COMPARATIVE EVALUATION OF BUTORPHANOL/PENTAZOCINE IN COMBINATION WITH XYLAZINE FOR KETAMINE ANAESTHESIA IN DOGS UNDERGOING ELECTIVE OVARIOHYSTERECTOMY

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The present study was carried out to evaluate the clinico-physiological and hematobiochemical effects of xylazine in combination with butorphanol or pentazocine for ketamine anaesthesia in female dogs undergoing elective ovariohysterectomy. The animals were randomly divided into groups A and B having 06 animals in each group. Atropine (0.04 mg/kg) followed 5 minutes later by xylazine (0.5 mg/kg) were administered IM in both groups. However, in group A, butorphanol (0.2 mg/kg) and in group B pentazocine (1 mg/kg) was administered IM along with xylazine. After 10 minutes, anaesthesia was induced using ketamine IV as a single bolus in both groups followed by maintenance with IV ketamine as and when needed during the surgery. Adequate sedation, muscle relaxation and analgesia followed by smooth and uneventful recovery were recorded in both groups. A significantly ($P<0.05$) reduced weak time and down time was recorded in the animals of group A which took longer duration in attaining sternal and standing position and recovery as compared to group B. The dose sparing effect of drugs on ketamine was significantly ($P<0.05$) higher in group A. Heart rate showed gradual and significant ($P<0.01$) increase at most of the time intervals in both groups. Respiratory rate and rectal temperature decreased significantly ($P<0.05$) in both groups. A significant ($P<0.05$) decrease in SpO_2 was recorded throughout the observation period in both groups. Haemoglobin, PCV and neutrophils decreased significantly ($P<0.05$) while glucose and BUN values increased non-significantly ($P>0.05$) at most of the time intervals. Lymphocyte and creatinine recorded a significant ($P<0.05$) increase during the observation period. Xylazine along with butorphanol or pentazocine produced a comparable degree of clinico-physiological and haemodynamic stability along with minimal changes in hematobiochemical parameters during ketamine anaesthesia in dogs undergoing elective ovariohysterectomy.

Keywords: Butorphanol, Ketamine, Ovariohysterectomy, Pentazocine, Xylazine.

The combination of alpha-2 adrenoceptor agonists with oipiods or benzodiazepenes has been found to enhance sedation and analgesia in dogs. Opioids like butorphanol, fentanyl, hydroxymorphone, buprenorphine and pentazocine have been recommended for use in combination with alpha-2 agonists and ketamine anaesthesia in dogs and cats (Barletta *et al*., 2011; Santosh *et al*., 2013; Sethi, 2015). A better cardiovascular stability was observed in dogs during ketamine anaesthesia following premedication with alpha-2 agonists and opioids (Ahmad, 2010; Rafee *et al*., 2016). The present study was therefore, designed to compare the effects of xylazine in combination with butorphanol or pentazocine for ketamine anaesthesia in canine patients subjected to elective ovariohyseterectomy.

Materials and Methods

The present study was carried out on 12 adult female dogs subjected to elective ovariohysterectomy. Atropine was administered @ 0.04 mg/kg IM followed after 5 minutes with xylazine @ 0.5 mg/kg body weight IM. However, in group A butorphanol @ 0.2mg/kg body weight IM while pentazocine @ 1 mg/kg body weight IM in the animals of group B in separate syringe was administered along with xylazine. Anaesthesia was induced after 10 minutes of premedication using ketamine IV in both groups. The maintenance of anaesthesia was carried out with incremental doses of ketamine IV as and when needed during the surgical procedure.

Weak time, down time, recovery time, sternal recumbency and complete recovery were recorded. Palpebral reflex was

considered as a measure of depth of sedation, jaw relaxation as a measure of muscle relaxation and pedal reflex as a measure of analgesia were recorded 0, 10, 15, 30, 45, 60, 75 and 90 min respectively as per the method.. Heart rate (HR-beats per min), respiratory rate (RR- breaths per min), rectal temperature (RT-^{0}C) and oxygen saturation of hemoglobin (SpO_2 -%) were recorded as per the standard procedures.

One ml venous blood was collected in heparinized (1:1000) disposable syringe at 0, 15, 30, 45, 60 and 90 min interval for estimation of haemoglobin (g/L), packed cell volume (L/L) and total leucocyte count ($x10^9$/L) as per the standard procedures. The values of DLC were expressed in percent. Four ml blood was collected in heparinized (1:1000) syringes (sodium fluoride for glucose) at the same time intervals. The blood samples were centrifuged at 3000 rpm for 5 min and plasma was separated and stored at -20^0C until assayed. The plasma samples were subjected for the estimation of plasma urea nitrogen (mmol/L) by DAM method, plasma glucose (mmol/L) by GOD/POD method and plasma creatinine (µmol/L) by alkaline picrate method.

The data were analyzed for statistical significance using SPSS software, version 20.0 (SPSS, Inc., Chicago, Illinois). Analysis of variance (ANOVA) and Duncan's multiple range tests (DMRT) were used to compare the means at different intervals among different groups. The mean values at different intervals were compared with their base values in each group using Paired "t" test. The subjective data generated from the scoring of various parameters were analyzed using Kruskal-Wallis one-way test. The statistical significance was assessed at $P<0.05$.

Result and Discussion

Clinical observations

A mildly depressed palpebral reflex was recorded at 10 min after premedication followed by moderately abolished reflex from 15 min onwards till 60 min interval in the animals of group A and 45 min in group B. However, very mildly depressed palpebral reflex was recorded at 75 and 90 min interval in both groups. Comparison between groups revealed that the palpebral reflex score was significantly ($P<0.05$) higher at 75 and 90 min interval in group A than group B. Mild to moderate palpebral reflex following administration of alpha-2 adrenoceptor agonists along with opioids in dogs have also been reported by Amarpal *et al*. (1996) and Rafee *et al.* (2015).

Jaw relaxation score in the animals of group A revealed mildly relaxed jaw at 10 min followed by moderate jaw relaxation up to 60 min interval and till 45 min in group B. However, mild jaw relaxation was recorded at 75 and 90 min interval and very mildly relaxed jaw tone at 75 and 90 min interval was recorded in group B. Moderate level of anaesthesia has been reported to cause complete loss of resistance to opening of jaws as also reported by Tranquilli *et al*. (2007). In the present study, mild relaxation of jaw was reported in both groups after premedication at 10 min and after recovery. Comparison between groups revealed that the jaw relaxation score was significantly ($P<0.05$) higher at 75 and 90 min interval in the animals of group A. The findings of the present study are in accordance with those stated by Sethi (2015) when combination of xylazine was used along with butorphanol or pentazocine in dogs under ketamine anaesthesia.

A very mild pedal reflex was recorded at 10 min interval in the animals of both groups followed by completely abolished pedal reflex from 15 min onwards till 45 min interval. However, very mild pedal reflex was recorded at 60 and 75 min interval followed by moderate pedal reflex at 90 min interval in both groups. Comparison revealed no significant difference in the pedal reflex score at different time intervals. The mechanism of analgesia produced by alpha-2 agonists is mediated by stimulating α-2 receptors at various sites in the pain pathway within the brain and spinal cord. The presence of very mild reflex following administration of alpha-2 agonists along with opioids might be due to synergestic activity

of drugs as reported earlier in dogs by Amarpal *et al.* (1996) and Rafee *et al*. (2015).

A significantly (P<0.05) lower weak time (3.42±0.26 v/s 4.28±0.31 min) and down time (4.44±0.30 v/s 5.60±0.20 min) was recorded in the animals of group A as compared to group B. Similar findings in both groups have been reported following administration of xylaine in combination with butorphanol in dogs (Sethi, 2015). The animals of group A had non-significantly (P>0.05) longer recovery time (16.40±2.02 v/s 14.80±1.81 min), sternal recumbency time (23.22±2.08 v/s 22.05±1.35 min) and standing time/complete recovery time (37.70±2.10 v/s 34.39±2.67) as compared to the animals of group B. The longer recovery time in group A could be attributable to synergestic action of butorphanol with xylazine. Synergestic action resulting in deeper sedation and prolonged recovery following administration of alpha-2 agonists along with butorphanol and ketamine in dogs and has also been reported by Rafee *et al*. (2016).

Physiological observations

A significant (P<0.01) increase in heart rate was recorded in the animals of group A after administration of preanaesthetic drugs. Heart rate increased gradually and significantly (P<0.01) from 15 min onwards till 60 min. However, HR decreased from 75 min onwards till end of observation period but the values were significantly (P<0.01) higher as compared to the baseline. Heart rate in group B revealed a non-significant (P>0.05) increase at 10 min interval followed by significant (P<0.01) increase from 15 min onwards till 60 min. However, HR decreased gradually at 75 and 90 min interval but the values were non-significantly (P>0.05) higher than the baseline. Comparison between groups revealed no significant (P>0.05) difference in HR at different time intervals. The findings of tachycardia even after premedication with alpha-2 agonist and opioids might be attributed to the concurrent administration of atropine. The effect of atropine lasts for 60 to 90 minutes and hence the decrease in HR values at 75 and 90 min interval could be due to effect of alpha-2 agonist and opioids to induce bradycardia.

Respiratory rate decreased significantly (P<0.05) as compared to the baseline value at most of the time intervals in both groups. However, there was no significant (P>0.05) difference in RR values between groups throughout the observation period. This decrease in RR might be due to direct depression of respiratory centre by preanaesthetic drugs as also reported earlier by Thurmon *et al.* (1996). Alpha-2 agonists have also been reported to cause decrease in RR due to CNS depression produced by stimulation of alpha-2 adrenoceptors. A dose dependent respiratory depression following use of opioids has been thought to be mediated by μ2 receptors leading to direct depression of brain-stem respiratory centre. Reduction in RR values after premedication with alpha-2 agonists along with opioids for ketamine anaesthesia have also been reported in dogs by Rafee *et al*. (2016) and Sethi *et al.* (2018).

A significant (P<0.05) decrease in rectal temperature was recorded in both groups till 60 min followed by non-significant (P>0.05) decrease at 75 and 90 min interval. The decrease in RT could be attributed to a decrease in heat production due to decreased muscular activity and also direct depression of hypothalamus. Ketamine has also been found to cause direct depression of thermoregulatory centre. Hypothermia following administration of alpha-2 agonists, opioids has also been reported to occur during ketamine anaesthesia in canine patients (Santosh *et al*., 2013; Acharya, 2014).

Oxygen saturation level of haemoglobin ($Sp0_2$) revealed a highly significant (P<0.01) decrease at most of the time intervals throughout the observation period in both groups. This decrease in $Sp0_2$ might be due to respiratory depression produced by various drugs used in both groups. Decreased values of SpO_2 during initial phase of study in both groups could be attributable to vasoconstriction caused by alpha-2 agonists. Similar findings of decreased SpO_2 values have also been reported following use of alpha-2 agonists in combination with opioids

for ketamine anaesthesia in dogs by Acharya (2014).

Hematological parameters

A non-significant (P>0.05) decrease in Hb values was recorded in the animals of group A at 15, 60 and 90 min interval while the values were significantly (P<0.05) decreased at 30 and 45 min interval as compared to baseline value. The values of Hb revealed significant (P<0.01) decrease from 15 min onwards till 60 min interval in the animals of group B. However, the values decreased non-significantly (P>0.05) at 90 min interval as compared to the base value. The values of PCV revealed a significant (P<0.05) decrease as compared to the baseline value throughout the observation period. Comparison between groups did not reveal any significant difference in Hb and PCV values in both groups. The decrease in Hb and PCV might be due to hemodilution arising due to fluid therapy or shifting of fluids from extravascular compartment to intravascular compartment in order to maintain cardiac output. Reduced Hb and PCV value following administration of alpha-2 agonists along with butorphanol in dogs have also been reported by Surbhi *et al*. (2010).

The values of TLC revealed a significant (P<0.05) decrease at 15 min interval followed by highly significant (P<0.01) decrease from 30 min onwards till completion of observation period in both groups. The difference in TLC between groups at different intervals was not significant. The decrease in TLC may be attributable mainly to the administration of alpha-2 agonists and decreased sympathetic activity. A decrease in TLC has also been reported in dogs following use of various alpha-2 agonists in combination with different opioid drugs by Amarpal et al. (1998) and Ahmad (2010).

A non-significant (P>0.05) increase in neutrophil count was recorded in both groups at 15 min interval followed by gradual increase reaching to significant (P<0.05) level from 30 min onwards till 60 min interval. However, neutrophil count decreased at 90 min interval but the values were still non-significantly (P>0.05) higher than the baseline value. A non-significant (P<0.05) decrease in lymphocyte count was recorded in group A at 15 and 90 min interval. However, the values decreased significantly (P<0.05) than the base value from 30 min onwards till 60 min interval. A non-significant (P<0.05) decrease in lymphocyte count was recorded throughout the observation period in animals of group B. The difference in neutrophil and lymphocyte count between groups at different intervals was not significant. An increase in neutrophil count along with concurrent fall in lymphocyte count has also been documented in canine patients following use of alpha-2 agonists in combination with pentazocine by Rafee (2013) and Sethi (2015).

Biochemical parameters

There was a non-significant (P>0.05) increase in plasma glucose value from the baseline at all time intervals in both groups. Comparison between groups did not reveal any significant difference in plasma glucose values at different intervals. Alpha-2 agonists have been reported to induce an increase in serum glucose by suppressing insulin release and/or stimulating glucagon release. Decrease in insulin and increase in blood glucose level following administration of alpha-2 agonists has also been reported in cats and dogs by Kanda and Hikasa (2008). Ketamine has also been reported to cause sympathetic stimulation leading to catecholamine release thereby leading to increased plasma glucose concentration. Similar findings have also been reported in dogs undergoing ketamine anaesthesia premedicated with alpha-2 agonists and opioids by Acharya (2014), Sethy (2015) and Rafee *et al*. (2017).

A gradual increase in plasma urea nitrogen was recorded in both groups from 15 onwards till 60 min interval but no significant (P>0.05) difference was recorded at any time interval as compared to the baseline. The increase in urea nitrogen might be attributed to temporary inhibitory effects of anaesthetic drugs on renal blood flow or due to increased hepatic urea production from amino acid

degradation. In contrast to our findings, decreased BUN values have been reported following premedication in dogs using xylazine and butorphanol (Surbhi *et al*., 2010).

The values of creatinine revealed significant (P>0.05) increase as compared to the baseline value from 15 min onwards till 60 min interval in group A. However, the values were increased non-significantly (P<0.05) at 90 min interval. A non-significant (P>0.05) increase in creatinine was recorded in group B at 15 and 90 min interval. However, the values were significantly (P<0.05) higher as compared to the baseline value from 30 min onwards till 60 min interval. Increased creatinine values have also been reported in dogs following administration of xylazine along with butorphanol/pentazocine by Sethi (2015). The rise in creatininate values within normal physiological range in our study might be due to continuous fluid therapy during the anaesthetic period which could have maintained enough renal blood supply and glomerular filtration rate.

It is concluded that xylazine along with butorphanol or pentazocine produced comparable degree of clinicophysiological and hemodynamic stability along with least alterations in hematobiochemical parameters during ketamine anaesthesia in dogs. Xylazine-butorphanol combination not only reduced the induction and maintenance dose of ketamine but also increased the duration of anaesthesia in dogs. Hence, both combinations may be recommended for injectable anaesthesia in clinical practice.

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