts for unassisted standing in group I, group II and group III were 6.66 ± 0.71, 5.00 ± 0.57 and 5.00 ± 0.36 respectively. Statistical analysis revealed no significant difference between the groups. The quality of recovery was 83.33 per cent smooth and 16.67 per cent rough in group III, 66.66 per cent smooth and 33.34 per cent rough in group II and 50.00 per cent smooth and 50.00 per cent rough in group I. The higher percentage of rough recovery and more number of attempts for unassisted standing were noticed in group I animals could be attributed to the enhanced plasma half life of ketamine by xylazine premedication (Muir et al., 1977; Matthews et al., 1998; Bienert et al., 2003; Wagner et al., 2008 and Sankar et al., 2010). In group II and group III the quality of recovery was smooth and mean time for recovery was longer as compare to group I which could be attributed adjunct action of the drugs (Lester et al., 2003; Muhammad et al., 2004; Mama et al., 2005; Hofmeister et al., 2010; Sankar et al., 2010; Thakur et al., 2011 and Driessen et al., 2011).

The quality of analgesia in group I, group II and group III were 2.83 ± 0.47, 1.83 ± 0.30 and 1.33 ± 0.21 respectively. Statistical analysis revealed that the quality of analgesia was significantly higher in group II and group III than group I. In the present study, Quality of analgesia produced in the group II and III was superior as compared to group I which could be due to analgesic action of nalbuphine and short term intra operative analgesia produced by xylazine and ketamine and the results could be concurred with Brunson and Majors (1987), Clarke and Paton (1988), Muhammad et al. (2004) and Thakur et al. (2011). In Mammals, antinociceptive effects of nalbuphine hydrochloride up to 3 – 6 hours as compared to butorphanol which is having only up to 3 – 4 hours as reported by Guzman et al. (2011). Combinations of opioids and anaesthetics have shown to produce additive and adjunct actions by reducing the total requirements of principal anaesthetic agent and long lasting analgesic action (Brunson and Majors, 1987; Muhammad et al., 2004 and Thakur et al., 2011).

The present study concluded that nalbuphine hydrochloride provided better quality analgesia and also adjunct action by significantly reducing the additional doses of ketamine for maintenance of anaesthesia for standard duration of 15 ± 1.04 minutes of surgery when it was combined with xylazine or xylazine and acepromazine premedicated horses. Hence this combination could be used in the field level for surgical procedures requiring 15 minutes.
REFERENCES


