EVALUATION OF CONTINUOUS PROPOFOL INFUSION IN XYLAZINE/MEDETOMIDINE AND BUTORPHANOL PREMEDICATED CANINE ORTHOPAEDIC PATIENTS

P. Kinjavdekar, Surbhi K. Tyagi, Amarpal, H. P. Aithal, A.M. Pawde and Vivek Malik, R. Sharma and M.C. Pathak
Division of Surgery, Indian Veterinary Research Institute
Izatnagar, U.P-243122.

Twelve canine orthopaedic patients were randomly divided into 2 groups X (xylazine) and M (medetomidine). Atropine @ 0.04 mg/kg body wt. IM was administered in all animals, followed 5 minutes later by xylazine (0.5 mg/kg body wt. IV) and butorphanol (0.02 mg/kg body wt. IV) in group X (n=6), whereas, in group M (n=6) medetomidine (10μg/kg body wt. IV) and butorphanol (0.02 mg/kg body wt. IV) were used for premedication. Induction and maintenance of anaesthesia was done by propofol. Ketoprofen was administered both preoperatively and postoperatively for five days. Pedal, palpebral, corneal reflexes and jaw tone abolished earlier in group M than group X. The induction dose of propofol in group M (1.76 ± 0.42 mg/kg) was significantly (P<0.05) lower than in group X (3.61 ± 0.75 mg/kg). The rate of infusion of propofol for maintenance in group M (0.26 ± 0.08 mg/kg/min) was also significantly (P<0.05) lower as compared to group X (0.41 ± 0.10 mg/kg/min). Both preanaesthetic combinations decreased heart rate and respiratory rate; propofol caused tachycardia and depression in respiratory rate and SpO₂. MAP increased after preanaesthetic administration in group M but decreased in group X. Propofol also caused slight hypotension. Neutrophilia was recorded in group X. Glucose and cortisol increased during the procedure in both groups. TIVA using xylazine/medetomidine-butorphanol-propofol produces good muscle relaxation and analgesia and may be used in distressed canine orthopaedic patients safely with minimum side effects. However, medetomidine combination had more dose sparing effect on propofol.

Keywords: Butorphanol, Canine orthopaedic patients, Ketoprofen, Medetomidine, Propofol, TIVA, Xylazine

Introduction

Orthopaedic surgeries are prolonged and painful procedures which necessitate adequate depth of anaesthesia, analgesia and good muscle relaxation during the procedure with minimal effects on vital body functions that can be achieved by a balanced anaesthetic technique involving a combination of drugs at low doses. Total intravenous anaesthesia (TIVA) is a suitable and safe technique, and can be used by veterinary practitioners with minimal facilities (Wagner and Hellyer, 2000; Johnston et al., 2002).

Alpha-2 adrenoceptor agonists like xylazine and medetomidine have sedative, analgesic and muscle relaxant properties that produce profound analgesia when combined with opioids (Sinclair, 2003). Thus a combination of α₂ agonists and opioid agonist at low dosage can be beneficial in providing basal anaesthesia for orthopaedic patients, which may potentially reduce the dose of induction and maintenance agents during anaesthesia.

Propofol has been used as repeat intravenous boluses (RIB) or continuous intravenous infusion (CII). Several manual infusion regimens for TIVA with propofol have been reported in dogs in various clinical trials (Nolan and Reid, 1993; Seliskar et al., 2007). The present study was planned to evaluate and compare TIVA using atropine, xylazine/medetomidine, butorphanol and CII propofol in canine orthopaedic patients.

Materials and Methods

Twelve canine orthopaedic patients requiring open reduction and intramedullary pin fixation of femur were divided randomly into groups X and M of six animals each. The animals were kept off feed for 12 hours before surgery but water was not withheld. Anamnesis regarding the breed, age, sex, cause of the fracture, time since fracture has occurred and primary treatment given, if any, was recorded.

Atropine (0.04 mg/kg body wt. IM) (Tropine; Neon Laboratories, Thane, India) was injected in all the animals. After 5 min xylazine (0.5 mg/kg body wt. IV) (Xylaxin; Indian
Immunologicals Limited, Hyderabad, India) was administered in the animals of group X and /medetomidine (10μg/kg body wt. IV) (Domitor; Orion Corporation, Farmos Group, Turku, Finland) in the animals of group M. Simultaneously butorphanol (0.02 mg/kg body wt. IV) (Butrum; Aristo Pharmaceuticals Private Limited, Raisen, India) was administered in the animals of both groups using separate syringes. Induction was achieved, after 5 min of the preanaesthetic medication, by propofol (Propofol; Neon Laboratories Limited, Mumbai, India) IV bolus till effect. Animal was then connected to intravenous line of propofol for maintenance of anaesthesia by CI. Ketoprofen (Ketop; Alembic Limited, Veterinary Division, Vadodara, India) (2 mg/kg) was administered preoperatively and postoperatively for 5 consecutive days in all the animals. The two treatments were compared on the basis of clinical, physiological, biochemical and haemodynamic parameters. Palpebral, corneal and pedal reflexes were observed before (0 min), 5 min after atropine (5 min), 5 min after xylazine/medetomidine and butorphanol administration (10 min), 5 min after induction with propofol (15 min) and then at regular 15 min interval (30, 45, 60, 75, 90, 105 min or until the end of the surgical procedure). The reflexes were graded on a 1 to 4 scoring scale as: 1 - No change in the reflexes; 2 - Moderate reflex; 3 - Sluggish reflex and 4 – Absence of reflex. Jaw tone to assess the extent of muscle relaxation was recorded and graded on a 1 to 4 scoring scale as: 1 – Normal tone; 2 - Moderate tone; 3 - Sluggish tone; and 4 - Absence of jaw tone. The total dose of propofol required for induction and infusion rate of propofol in mg/kg/min was calculated in each group. The recovery time (min) was recorded as the time from stopping of CI to propofol to appearance of the reflexes.

Venous blood samples were collected at 0 hr, ½ hr and 1 hr intervals after administration of the drugs, for estimation of haemoglobin (g/L) (Sahli’s haemoglobinometer method), DLC (%) (Giemsa stain), TLC (x10⁷/L) (Neubauer’s chamber) and PCV (L/L) (Microhematocrit method). Plasma glucose (mmol/L) (GOD/POD method), plasma urea nitrogen (mmol/L) (DAM method) and creatinine (μmol/L) (Alkaline picrate method) were estimated using diagnostic kits (Span diagnostic kits, Surat, India). Cortisol (U/L) was measured by Radio Immuno Assay (RIA) using RIA kit (Immunootech diagnostic kit, Czech Republic).

Analysis of variance (ANOVA) was used to compare the means at different intervals between the two groups. Paired “t” test was used to compare the mean values at different levels with their respective base value in each group. Data obtained from the scoring of the reflexes was analysed using Kruskal Wallis test for comparison between the groups (Snedecor and Cochran, 1994). A value of P<0.05 was considered significant.

Results and Discussion

Depth of analgesia, sedation and muscle relaxation during preanaesthetic period were greater in group M as compared to group X which may be due to high potency of medetomidine owing to its higher specificity and selectivity for α₂- adrenoreceptors than xylazine. Loss of jaw tone which signified muscle relaxation by α₂-agonists might be attributed to inhibition of alpha₂-adrenoceptors at the interneuron level of the spinal cord (Paddleford and Harvey, 1999; Sinclair, 2003). After induction of anaesthesia with propofol analgesia, sedation and muscle relaxation did not vary between the groups. Mechanisms behind muscle relaxation by propofol are peripheral and/or central in origin affecting any part of the motor pathway, from cortical motor neurons down to the muscle cells (Ummenhofer et al., 1998). After the administration of propofol a complete ventromedial rotation of the eyeball was observed as reported in earlier studies (Hughes and Nolan, 1999).

Dose of propofol for the induction was titrated to effect using various reflexes and responses of the individual patient. The induction dose of propofol in group M (1.76 ± 0.42 mg/kg) was significantly (P<0.05) lower than that in group
X (3.61 ± 0.75 mg/kg) (Fig.1). The rate of infusion of propofol was 0.26 ± 0.08 mg/kg/min in group M and 0.41 ± 0.10 mg/kg/min in group X (Fig.2) for maintenance of anaesthesia. The dose of propofol for induction without premedication ranges between 6-8 mg/kg, (Zoran et al., 1993) whereas premedication with α2-agonists and butorphanol have reduced the induction dose considerably. The dose needed for induction corroborated the observation of earlier studies (Bufalari et al., 1996; Short and Bufalari, 1999). A synergism between α2-agonists and opioid (butorphanol) owing to the same location of their receptors in the brain (Rauser and Lexmaulova, 2002; Sinclair, 2003) might have contributed to the reduction in the dose of propofol. Dose of propofol for induction and maintenance was lower with medetomidine which might be due to better basal anaesthesia provided by medetomidine as compared to xylazine.

Longer recovery time was recorded in group M (21.60 ± 9.94 min) than group X (12.80 ± 2.74 min) and may be attributed to more sedative effect of medetomidine. Recovery from anaesthesia was uneventful and smooth which may be due to lipid solubility, high rate of redistribution, hepatic and extra hepatic metabolism and rapid renal excretion of propofol (Simons et al., 1991; Tranquilli et al., 2007).

Heart rate increased non-significantly (P>0.05) after atropine administration which could be attributed to the vagolytic action of atropine sulphate (Hendrix and Robinson, 1997). In group X, the HR decreased slightly after administration of xylazine-butorphanol.
whereas it decreased significantly (P<0.05) in group M after administration of medetomidine-butorphanol that may be attributed to their bradycardiac action (Amarpal et al., 1999, Ko et al., 2000). Thereafter, after induction of anaesthesia with propofol, HR increased in both groups reaching base values, which might be due to increase in the myocardial blood flow, stimulation of cardio-excitatory centre of brain or stimulation of sympathetic nervous system (Haberer et al., 1993; Ko et al., 1999).

Alpha2-agonists decrease RR by direct depression of the respiratory centres (Kumar and Thurmon, 1979; Rings and Muir, 1982; Pypendop and Verstegen, 1998). Butorphanol is reported to have minimum pulmonary effect, but may cause mild lowering of respiratory rate in dogs (Carpenter et al., 2005). Our findings are in accordance with the results of earlier studies in which a greater respiratory depression was observed when α2-agonists were used in combination with butorphanol (Pypendop and Verstegen, 1999; Short and Bufalari, 1999). Propofol can also induce significant depression of respiratory function, depressing central inspiratory drive and the ventilatory response to arterial carbon dioxide tension (Goodman et al., 1987). The rate of administration of propofol has been reported to be an important factor for respiratory depression. It was found that when the rate of infusion of propofol was increased, the RR decreased (Beths et al., 2001). A similar inverse relation was found between respiratory rate and the rate of infusion of propofol in the present study which was useful to adjust the rate of infusion of propofol.

Rectal temperature decreased significantly after the administration of xylazine/medetomidine and butorphanol and a further decrease was recorded after propofol administration that can be due to generalized sedation, depression of thermoregulation, reduced BMR, reduced muscle activity, depression of peripheral circulation and vasodilatation (Muir and Gadawski, 1998).

Mean arterial pressure increased soon after the administration of atropine (Fig. III). It increased further after medetomidine and butorphanol administration. The increase in MAP caused by medetomidine may be attributable to vasoconstriction due to stimulation of α2-adrenoceptors in smooth muscles of blood vessels (Lemke, 2004). Propofol causes a transient decrease in SBP, DBP, and MAP mainly due to a decrease in peripheral vascular resistance, decreased sympathetic outflow, myocardial depression, a direct vasodilator action on capacitance vessels (Cullen and Reynoldson, 1993). Decrease in MAP after 30 min in the present study may be attributable to the action of propofol.

![Graph showing change in MAP over time](image)

Oxygen saturation of haemoglobin (SpO2) decreased after induction with propofol (Fig. IV) which may be due to respiratory depression at anaesthetic dosages as also reported in earlier studies (Beths et al., 2001) However, during most of the period of the present study SpO2 values were maintained in the normal range in both groups.

Haemoglobin, PCV and TLC (Table 1) decreased in both groups for a short period. It may be due to shifting of fluid from the extra vascular compartment to the intravascular compartment in order to maintain the cardiac output, sequestration of circulating erythrocytes in spleen or other reservoirs due...
to decreased sympathetic stimulation or haemodilution in response to fluid therapy (Wagner et al., 1991; Skarda and Muir, 1994). Further, both α₂-agonists and propofol have been reported to cause a decrease in haemoglobin and PCV in dogs (Amarpal et al., 1998; Venugopal et al., 2002; Khan et al., 2006).

Differential leukocyte count showed an increase in neutrophils and a corresponding decrease in lymphocytes as a result of anaesthetic stress in group X only. Stress leads to adrenocortical stimulation and subsequent effects of glucocorticoids on circulating neutrophils (Solimon et al., 1965).

The base values of glucose and cortisol in animals (Table 1) were significantly higher than the normal physiological range. This increase may be attributed to the, traumatic stress, anaesthetic stress and surgical stress though the increase was minimal. Hyperglycaemia observed in the present study may be due to α₂-adrenergic inhibition of insulin release by stimulation of α₂-receptors in the pancreatic β- cells (Angel and Langer, 1988), decreased glucose utilization (Cullen, 1996; Burton et al., 1997), and due to increased glucose production in the liver (Hsu and Hummel, 1981).

### Table 1: Haematobiochemical parameters after xylazine/medetomidine-butorphanol and propofol administration in canine orthopaedic patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>0 min</th>
<th>30 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (gm/L)</td>
<td>X</td>
<td>11.40 ± 0.78</td>
<td>10.40 ± 0.59</td>
<td>9.75 ± 1.09</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>14.04 ± 1.40</td>
<td>12.28 ± 1.92</td>
<td>12.60 ± 1.07</td>
</tr>
<tr>
<td>Pcv (L/L)</td>
<td>X</td>
<td>0.44 ± 0.06</td>
<td>0.42 ± 0.06</td>
<td>0.37 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>0.50 ± 0.07</td>
<td>0.47 ± 0.08</td>
<td>0.40 ± 0.01</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>X</td>
<td>5.95 ± 0.63</td>
<td>6.93 ± 0.52</td>
<td>8.18 ± 0.90</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>5.66 ± 0.43</td>
<td>6.10 ± 0.59</td>
<td>6.51 ± 0.40</td>
</tr>
<tr>
<td>Cortisol (U/L)</td>
<td>X</td>
<td>58.85 ± 12.26</td>
<td>58.75 ± 6.33</td>
<td>50.20 ± 16.24</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>90.90 ± 12.86</td>
<td>96.84 ± 12.40</td>
<td>81.96 ± 10.24</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>X</td>
<td>176.53 ± 24.26</td>
<td>155.05 ± 29.67</td>
<td>143.12 ± 39.94</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>122.16 ± 31.06</td>
<td>190.76 ± 16.02</td>
<td>181.57 ± 30.26</td>
</tr>
<tr>
<td>Urea Nitrogen</td>
<td>X</td>
<td>0.58 ± 0.11</td>
<td>0.61 ± 0.07</td>
<td>0.65 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>1.94 ± 0.71</td>
<td>1.37 ± 0.71</td>
<td>1.67 ± 0.71</td>
</tr>
</tbody>
</table>

Non significant changes in PUN were observed, which suggested that kidney function and renal blood flow were maintained possibly due to continuous infusion of fluid. The results of the present study conformed to the observations of earlier studies that reported no such changes in BUN after xylazine injection in goats (Kumar and Thurmon, 1979) and dogs (Khan et al., 2006). Creatinine level increased in group M at 30 min. interval and returned to normal range after that, which could be attributable to increased creatinine production from muscle damage and amino acid degradation in few animals (Eichner et al., 1979; Hugar, 1993).

### Conclusion

Total Intravenous anaesthesia with xylazine-butorphanol–propofol and medetomidine-butorphanol–propofol can be
employed safely for anaesthetic management of canine orthopaedic patients. However, the latter may be preferred over the former, owing to better basal anaesthesia and lesser doses of propofol required for induction and maintenance of anaesthesia.

References


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