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

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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 $SpO_2$. 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

**O**rthopaedic 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 $\alpha_2$ 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 CII. 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 CII of propofol to appearance of the reflexes.

Heart rate (HR-beats/min.), respiratory rate (RR-breaths/min.), rectal temperature (RT-$^0$C), and mean arterial pressure (MAP mm of Hg) by non-invasive blood pressure monitor (Surgivet, Smith medical TM, Inc, Waukesha, W.I., 53186) were also recorded at the same time intervals as for the reflexes. After induction of the anaesthesia, haemoglobin oxygen saturation ($SpO_2$ %) was recorded by pulse oxymeter (Nonin Medical Inc. MPLS, MN. USA) at 15, 30, 45, 60, 75, 90, 105 min or until recovery.

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 ($x10^9$/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 (Immunotech 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 $\alpha_2$- adrenoreceptors than xylazine. Loss of jaw tone which signified muscle relaxation by $\alpha_2$-agonists might be attributed to inhibition of alpha$_2$-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 $\alpha_2$-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 $\alpha_2$-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.

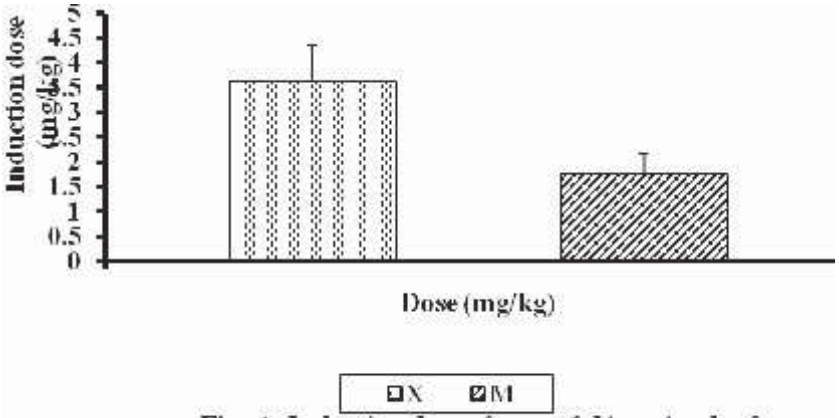


**Fig. 1: Induction dose of propofol in animals of group X(xylazine) & group M(medetomidine)**

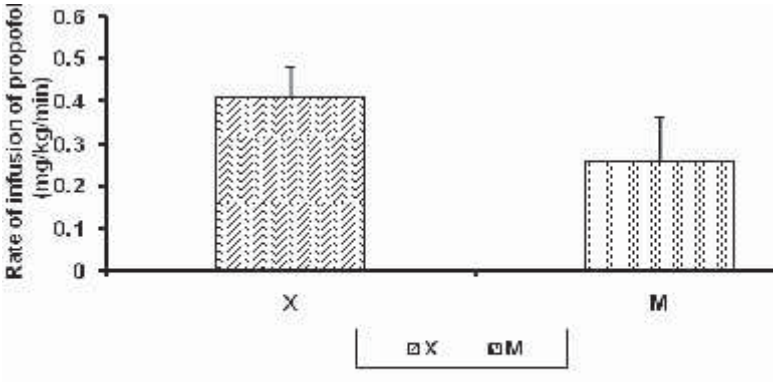


**Fig. 2: Rate of infusion of propofol in animals of group X(xylazine) & group M(medetomidine)**

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).

Alpha$_2$-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 $\alpha_2$-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 $\alpha_{2B}$ 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.

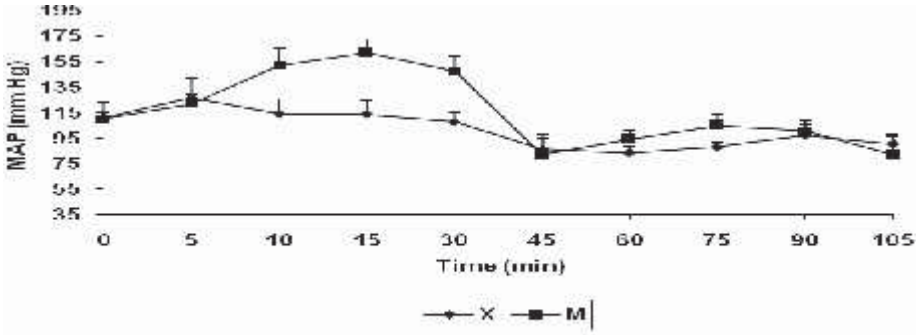


Fig. 3: Mean arterial pressure in animals of group X(xylazine) and group M(medetomidine)

Oxygen saturation of haemoglobin ($SpO_2$) 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 $SpO_2$ 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

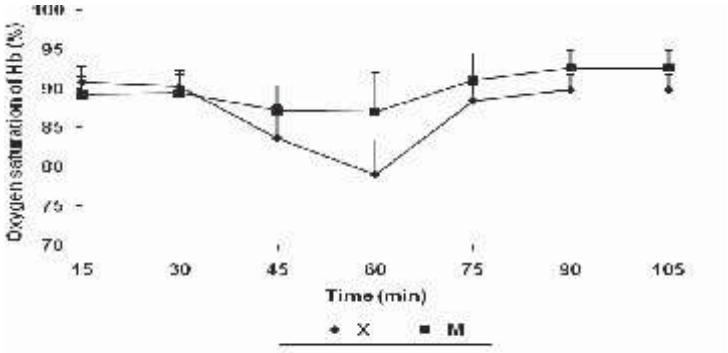

Fig. 4: Oxygen saturation of Hb in animals of group X(xylazine) & group M(medetomidine)

to decreased sympathetic stimulation or haemodilution in response to fluid therapy (Wagner *et al.,* 1991; Skarda and Muir, 1994). Further, both $\alpha_2$-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 $\alpha_2$-adrenergic inhibition of insulin release by stimulation of $\alpha_2$-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**

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

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**


Amarpal, Aithal, H. P., Singh, G. R and Bisht, G. S. (1999). Preemptive effect of epidural ketamine for analgesia in dogs. *Indian Vet. J.,* **76:** 300-303.

Amarpal, Aithal, H. P., Kinjavdekar, P. and Pratap, K. (1998). Physiological, haemo -dynamic and haematological changes due to medetomidine-pethidine induced neuroleptanalgesia in experimental dogs. *Indian J. Anim. Sci.,* **69**: 106-108.

Angel, I. and Langer, S. Z. (1988). Adrenergic induced hyperglycaemia in anaesthetize-d rats:involvement of peripheral a2-adre-noceptors.*Eur.J.Pharmaco.,***154**:191–196.

Beths, T., Glen, J., Reid, J., Monterro, A. and Nelan, A. (2001). Evaluation and optimiz ation of a target controlled infusion system for administered propofol to dogs as part of total intravenous anaesthetic technique during dental surgery. *Vet. Rec.,* **148:** 198-203.

Bufalari, A., Short, C. E., Giannoni, C. and Vainio, O. (1996). Comparative responses to propofol anaesthesia alone and with alpha 2-adrenergic medications in a canin -e model. *Acta Vet. Scand.,* **37**: 187-201.

Burton, S., Lemke, K. A., Ihle, S. L. and Mackenzie, A. L. (1998). Effects of medetomidine on serum osmolality; urine volume, osmolality and pH; free water clearance; and fractional clearance of sodium, chloride, potassium, and glucose in dogs. *Am. J. Vet. Res.,* **59**: 756–761.

Carpenter, R. E., Pettifer, G.R. and Trarquilli, W.J.(2005).Anaesthesia for Geriatric pati -ents. *Vet. Clin. Small Anim.,***35:**511-580.

Cullen, L. K. (1996). Medetomidine sedation in dogs and cats: A review of its pharmacology, antagonism and dose. *Br. Vet. J.,* **152**: 519-535.

Cullen, L. K. and Reynoldson J. A. (1993). Xylazine or medetomidine premedication before propofol anaesthesia. *Vet. Rec.,* **132:** 378-383.

Eichner, R. D., Prior, R. L. and Kvascnicka, W. G. (1979). Xylazine induced hyperglycem ia in cattle. *Am. J. Vet. Res.,***40:**127-129.

Goodman, N.W., Black, A. M. S. and Carter, J. A. (1987). Some ventilatory effects of propofol as sole anaesthetic agent. *Br. J. Anaesth.,* **59**: 1497-1503.

Hendrix, P. K. and Robinson, E. P. (1997). Effects of a selective and a nonselective muscranic cholinergic antagonist on hear t rate and intestinal motility in dogs. *J. Vet. Pharmacol. Therap.,* **20**: 387-395.

Hsu, W.H. and Hummel, S. K. (1981).Xylazine induce hyperglycaemia in cattle: A possi -ble involvement of $\alpha_2$-adrenergic receptors regulating insulin release. *Endocrinol.,* **109**: 825-829.

Hugar, B. (1993). Studies on medetomidine as preanaesthetic to ketamine anaesthesia in goats.MVSc.Thesis submitted to dee med Universityof IVRI, Izatnagar, India.

Hughes, J. and Nolan, A. (1999). TIVA in greyhounds: pharmacokinetics of propofol and fentanyl-a preliminary study. *Vet. Surg.,* **28:** 513-524.

Johnston, G. M., Eastment, J. K., Wood, J. L. *et al.* (2002). The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results of phases 1 and 2. Vet. *Anaesth. Analg.,* **29:** 159-170

Khan, K. M., Mehsare, S. P., Pawshe, D. B, Patil, R. B. and Rahman, S. (2006). Effect of midazolam as a preanaesthetic to propofol anaesthesia in canine on haematological and biochemical parameter. *Vet. World,* **5**: 77-80.

Ko, J. C. H., Lange, D. N., Mandsager, R. E., Paytom, M. E., Bowen, C., Kamata, A. and Kuo, W.C. (2000).Effects of butorph -anol and carprofen on the minimum alve olar concentration of isoflurane in dogs. *J.Am. Vet. Med. Assoc.*,**217**:1025-1028.

Ko, J. C. H., Golder, F. J., Mandsager, R. E., Heaton-Jones, T., Mattern, K. L. (1999). Anaesthetic and cardiorespiratory effects of a 1:1 mixture of propofol and thiopental sodium in dogs. *J. Am. Vet. Med. Assoc.,* **215**: 1292-1296.

Kumar, A. and Thurmon, J. C.1979. Cardiopulmonary, haematocytologic and biochemical effects of xylazine in goats. *Lab. Anim. Sci.,* **29**: 486-491.

Lemke, K. A. (2004). Peri-operative use of sele ctive alpha-2 agonists and antagonists in small animals.*Can.Vet.J.* **45:**475-480.

Muir, W.W. and Gadawski, J. E. (1998).

Respiratory depression and apnea induced by propofol in dogs. *Am. J. Vet. Res.,* **59**:157–161.

Nolan, A. and Reid, J. (1993). Pharmacotherap-eutics of propofol administered by infusi -on in dogs undergoing surgery. *Br. J. Anaesth.,* **70**: 546-551.

Paddleford, R. R., and Harvey, R. C. (1999).Al pha$_2$ agonists and antagonists.*Vet.clin. NorthAm.SmallAnim.Pract.,***29**:737–745.

Pypendop, B. H. and Verstegen, J. P. (1999). Cardiorespiratory effects of a combination of medetomidine, midazolam and butorph anol in dogs.*Am.J.Vet.Res.,***60**:1148-1154.

Pypendop, B.H. and Verstegen, J.P. (1998). Haemodynamic effects of medetomidine in the dog. A dose titration study. *Vet. Surg.,* **27**: 612-622.

Rauser, P. and Lexmaulova, L. (2002). Clinical comparison of medetomidine-butorphanol and medetomidine-buprenorphine combin ations for intravenous premedication of general anaesthesia in the dog. *Acta Vet. Brno.,* **71:** 69-76.

Rings, D.M. and Muir, W.W. (1982). Cardiopul -monary effects of intramuscular xylazine -ketamine in calves. *Can. J. Comp. Med.,* **46**:386-389.

Seliskar, A., Nemec, A., Roskar, T. and Butinar J. (2007). Total intravenous anaesthesia with propofol or propofol / ketamine in spontaneously breathing dogs premedicat ed with medetomidine.*Vet.Rec.,***160:**85-91

Short, C.E. and Bufalari, A. (1999). Propofol anaesthesia. *Vet. Clin. North Am. Small Anim. Pract.,* 29: 747-778.

Simons, P.J., Cockshott, I D., Douglas, E. J., Gordon, E. A, Knott, S. and Ruane, R.J. (1991). Species differences in blood profiles, metabolism and excretion of 14-C Propofol after dosing to rat, dog and rabbit. *Xenobiotica,* **21:** 1243-1256.

Sinclair, M. D. (2003). A review of the physiological effects of alpha$_2$ agonists related to the clinical use of medetomidine in small animal practice. *Can. Vet. J.,* **44**: 885-897.

Skarda, R. T. and Muir, W. W. (1994). Caudal analgesia induced by epidural or subarachnoid administration of detomidine hydrochloride solution in mares. *Am. J. Vet. Res.,* **57**: 193-200.

Snedecor, G.W. and Cochran, W.G. (1994). Statistical Methods. 8th edn. Iowa State University Press, Ames, IA.

Solimon, M.K., Amrousi, S.E., and Khamis, M. Y. (1965). The influence of tranquilizers and barbiturate anaesthesia on the blood picture and electrolytes of dogs. *Vet. Rec.,* **77**: 1256.

Tranquilli, W. J., Thurmon, J. C. and Grimm, K, A. (2007). Injectable and alternative anaesthetic techniques. In: *Veterinary Anaesthesia* (4$^{th}$ edn), Lumb WV, Jones E W, (eds), Blackwell publishing, pp 273-300.

Ummenhofer, W. C., Kindler, C., Tschaler, G., Hampl, K. F., Drewe, J. and Urwyler, A. (1998). Propofol reduces succinyl cholin -e induced increase of masseter muscle tone. *Can. J. Anaesth.,* **45**: 417–423.

Venugopal, A., Chandrasekhar, E. L. and Haragopal, V. (2002). Effects of propofol- ketamine anaesthesia with or without premedication in dogs. *Indian J. Vet. Surg.,* **23**: 106-107.

Wagner, A. E., Muir, W.W.III and Hitchcliff, K.W.(1991). Cardiovascular effects of xylazine and detomidine in horses. *Am. J. Vet. Res.,* **52**: 651-657.

Zoran, L. D., Riedesel, D.H. and Dyer, D. C. (1993). Pharmacokinetics of propofol in mixed-breed dogs and greyhounds. *Am.J.Vet.Res.,***54:**755-760.

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