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RESEARCH ARTICLE

CLINICAL EVALUATION OF TOTAL INTRAVENOUS ANESTHESIA WITH KETAMINE – MIDAZOLAM MIXTURE IN BUTORPHANOL - DEXMEDETOMIDINE - ACEPROMAZINE PREMEDICATED EQUINES

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ABSTRACT

Horses under general anesthesia are prone to considerable risk of morbidity and mortality. The present study was conducted to evolve a safe and a reliable total intravenous anesthetic (TIVA) protocol to effect minimal cardiopulmonary alterations as well as to reduce post anesthetic morbidity and mortality in horses for field practice. Group I horses were premedicated with dexmeditomedine-acepromazine-butorphanol, induced and maintained with ketamine –midazolam mixture and in group II horses xylazine-butorphanol as premedicants and induced and maintained with ketamine alone. Anesthetic, cardiopulmonary, venous blood gas analysis, serum biochemical and horse grimace scale parameters were recorded. The mean sedation time was significantly less in group I. The group I horses required half of ketamine dose for 30 minutes of anesthesia as compared to group II horses. There were no significant variations in mean arterial pressure, the heart rate progressively decreased and returned to base value after recovery. The horse grimace scale revealed that the group I horses showed less pain score as compared to that of group II horses. Dexmeditomidine –acepromazine-butorphanol premedicated horses, induced and maintained with ketamine-midazolam mixture is an evolved total intravenous anesthetic (TIVA) protocol which is safe and reliable with no or minimal alterations in cardiopulmonary parameters. The new anesthetic protocol minimizes untoward post morbidity and mortality in horses. This TIVA protocol was found to be an ideal anesthetic for field practice producing 30 minutes of safe anesthesia.

Key words: *Equines- Ketamine-midazolam, Intravenous anesthesia.*

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INTRODUCTION

General anesthesia is undoubtedly a challenging field in equines as the horses are more prone to morbidity and mortality during post anesthetic periods as compared to small animals or humans [30], being one per cent [80] which was attributed to ventilation-perfusion mismatch and hypotension. Total intravenous anesthesia (TIVA), the sole use of intravenous drugs to induce and maintain anesthesia is the most common method to anesthetize equines. Due to its relative ease of use, less expensive, absence of risk of inhalant anesthetic hazards which require no scavenging system, lesser stress response as compared to inhalant anesthetics. With minimal or no cardiac depression at clinical doses and most certainly suitable for field practice which is generally accompanied with smooth and safe recovery. TIVA may have several additional advantages over inhalant technique in horses including superior cardiopulmonary stability and severe metabolic and hormonal changes [45]. Total intravenous anesthesia could be utilized to obtain stable unconsciousness, muscle relaxation and analgesia thus achieving the desired anesthetic triad with minimal side effects especially useful where there is lack of oxygen source or expensive anesthetic equipment in field practice. Total intravenous anesthesia (TIVA) for short procedures seems to carry a lower risk of intra-anesthetic mortality than inhalant agents [5, 30]. The alteration in concentration of anesthetic vapor to provide surgical plane of anesthesia causes dose dependant cardio-pulmonary depression, intra operative hypotension and hypoventilation [66]. Stable cardio-vascular function and excellent quality of recovery are primarily important factors to be considered while developing a new anesthetic protocol in equines. TIVA is often practiced in equines with a mixture of xylazine, ketamine and guaifenesin [67]; wherein, guaifenesin when exceeds the clinical dose of 100 mg/kg body weight paradoxically induces muscle contractions. Midozalam, a benzodiazepine derivative which is more potent than diazepam with good muscle relaxation is an ideal one to replace guaifenesin in TIVA regimen. Dexmeditomidine is a potent alpha-2 adrenergic agonist with analgesic and sedative properties which is used as a premedicant and can be an alternative to xylazine in formulating the anesthetic regimen. Acepromazine is included as a premedicant due to its cardiac anti arrhythmic property. The objective of the study was to evaluate the anesthetic and cardiopulmonary parameters during the total intravenous anesthesia using midazolam - ketamine mixture in butorphanol-dexmedetomidine- acepromazine premedicated horses

and compared with ketamine in butorphanol- xylazine premedicated horses.

MATERIALS AND METHODS

The clinical study was conducted in horses of either sex referred to the Equine Unit of the Madras Veterinary College Teaching Hospital, Chennai, Tamil Nadu, India, for surgical procedures warranting general anesthesia. On admission, the horses were subjected to pre operative check up that included physiological observations, hematology and serum biochemical analysis. The horses were dewormed and immunized with 20 L/F units of tetanus toxoid [29] preoperatively. The American Society of Anesthesiologists (ASA) classification was adopted to categorize the health status of the horses [31]. The 12 horses selected on the basis of ASA 1 status were randomly allotted to Group I and Group II each consisting of 6 horses. Feed was withheld for 12 hr but not water prior to anesthesia [54]. All the horses in group I and II were premedicated with butorphanol[1] (0.01 mg/kg BW) intravenously and after20 min, group I horses were administered with Dexmedetomidine2 (5.00 µg/kg BW) intravenously followed by acepromazine3 (0.03 mg/kg intravenously 15 min later. Group II horses were administered with xylazine (1.10 mg/kg BW) intravenously 20 min after the administration of butorphanol. At peak sedation, a mixture of ketamine hydrochloride5 and midazolam6 was administered intravenously at the dose rate of 2.00 and 0.05 mg per kg body weight respectively in group I horses. The mixture was prepared from midazolam (5.00 mg/ml) and ketamine (50 mg/ml) and administered at a dose rate of 0.25 ml and 1.00 ml respectively per 25 kg body weight. In group I horses, during the surgical procedures, the required quantity of the anesthetic mixture was administered as intermittent bolus intravenously to maintain anesthesia. In group II horses, ketamine hydrochloride was administered at a dose rate of 2.20 mg per kg body weight intravenously and was maintained using the required dose of ketamine intravenously. After the surgical procedure, the horses were left undisturbed and the quality of recovery was recorded. Following recovery, the horses were stabled and observed for any post anesthetic complications. The anesthetic parameters studied were: mean time for sedation in minutes, quality of sedation: Sedation score (1 to 5) - profound to absent, response to tactile stimulation (Picking the neck) (1 to 3) - absent to moderate, response to auditory stimulation (Clapping hands) (1 to 4) - absent to strong, mean time for induction in minutes, quality of induction (1 to 5) - excellent to very poor, quality of surgical anesthesia (1 to 4) – excellent to poor, total dose of ketamine/ midazolam, mean time for recovery in minutes and quality of recovery (1 to 5) - excellent to very poor. Qualitative pain scoring system was analyzed using Horse Grimace Scale (HMS) post-operatively which was based on stiff backward ears, orbital tightening, tension above the eye area, prominent strained chewing muscles, mouth strained, pronounced chin, strained nostrils and flattening of the profile of the nostrils. Mean rectal temperature, cardiopulmonary parameters- mean heart rate, mean arterial pressure, capillary refill time, electrocardiography, mean respiratory rate, saturated partial pressure of oxygen, venous blood gas analysis preoperatively, intra-operatively and post-operatively were recorded.

Statistical analysis: The data obtained was statistically analyzed using completely randomized block design and one way ANOVA was used to compare the means of the parametric values. The statistical data was done using SPSS 17 software.

RESULTS

The mean ± SE of anesthetic parameters were shown in Table 1. The study revealed that the group I animals attained peak of sedation in a shorter period (5.27 ± 0.27 min) than group II (9.60 ± 0.41 min) horses. The sedation score, response to tactile stimulation and response to auditory stimulation did not vary statistically ($P<0.05$). The time for induction did not vary between groups but the quality of induction varied significantly ($P >0.05$) with better quality of induction in group I. The quality of anesthesia was excellent to good in group I and good to fair in group II. The calculated dose of ketamine and midazolam required for 30 minutes was 1.25 ± 0.25 and 1.00 ± 00 mg per kg body weight in group I and 2.67 ± 0.33 of ketamine in group II. The dose of ketamine required for 30 min of anesthesia was half of that of group II. On perusal of mean it revealed better quality of recovery in group I horses than in group II horses. The mean time for recovery in min was 12.33 ± 0.76 and 17.00 ± 1.09 in group I and II respectively. Statistical analysis revealed significant variation between groups. The quality of recovery was scored 1 to 5 (excellent to very poor). The quality of recovery was 1.33 ± 0.21 and 2.16 ± 1.67 in group I and II respectively. The perusal of mean revealed better quality of recovery in group I horses than in group II horses. In the present study, two observers blinded by the treatment groups and not related to the study was trained using “Awin” animal welfare indicator-horse grimace scale application (Awin, 2014) and had evaluated the 36 (6x2x3=36) photographs. The findings (Table 2) in thecurrent study revealed that horses premedicated with dexmede tomidine acepromazine - butorphanol, induced and maintained with ketamine-midazolam had a significantly lower pain score on 1st, 2nd and 3rd post-operative days as compared horses that were premedicated with xylazine-butorphanol, induced and maintained with ketamine alone. In order to avoid bias, the analgesics used in treatment of post-operative pain were kept constant in both the groups.

The mean ± SE of rectal temperature were shown in Table 3. Statistical analysis revealed significant ($P<0.05$) reduction in the mean rectal temperature in both the groups: after sedation, after induction, during maintenance and after recovery. The mean ± SE of cardiopulmonary parameters were shown in Table 3. Statistical analysis revealed the progressive decrease in mean heart rate in both the groups. The reduction in heart rate after sedation and after induction were significantly ($P < 0.01$) lesser than the pre-operative value in both the groups which returned to base value after recovery. Mean arterial blood pressure did not vary significantly in both the groups. The mean capillary refill time increased significantly in both the groups after sedation, after induction, during maintenance and after recovery, however after recovery, the values returned to the base values. Electrocardiographic study revealed no significant changes except reduction in heart rate and increase in amplitude of P wave following the sedation with dexmedetomidine-acepromazine-butorphanol and mild cardiac arrhythmias in xylazine-butorphanol premedicated horses. In both the groups increase in the amplitude of the QRS complex was noticed. In the present study no change was noticed in configuration of electrocardiogram. The mean ± SE of blood gas analysis values were shown in Table 4. Statistical analysis revealed significant ($P< 0.01$) reduction in mean SpO2 in both the groups after sedation, after induction, during maintenance and after recovery. Group I horse maintained higher ($P< 0.01$) mean percentage after sedation, after induction, during maintenance and after recovery when compared with group II horses. Pulse oximetry revealed the hemoglobin saturation and was expressed in percentage. Following premedication the saturated partial pressure of oxygen decreased significantly in group I horses as xylazine decreased the respiratory rate and produced ventilation-perfusion mismatch. The partial pressure of carbon dioxide increased and oxygen in venous blood decreased after sedation, after induction and during maintenance in both the groups. Statistical analysis of the bicarbonate level revealed significant ($P< 0.01$) increases in values after induction, during maintenance and before recovery in both the groups. Statistical analysis revealed significant ($P< 0.01$) increase in hematocrit values after sedation, after induction and during maintenance in both the groups. The variations in hematocrit and biochemical parameters were within the normal range throughout the period of study. The mean ± SE of blood urea nitrogen values were shown in Table 5. Statistical analysis revealed no significant difference in blood urea nitrogen

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values between both the groups of horses. The mean ± SE of creatinine values were shown in Table 5. Statistical analysis revealed a significant increase (P< 0.05) in the creatinine value during the post operative period in horses of group II when compared with group I horses. The variations were within the normal range throughout the period of study. The mean ± SE of alanine transaminase and aspartate amino transferase values were shown in Table 5. Statistical analysis revealed no significant difference in alanine transaminase and aspartate amino transferase values between both the groups of horses. No intra-operative or post operative anesthetic/ surgical complications were recorded in this study.

DISCUSSION

The shorter duration of time could be attributed to the synergistic effects of dexmedetomidine with acepromazine and butorphanol [1, 22, 61, 71,72,64,75]. Butorphanol also has an additive, synergistic and complementary effect with alpha-2 adrenergic agonists and other opioids which reduced the duration of sedation time [10]. The mean values revealed better quality of sedation in group I horses than in group II horses which could be due to the effect of dexmedetomidine as it was a potent, selective, specific alpha-2 adrenergic agonist [71]. The intense sedation and severe ataxia following administration of dexmedetomidine as indicated by decrease in head height and elevation of gait scores was alsoreportedby [61].Acepromazine and butorphanol synergisticallyacted with dexmedetomidine in inducing smooth sedation as observed in this study [17, 63]. The quicker induction in both the groups could be attributed to the effect of ketamine which could induce anesthesia in one arm brain circulation [7], it's effect on opioid receptors, muscarinic receptors and voltage sensitive calcium channels [32] and activation of mono aminergic descending inhibitory system [37]. Midazolam as a benzodiazepine derivative acted on the gamma amino butyric acid receptor which had anxiolytic, muscle relaxant, anti-convulsive effects that would potentiate or enhance the sedative and hynoptic effects of injectable anesthesia [60, 64]. Zamur and Neto [81] also reported that midazolam had sedative effect characterized by lowering of head and ataxia without action on nociception in horses. The smooth and better quality of induction in horses induced with ketamine-midazolam could be attributed to the combined effect of ketamine and midazolam and also, to the premedicants already administered namely dexmedetomidine-acepromazine- butorphanol. The reduction in dose of ketamine and excellent to good quality of anesthesia could be due to the synergistic action of ketamine and midazolam [45,69]. Good quality of anesthesia could be observed when ketamine was co-administered with butorphanol and dexmedetomidine to maintain anesthesia in horses [54]. Butorpahnol reduced the dose for halothane [11]. The better quality of sedation and reduction in dose of ketamine in horses maintained with ketamine and midazolam was due to the fact that the horses were already premedicated with dexmedetomidine-acepromazine-butorphanol. The shorter recovery with excellent to good quality of recovery was due to lesser quantity of ketamine administration during maintenance as compared with the high dose rate in horses that were maintained with ketamine alone. The elimination half life of ketamine depended on the dose of ketamine which ranged from 2.80 min to 42.70 min [39].

The findings in the current study revealed that horses premedicated with dexmedetomidine-acepromazine-butorphanol induced and maintained with ketamine - midazolam had a significantly lower pain score on 1st, 2nd and 3rd post-operative days when compared with horses that were premedicated with xylazine-butorphanol, induced and maintained with ketamine alone which could be attributed to the synergistic and additive action of dexmedetomedine a novel analgesic along with butorphanol in significantly reducing post-operative pain [1,22,61,62,71,72,74,75]. Statistical analysis revealed significant reduction in the mean rectal temperature in both the groups: after sedation, after induction, during maintenance and after recovery which could be attributed to the reduction in basal metabolic rate due to the effects of anesthesia and ancillary drugs and its interference of the drugs with thermoregulatory centers and muscular activity [56, 68]. Alpha-2 adrenergic agonists depleted the catecholamines in the thermoregulatory centers and rendered the horses either to become hypothermic or hyperthermic according to the environmental temperature [54]. Alpha-2 adrenergic agonists when administrated they induced reduction in heart rate due to increase in vagal tone [34, 50], arterioventricular block [12, 51, 53, 56,58] , blocking the central and peripheral alpha adrenoreceptor [40], alteration in parasympathetic tone [28, 41, 79], and inhibition of sympathetic nervous system [28]. Acepromazine also induced reduction in heart rate due to its alpha adrenergic blockade [35], inhibition of centrally mediated pressor reflex, myocardial depression and negative ionotropic effect [19]. Brock [8] reported that administration of acepromazine induced only occasional bradycardia and was attributed to the depression of vasomotor activity and alpha receptor blocking action [21]. Ketamine was known for increasing the heart rate due to its effect on inhibition of vagal component [20, 49], positive inotropic effect [2,78], increased sympathetic effect and reflexogenic change in autonomic nervous system [2]. Hopster et al. [23] reported that midazolam did not alter the hemodynamic variables which indicated that the cardiac perfusion was not altered. While comparing the mean heart rate between after sedation, after induction, during maintenance and after recovery the horses in group I maintained a higher mean heart rate as dexmedetomidine had a minimal cardiac effect while comparing with xylazine [16,24, 33,38,56,73,80], and acepromazine had a protective action on myocardium [24]. Marcilla et al. [48] and Congdon et al. [14] reported depression of cardiac function and cardiac arrhythmias following administration of dexmedetomidine in horses. In present study the co administration of acepromazine would have prevented the deleterious effects of dexmedetomidine. Though ketamine had cardio-stimulatory effect, the dose requirement for maintenance was less in horses that were induced and maintained with ketamine-midazolam mixture as compared with ketamine alone. Cardiovascular function assessment is difficult under clinical conditions; heart rate and arterial pressure are the only objective variables monitored routinely. Many consider MAP maintenance in excess of 75mmHg is important if myopathy is to be prevented [77]. Ketamine due to its sympathomimetic effect and direct or indirect reflexogenic change in the autonomous nervous system had the tendency to increase blood pressure [2, 20]. Folts et al. [20] reported though the heart rate and cardiac work increased following the administration of ketamine, the coronary blood flow appeared to be insufficient to meet the metabolic demands of the myocardium hence the cardiac output tend to decrease during prolonged ketamine administration. The increased vascular tone induced by ketamine was eliminated by the action of xylazine and dexmedetomidine [1, 2, 9, 12, 20, 22, 34, 38, 40, 56, 58,61,71,72,74,75]. Acepromazine also induced peripheral vasodilatation and reduction in blood pressure [18,25,35,51,53,55,66]. When comparing the means between the groups, the mean capillary refill time in group I horses showed higher trend than that of group II horses as reported by Cornick- Seahorn [15]. Ketamine had sympathomimetic effect resulting in increased heart rate and elevated blood pressure [38], these effects were counteracted by the action of xylazine which resulted in reduction in cardiac output and peripheral vasodilatation [40, 41]. Brock [8] reported that acepromazine also had depression of central vasomotor action resulting in dilation of cutaneous blood vessels. There was a mild increase with minimal alteration in mean capillaryrefill time of horses, premedicated with dexmedetomidine-acepromazine-butorphanol, induced and maintained with ketamine- midazolam suggested that this combination had minimal effect on capillary refill time when compared with horses premedicated with xylazine-butorphanol, induced and maintained with ketamine alone. Kerr et al. [33], Muir et al. [51], Lele and Bhokre [40], Nilsfors et al. [53] and Wagner et al. [76] reported arterioventricular block following intravenous administration of xylazine. Wright [78] reported that either xylazine or ketamine administered alone or in combination potentially induced cardiac arrhythmia. Acepromazine had a protective action on myocardium [24, 48]. Depression of cardiac function and cardiac arrhythmias following administration of dexmedetomidine was observed in horses [14]. In the present study the co-administration of acepromazine prevented the deleterious effects of dexmedetomidine and cardiac arrhythmia was noticed in

group II due to increased xylazine sensitivity of myocardium to circulatory catecholamines and predisposing to cardiac arrhythmia [40, 53]. Kerr et al. [33] and Purohit et al. [58] reported an increase in respiratory rate following administration of xylazine in horses followed by decrease. The reduction in respiratory rate following xylazine administration was mediated by the suppression of the baro and adrenergic receptors and the findings concurred with Kerr et al. [33] and Popovic et al. [56]. It could be concluded that the mean respiratory rate was decreased minimally in group I when compared to group II horses.

Thereductionin saturated partial pressure of oxygen following ketamine administration could be attributed to the direct relaxant effect of ketamine on bronchial smooth muscle and hypoventilation [52]. Klein et al. [36] reported that xylazine had a significant influence on respiratory mechanism mainly during inspiration which could be attributed to the high changes dynamically caused in the upper airway diameter due to muscle relaxation property. When the mean SpO2 percentage was compared between groups the horses that were premedicated with dexmedetomidine-acepromazine-butorphanol, induced and maintained with ketamine-midazolam maintained higher mean percentage after sedation, after induction, during maintenance and after recovery due to compensation by the increased tidal volume caused by acepromazine [57] when compared with horses that were premedicated with xylazine-butorphanol, induced and maintained with ketamine alone. The findings of the present study concurred with Sankar et al. [65], Lerche [42], Valverde [71]and Toholj et al. [69]. The variations in BUN and Creatinine values were within the normal range throughout the period of study and concurred with the observations of Jacobson [26], Traynor and Hall [70], Malik et al. [46] and Malik et al. [47]. The variations in Alanine transaminase values and Aspartate amino transferase values were within the normal physiological range throughout the period of study indicating no interference to hepatic blood flow and lack of insult to hepatocytes and muscle fibres [3]. This study indicated that Dexmedetomidine-acepromazine-butorphanol premedicated equines, induced and maintained with ketamine–midazolam mixture as a total intravenous anesthetic (TIVA) protocol is safe and reliable with minimal or no significant alteration in cardiopulmonary parameters with minimal post anesthetic morbidity and mortality in horses. This protocol is found to be ideal for field practice to produce safe anesthesia up to 30 minutes.

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