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Haemato-biochemical changes during nalbuphine xylazine-acepromazine-ketamine anaesthesia in horses

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The objective of the study was to evaluate cardiopulmonary and haematobiochemical changes and stress response associated with administration of nalbuphine HCl during ketamine anaesthesia in horses premedicated with xylazine or xylazine-acepromazine. Eighteen clinical cases of horses brought for diagnostic and surgical procedures requiring general anaesthesia were randomly divided into three groups, I, II and III, each consisting of six animals. All the horses were premedicated with glycopyrrolate 0.02 mg/kg b.wt, i.v. Horses in group I and group II were administered xylazine HCl 1.10 mg/kg b.wt, i.v. In group III, 0.50 mg/kg b.wt xylazine HCl was administered i.v., followed by acepromazine 0.02 mg/kg b.wt, i.v. Before induction of anaesthesia, nalbuphine HCl was administered in group II and group III animals @ 0.75 mg/kg b.wt, i.v. Ketamine HCl was administered i.v. to induce anaesthesia @ 2.20 mg/kg b.wt and maintained with 0.50 mg/kg b.wt in required cases for duration of 15±1.04 min. The heart rate increased during intraoperative period reached baseline value 6 hr after surgery. The respiratory rate and mean saturated partial pressure of oxygen decreased significantly during intraoperative period. Haemoglobin, PCV, TEC and TLC decreased significantly; the neutrophil and monocyte counts increased and the lymphocyte count decreased significantly during intraoperative and postoperative period in all the groups. The blood glucose, creatinine, plasma cortisol and plasma catalase activity significantly increased during intraoperative period and postoperative period. The total protein values significantly decreased during the intraoperative period in all the groups. To conclude, administration of nalbuphine HCl did not produce any marked changes in cardiopulmonary, haematobiochemical parameters and produced less stress response.

Keywords: Acepromazine, Horse, Ketamine, Nalbuphine, Xylazine.

The most widely used premedicant xylazine produces sedation, analgesia and muscle relaxation through alpha-2 adrenergic receptor mediated inhibition of norepinephrine release (Haskins *et al.*, 1975; Gleed, 1987). The undesirable side effects produced by xylazine are second degree atrio-ventricular block, cardiac arrhythmias, bradycardia, hypotension and sensitisation of myocardium to circulating catecholamines (Purohit *et al.*, 1981; Kitzman *et al.*, 1984; Yamashita *et al.*, 2000). Although xylazine is used widely as a sedative agent before anaesthetic induction, a phenothiazine derivative, acepromazine is occasionally combined to enhance sedation (Klein and Sherman, 1977) and also to provide a potentially beneficial antiarrhythmic effect (Cruz *et al.*, 2011).

Opioid analgesics are commonly administered in addition to general anaesthetics to provide analgesia and to reduce the dose and side effects of principle anaesthetic drug. 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, similar to widely used opioid agent butorphanol. However, systemic effects of opioids could be unpredictable when used alone without sedation, which might cause CNS excitation and potential gastrointestinal side effects (ileus), hence should be accompanied by tranquilization or sedation with an alpha-2 agonist in horses (Mudge and Bramlage, 2007).

The purpose of this study was to evaluate cardiopulmonary and haematobiochemical changes, and stress response associated with administration of nalbuphine HCl in xylazine or xylazine-acepromazine premedicated horses under ketamine anaesghesia.

Materials and Methods

The clinical study was conducted on 18 horses of either sex brought for castration (7 Kathiawari horses, 4 Marwari horses and 2 ponies), traumatic lacerated wound (4 Kathiawari horses) and tumour excision (one Indian Through bred). 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 hr and 6 hr, respectively prior to anaesthesia. On the day of surgery all the

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horses were groomed thoroughly and mouth was washed with plain water to remove any food particles. All the anaesthetic trials were conducted in the forenoon to avoid diurnal variations.

All the horses were premedicated with glycopyrrolate, 15 min before administration of xylazine 0.02 mg/kg b.wt, i.v. Horses in groups I and II were administered with xylazine 1.10 mg/kg b.wt, i.v.; whereas in group III xylazine was administered 0.5 mg/kg b.wt, followed by acepromazine 0.02 mg/kg b.wt, i.v. Before induction of anaesthesia, nalbuphine HCl was administered in group II and group III horses @ 0.75 mg/kg b.wt, i.v. Ketamine HCl 2.20 mg/kg b.wt was administered i.v. to induce anaesthesia and anaesthesia was maintained with 0.5 mg/kg b.wt of ketamine as per the requirement for a period of 15±1.04 min.

The cardiopulmonary parameters studied were heart rate (HR-beats/min), electrocardiograph (ECG), respiratory rate (RR-breaths/min) and peripheral capillary oxygen saturation (SpO_2%). Haematobiochemical parameters studied were haemoglobin (Hb-g/dL), total erythrocyte count (TEC-million/mm^3), total leucocyte count (TLC-thousands/mm^3), packed cell volume (PCV-%), differential count (DLC-%), total serum protein (g/dL), blood glucose (mg/dL), creatinine (mg/dL), blood urea nitrogen (mg/dL), plasma cortisol level (ng/mL) and plasma catalase activity (μM of H_2O_2 decomposed/min/ mg protein). All the parameters were assessed preoperatively, intraoperatively, postoperatively and after 6 hr of surgery. The data obtained were statistically analyzed using completely randomized block design as a statistical tool. Differences between the data were considered significant when $P<0.05$.

Results and Discussion

A significant increase ($P<0.05$) in HR was noticed during the intraoperative period as well as postoperative period in all three groups (Table 1). The HR reached baseline value 6 hr after surgery. In the present study, electrocardiograpy revealed no significant changes in any of the three groups except for an increase in the amplitude of P wave and QRS complex following administration of xylazine.

Administration of xylazine produced bradycardia, which was mainly attributed to the direct depressive effect on cardiac pacemaker or stimulation of parasympathetic nervous system or inhibition of sympathetic nervous system (Verstegen *et al.,* 1991; Jain *et al.,* 2006; Linardi *et al.,* 2008). Acepromazine also might have contributed to bradycardia due to depression of vasomotor action and alpha adrenergic receptor blocking action (Klein and Sherman, 1977; Brock, 1994; Gaikwad *et al.,* 2006). Glycopyrrolate abolished the side effects caused by xylazine and acepromazine mainly bradycardia, second degree AV block, decreased cardiac output and hypotension, which could be attributed to positive chronotropic and ionotropic action, vagolytic or parasympatholytic action (Kerr *et al.,* 1972; Pimenta *et al.,* 2011) and altered myocardial function (Grubb *et al.,* 1999). Guzman *et al.* (2011) observed antinociceptive effects up to 3 hrs and studied the "ceiling effect" of nalbuphine HCl in birds. The authors also cited that nalbuphine had a low incidence of undesirable effects in mammals and considered to be superior to similar drug, butorphanol because nalbuphine did not increase cardiac oxygen requirements and cardiac work in cardiac compromised patients, nor did it prolong the duration of respiratory depression with higher dose (ceiling effect) as seen with butorphanol.

The respiratory rate decreased significantly ($P<0.05$) during the intraoperative period in all the three groups. The RR reached baseline value during the postoperative period. Klein *et al.* (2006) reported highly dynamic changes in upper airway diameter mainly during inspiration due to muscle relaxation caused by xylazine. Some studies report respiratory depression after administration of kappa agonists like nalbuphine (Mudge and Bramlage, 2007; Hackett and Hassel, 2009), but Guzman *et al.* (2011) have reported that administration of nalbuphine did not prolong the duration of respiratory depression with higher dose (ceiling effect) as seen with butorphanol.

SpO_2 revealed a significant decrease ($P<0.05$) during the intraoperative period in all the three groups (Table 1). Following premedication, SpO_2 decreased significantly, which could be due to the action of xylazine in producing ventilation-perfusion mismatch. Anaesthetic agents during induction and maintenance reduce the RR, minute volume and increase dead space, which in turn produce the ventilation-perfusion mismatch (Moens *et al.,* 1998; Robertson and Bailey, 2002). The values came near to base line postoperatively, which could be due to compensation by increased tidal volume and increased cardiac output in turn leading to more tissue oxygen delivery and bronchodilatation by glycopyrrolate (Singh *et al.,* 1997) and acepromazine (Popovic *et al.,* 1972).

Table 1: Mean±S.E. values for heart rate, respiratory rate, spo_2, haemoglobin, total erythrocyte count and packed cell volume.

Parameters	Group	Preoperative	Intraoperative	Postoperative	After 6 hours	f-value
Heart Rate	I	47.50±1.11^{c}	54.33±1.14^{e}	50.83±1.19^{d}	49.16±1.30^{cd}	14.291*
(beats/min)	II	37.50±1.17^{a}	45.66±1.33^{b}	42.00±1.12^{ab}	41.00±1.59^{a}	
	III	38.83±1.88^{a}	46.00±2.01^{bc}	40.83±1.72^{a}	39.16±0.79^{a}	
Respiratory Rate	I	15.66±1.05^{c}	13.00±1.18^{a}	15.16±0.94^{b}	12.83±0.60^{a}	3.301*
(breaths/min)	II	13.33±1.20^{a}	11.66±0.55^{a}	12.50±0.76^{a}	13.83±1.19^{ab}	
	III	16.16±0.60^{e}	12.50±0.42^{a}	12.67±0.67^{a}	16.00±0.57^{d}	
S_pO_2	I	96.13±1.29^{b}	86.94±0.79^{a}	90.32±0.94^{a}	-	8.142*
(%)	II	97.24±1.45^{b}	84.57±1.24^{a}	92.66±0.87^{a}		
	III	94.33±1.99^{ab}	82.31±1.54^{a}	89.87±1.89^{a}		
Haemoglobin	I	14.75±0.97^{bc}	13.85±0.51^{b}	13.85±0.84^{b}	13.90±0.42^{b}	2.851*
(g/dL)	II	15.50±0.34^{c}	14.20±0.53^{b}	14.65±0.26^{b}	15.13±0.31^{c}	
	III	13.70±0.79^{ab}	11.80±0.62^{a}	12.85±0.67^{a}	12.86±0.66^{a}	
TEC	I	8.25±0.46^{a}	7.55±0.40^{a}	7.63±0.30^{a}	8.00±0.44^{a}	2.380*
(millions/cmm)	II	9.30±0.25^{c}	8.56±0.17^{ab}	8.70±0.23^{b}	8.98±0.24^{bc}	
	III	7.88±0.70^{a}	7.02±0.69^{a}	7.05±0.64^{a}	7.41±0.69^{a}	
PCV	I	41.20±1.28^{a}	38.01±2.85^{a}	39.40±1.48^{a}	40.13±1.41^{a}	3.792*
(%)	II	47.01±1.09^{d}	44.03±0.80^{b}	45.78±1.59^{c}	47.06±0.79^{ab}	
	III	41.38±2.39^{ab}	36.78±2.28^{a}	38.12±2.17^{a}	39.45±2.51^{a}	

Means bearing different superscripts (alphabets) in a parameter differ significantly (P<0.05)

Hb values showed a significant decrease during the intraoperative and postoperative period in all the three groups (P<0.05), which returned to normal at 6 hr after surgery (Table 1). When compared between the groups, there was a significant decrease in the values during the intraoperative period and 6 hr after surgery in group III as compared to groups I and II. Similarly, a significant decrease in the PCV values was noticed during the intraoperative and postoperative periods in all three groups (P<0.05). The PCV values returned to normal level at 6 hr after surgery. A significant decrease (P<0.05) was seen in the circulating RBC values during intraoperative and postoperative period in all three groups. The values reached normal range at 6 hr after surgery. The fall in haematocrit and other haematological values could be attributed to haemodilution due to hypotension, and pooling of erythrocytes in the spleen by splenic relaxation due to central depression and alpha adrenergic action of xylazine (Mackenzie and Snow, 1977; Wagner *et al.*, 1991). Acepromazine caused dose dependent decrease in haematocrit value as reported by Ballard *et al.* (1982) and also caused transient reduction in the packed cell volume (Brock, 1994) by their effects on alpha receptor mediated action.

There was non-significant decrease (P>0.05) in the TLC values during the intraoperative period in all the three groups. The values returned to normal during the postoperative period. A significant increase (P<0.05) in the neutrophil count and decrease in lymphocyte count was observed during the intraoperative and postoperative periods in all three groups. The values reached to normal levels at 6 hr after surgery. No significant difference between the groups was observed. Monocyte count also increased significantly during the intraoperative and postoperative periods in all three groups (P<0.05). The values remained elevated at 6 hr after surgery. No significant difference in the eosinophil count was recorded throughout the period of study in all three groups.

The present study revealed neutrophilia after premedication in all the three groups followed by lymphocytopenia, eosinopenia and monocytosis simulating the classic stress leukogram. However, the values returned to the baseline value at 6 hr. The change in the pattern of differential count in terms of stress leukogram was marked when the horses were induced and maintained with ketamine (Sankar *et al.*, 2010; Malik *et al.*, 2011). Stashak (1991) stated that stress response as a consequence of tissue injury either physical,

Table 2: Mean±S.E. values for BUN, creatinine, blood glucose, total protein and plasma cortisol.

Parameters	Group	Preoperative	Intraoperative	Postoperative	After 6 hours	f-value
BUN	I	25.76±1.63^{a}	25.03±1.57^{a}	25.96±1.67^{a}	25.86±1.53^{a}	1.605
(mg/dL)	II	24.84±0.50^{a}	24.99±0.69^{a}	27.44±0.76^{a}	24.28±0.77^{a}	
	III	25.65±0.49^{a}	27.69±0.65^{ab}	28.59±0.65^{b}	27.51±0.72^{a}	
Creatinine	I	1.78±0.05^{a}	1.94±0.10^{c}	1.89±0.09^{bc}	1.85±0.06^{b}	2.879*
(mg/dL)	II	1.65±0.08^{a}	2.00±0.08^{d}	2.05±0.07^{e}	1.76±0.05^{a}	
	III	1.58±0.09^{a}	1.86±0.08^{b}	1.80±0.07^{ab}	1.72±0.08^{a}	
Blood Glucose	I	44.28±1.97^{a}	74.51±7.99^{c}	83.62±3.92^{c}	48.91±3.17^{ab}	108.276*
(mg/dL)	II	40.20±2.70^{a}	81.98±6.42^{c}	100.56±2.70^{d}	86.26±5.26^{c}	
	III	57.35±2.84^{b}	151.91±6.33^{e}	192.90±5.04^{e}	164.40±5.23^{e}	
Total Protein	I	7.24±0.17^{de}	7.07±0.16^{d}	7.30±0.12^{e}	7.32±0.09^{e}	12.123*
(g/dL)	II	6.78±0.16^{d}	6.03±0.08^{b}	6.66±0.12^{cd}	6.60±0.15^{c}	
	III	5.83±0.35^{ab}	5.34±0.27^{a}	5.53±0.33^{a}	5.53±0.31^{a}	
Plasma Cortisol	I	18.60±0.15^{a}	113.27±2.42^{f}	134.12±4.17^{h}	99.41±1.3^{c}	237.736*
(ng/mL)	II	18.67±0.19^{a}	109.13±2.02^{ef}	124.54±2.10^{g}	93.76±3.21^{c}	
	III	18.02±0.59^{a}	101.19±3.78^{cd}	104.54±1.51^{d}	82.77±5.38^{b}	

Means bearing different superscripts (alphabet) in a parameter differ significantly (P<0.05)

chemical, surgical or due to infection would lead to a response in vascular, cellular and localized changes, which results in vasoconstriction, endothelial cell separation, diapedesis of leukocytes, and fibrin plug formation in the process of inflammation.

The BUN (mg/dL) values revealed no significant difference during the period of study in all three groups (Table 2). A significant increase (P<0.05) in the creatinine values was recorded during intraoperative and postoperative periods in all the three groups, the values reached near normal level at 6 hr after surgery. There was no significant difference among the groups during the period of study. Creatinine is formed by the spontaneous condensation and dehydration of muscle creatinine. Factors such as cytokines, increase the endogenous muscle catabolism during stress, which results in the release of creatinine in the circulation (Malik *et al.*, 2011).

A significant increase (P<0.05) in the blood glucose level was recorded during the intraoperative and postoperative periods in all the three groups. The values remained higher even at 6 hr after surgery. There was a significant increase in the blood glucose values during the intraoperative and postoperative periods in groups II and III as compared to group I. Increase in blood glucose level was attributed to increased level of glucocorticoid hormone (Clarke *et al.*, 1970), inhibition of insulin secretion (Robertson *et al.*, 1990), increased glucagon secretion leading to hepatic glycogenolysis and gluconeogenesis from amino acids (Muir, 2008), and increased protein degradation as a response to surgical stress and trauma (Traynor and Hall, 1981; Udelsman and Holbrook, 1994).

The total protein (g/dL) values revealed a significant decrease (P<0.05) during the intraoperative period in all the three groups. The values returned to near normal level during the postoperative period and at 6 hr after surgery. Among the different groups, groups II and III had a significant decrease in the protein values during the intraoperative and postoperative periods as compared to group I. Reduction in the total serum protein level during the intraoperative period in the three groups could be attributed to protein degradation caused by surgical stress and trauma (Traynor and Hall, 1981) and expanded intravascular volume (Brock, 1994).

The plasma cortisol increased significantly (P<0.05) during the intraoperative and postoperative periods in all the three groups. The values returned to normal level at 6 hr after surgery. Among the groups, the values in groups II and III were significantly lower during the intraoperative period than that of group I. The reasons attributed were decreased breakdown of plasma cortisol due to reduction in hepatic blood flow during surgery and elevation of plasma half life of cortisol. In the present study elevation of plasma cortisol level during intraoperative period could be mainly attributed to xylazine via alpha-2 adrenergic actions. In xylazine-nalbuphine and xylazine-

acepromazine-nalbuphine premedicated horses plasma cortisol level was lower as compared to only xylazine premedicated horses, which could be attributed to the adjunct and analgesic action of nalbuphine (Brunson and Majors, 1987; Muhammad *et al*., 2004; Sellon *et al*., 2004). Goleteni *et al*. (2007) reported nalbuphine did not increase the cortisol and ACTH level in humans.

There was a significant increase ($P<0.05$) in plasma catalase activity values throughout the period of study in all the three groups, with no significant difference among the groups. Perkarkova *et al*. (2001) reported that repeated peripheral painful stimulation might act as a promoter of the oxidative stress mechanism causing damage to the biomolecules inside the cell. The authors also stated that analgesic agents act by scavenging the free radicals. In the present study, plasma catalase activity increased significantly in xylazine premedicated horses as compared to xylazine-nalbuphine premedicated horses and xylazine-acepromazine-nalbuphine premedicated horses, which could be due to enhancement of scavenging the free radicals by administration of nalbuphine.

In conclusion, the administration of nalbuphine HCl did not produce any marked changes in cardiopulmonary and haematobiochemical parameters, and can be included in equine anaesthetic regimen for surgical and diagnostic procedures for duration of about 15 min.

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