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Haemodynamic and Haemato-Biochemical Changes with Ketamine, Propofol and Ketofol as Constant Rate Infusion Anesthesia for Elective Ovariectomy in Dogs

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ABSTRACT

Background: Combination of glycopyrrolate, butorphanol, xylazine as premedication and induction with propofol and maintenance with ketamine, propofol and propofol mixtures (Ketofol 1:1) as constant rate infusion (CRI) would have the ability to maintain better hemodynamic and reduce the dose of general anesthesia for maintenance. This technique once gets standardized; it may transfer to field veterinarians for elective ovariectomy under a routine animal birth control programme (ABC) for safe handling of canines. Therefore, the present study was designed to evaluate haemodynamic and haemato-biochemical changes with Ketamine, Propofol and Ketofol as CRI anesthesia in dogs.

Methods: The study was conducted on 18 female dogs during 2019-2021 and these animals were randomly divided into three experimental groups, each group (I, II and III) containing six animals. All animals were pre-medicated with glycopyrrolate @ 0.01 mg/kg b.wt I/M followed by inj. butorphanol 0.2 mg/kg b.wt and xylazine 1mg/kg b.wt I/M after 5 minutes by using different syringes. After 10 minutes of xylazine, animals were induced (till effect) with propofol and immediately just after induction animals were maintained with constant rate infusion of ketamine, propofol and ketofol 1:1 along with normal saline @ 10 ml/kg/hr.

Result: Cardiovascular parameters showed that the value of systolic arterial pressure increased significantly ($P<0.05$) after pre-medication in all three groups in comparisons to respective base values. Value of diastolic arterial pressure increased significantly ($P<0.05$) after pre-medication in groups I and II, whereas non-significantly ($p>0.05$) in group III in comparisons to respective base values. Hemoglobin and PCV values decreased non-significantly after pre-medication and remained non-significantly lower at various intervals in comparison to respective base values during observation periods except at recovery in group II. Changes in TLC did not show a definite pattern and values of TEC in all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period.

Key words: Constant rate infusion anesthesia, Dogs, Elective ovariectomy, Ketamine, Ketofol, Propofol.

INTRODUCTION

Anesthetic agent and their metabolites, underlying diseases, drug reaction and surgery adversely affect renal and hepatic function (O'Connor *et al*., 2010). The purpose of anesthesia is to produce a convenient, safe, effective analgesia, sedation and reversible unconsciousness of the animals, so that surgical intervention may be conducted with minimum stress, discomfort, pain and toxic side effects to the patients (William *et al*., 2007). Butorphanol is a potent opioid analgesic for managing acute nociceptive pain like injury, peri-operative and post-operative pain, visceral and chronic pain (Ahsam *et al*., 2020). In veterinary anesthesiology, xylazine is usually used in combination with ketamine during anesthetic applications. Administration of ketamine alone increases heart rate and means arterial pressure. To minimize these unwanted effects, ketamine is generally administered in combination with other drugs like benzodiazepines and alpha-2 agonists (Ozkan *et al*., 2010). At present time depending on the species, age, breed and physical condition of animals, the drug is commonly used in combination with benzodiazepines tranquilizers and alpha-2-adrenergic agents (Mahmud *et al*., 2014). The objective of constant rate infusion (CRI) prevents the sudden peaks and valleys associated with intermittent I/V boluses and I/M injection and also maintains a stable plane of anesthesia superiorly to boluses (Pablo, 2011). Propofol is a water-insoluble hypnotic alkyl phenol. It is formulated in a lipid

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emulsion containing extracts of soya and egg protein (Kastner *et al*., 2015). It is a suitable drug for the induction and maintenance of anesthesia by CRI (Musk *et al*., 2005). The advantages of propofol include rapid onset of action with smooth induction and recovery (Njoku, 2015). On the flip view propofol as total intravenous anesthesia (TIVA) in dogs is associated with dose-dependent hypotension due to reductions in both myocardial contractility and systemic vascular resistance (Nagashima *et al*., 2000). The combination of ketamine with propofol nullifies deleterious effects on one another and maintains haemodynamic ability (Kennedy and Smith, 2015). Single syringe administration of ketamine and propofol as ketofol admixtures was effective and safe for painful procedures in procedural sedation and analgesia (Willman and Andolfatto, 2007). Combination of glycopyrrolate, butorphanol, xylazine as premedication and induction with propofol and maintenance with ketamine, propofol and propofol mixtures (Ketofol 1:1) as CRI would have the ability to maintain better hemodynamic and reduce the dose of general anesthesia for maintenance. There are very few reports regarding ketamine, propofol and ketofol using CRI in dogs along with that appropriate premedication (Intelisano *et al*., 2008). This technique once gets standardized; it may transfer to field veterinarians for elective ovariectomy under a routine animal birth control programme (ABC) for safe handling of canines. Therefore, the present study was designed to evaluate haemodynamic and haemato-biochemical changes with Ketamine, Propofol and Ketofol as CRI anaesthesia in dogs.

MATERIALS AND METHODS

The present clinical study was carried out at Department of Veterinary Surgery and Radiology, Bihar Veterinary College, Patna, on 18 clinical cases of female dogs irrespective of age and weight presented for routine ovariectomy operation during 2019-2021. All dogs were randomly divided into three groups (as Group I, Group II and Group III) of six animals in each. All dogs were randomly divided into three groups (as Group I, Group II and Group III) of six animals in each (Table 1). All experimental animals were examined with Ultrasonography for any reproductive abnormality. The bitches presented for elective ovariectomy were selected for this study after obtaining written consent from the respective owners. The animals were subjected to preoperative check-ups comprising haemato-biochemical and haemodynamic parameters. The animals were kept off-fed for a minimum of 12 hours prior to the trial of anesthesia. After preparation of the animal, blood was withdrawn at 0 min from the cephalic vein and glycopyrrolate (Pyrolate Neon Laboratories, Palghar, Thane) was given @ 0.01 mg/kg b.wt intramuscularly at right lumbar epaxial muscles followed by inj. Butorphanol (Butodol; Neon laboratories, Palghar, Thane) @ 0.2 mg/kg b.wt and xylazine (Xylaxin; Indian Immunological Ltd, Telangana) @ 1mg/kg b.wt were injected intramuscularly after 5 minutes at left lumbar epaxial muscles by using different syringes. After 10 minutes of butorphanol, animals were induced till effect with propofol and immediately just after induction animals were intubated and constant rate infusion of ketamine (Ketmin 50; Themis Medicare Ltd, Uttarakhand), propofol (Nirfol 1%; Aculife healthcare private limited, Ahmedabad) and ketofol 1:1 (Mixture prepared in a single syringe from commercial ketamine, propofol and normal saline by BASU, Patna started along with normal saline @ 10 ml/kg/hr by micro infusion set and infusion of anesthesia was stopped at last skin suture. The animals were kept in a normal environment throughout the study period.

For cardiovascular parameters the cuff of the NIBP monitor will be tied around the forearm for monitoring systolic and diastolic blood pressures. The variables were taken recorded before administration of the drug (0 min) and 10 minutes after pre-medication and 15, 30 and 60 minutes during surgery and after recovery (120 min). For Hematological parameters Hemoglobin (Hb), PCV, TEC and TLC were estimated using standard procedures. For biochemical observation serum was used for the estimation of biochemical parameters like glucose (mg/dl); blood urea nitrogen (BUN mg/dl); creatinine (mg/dl); aspartate aminotransferase (AST-IU/L). All the collected data were statistically analyzed using SPSS software version 23. Mean ± SE was determined by the descriptive statistics method. Single Factor Analysis of variance (ANOVA), Duncan's multiple range test (DMRT) was used to compare the mean at different time intervals amongst the different groups and compare the mean values at different intervals with their respective base values in each group (Snedecor and Cochran, 1994).

RESULTS AND DISCUSSION

Value of blood pressure increased significantly ($P<0.05$) after pre-medication in all three groups in comparison to respective base values. Comparison within groups showed that blood pressure non-significantly decreased at 15 minutes and then gradually increased up to maintenance of anesthesia in group I and III, whereas in group II, blood pressure gradually decreases from 15 minutes to the entire period of maintenance of anesthesia in comparison to after pre-medication. Transient initial hypertension of variable duration after administration of alpha-2 agonists was also due to the stimulation of peripheral alpha-2B agonist receptors (Link *et al*., 1996). A CRI ketamine via sympathetic stimulation also leading to increases in myocardial contractility and systemic vascular resistance which in turn increases systolic arterial blood pressure (Furuya *et al*., 2001). Hypertension produced by alpha2-agonists was in accordance with the earlier studies in dogs (Ahmad, 2009). A significant increase in systolic blood pressure was also observed in horses after administration of xylazine-butorphanol combination (Robertson and Muir, 1983). In a similar study, a decrease in arterial pressure after medetomidine butorphanol administration (Ahmad, 2009) was reported in dogs and alpha2-agonists with fentanyl

administration (Singh, 2011) in buffalo calves. Comparison between the groups showed that systolic arterial pressure non- significantly (p>0.05) change from pre-medication to 15 minutes during maintenance of anesthesia. CRI maintenance of propofol may be a reason because propofol causes vasodilation in comparison to groups I and III. According to the present study, Cima *et al*. (2016) reported that ketofol (1:1) group produces high MAP than the propofol group during the entire period of maintenance of anesthesia. This corroborates the ketamine inhibits the depressing effects on the cardiovascular system caused using propofol (Mair *et al*., 2009). The values of blood urea nitrogen changed non-significantly (p>0.05) at various time intervals from respective base values during the observation period in all three groups. This finding was supported by Kumar *et al*. (1983) in goat after xylazine administration. In the present study, the decrease in BUN in all groups might be due to the continuous infusion of intravenous fluids thus maintaining normal kidney functions. However, Jena *et al.* (2014) recorded a non-significant increase in BUN after premedicated with dexmedetomidine and anaesthetized with propofol. In the present study serum, creatinine levels decreased non-significantly (p>0.05) in all groups at various time intervals in comparison to respective base values during the observation period. Comparison between the groups showed that aspirate serum creatinine non-significantly (p>0.05) change at various intervals of time during the observation period. In accordance with to present study. Singh (2011) observed a significant decrease in the plasma creatinine in animals after administration of alpha2-agonists in combination with fentanyl maintained with isoflurane. However, Jena *et al.* (2014) reported an increase in serum creatinine values between ten minutes to sixty minutes after pre-medication. The value of blood glucose level in the animals of all the three groups was increased non-significant during the observation period in comparison of the respective baseline values. The present study was also supported by Hikasa *et al.* (2002) that reported a non-significant increase in blood glucose value during sevoflurane and isoflurane anesthesia in healthy sheep. The cause of hyperglycemia may be attributed to the α-2 adrenergic inhibiting the release of insulin from the beta-pancreatic cells and increases glucose production in the liver (Gasthuys *et al*., 1987). The high rise of glucose value during the observation period in comparison of the respective baseline values also due to decreased membrane transport of glucose decreased utilization of glucose, impaired insulin activity and increased adrenocortical hormone concentrations in the blood plasma in dogs (Burton *et al*., 1997). However, Bayan *et al.* (2002) in cats observed a significant increase in serum glucose levels during propofol anesthesia. Based on present observations, it could be stated that propofol aggravates hyperglycemic effect of an alpha-2 agonist. The findings of this study are in general agreement with that of Jena *et al.* (2014). The values of aspartate aminotransferase in all groups changed non-significantly (p>0.05) at various time intervals in comparison to respective base values during the observation period. Comparison between the groups showed that AST values non-significantly (p>0.05) changes at various intervals of time during the observation period. A non-significant transient increase in SGOT values during sedation and anesthesia in the present study could be due to rapid distribution and clearance of propofol by hepatic and extra-hepatic sites (Branson and Gross, 1994). The slight alteration in hepatic values indicates minimum or no effect of propofol on the liver and other body tissues (Bayan *et al*., 2002). Akbar *et al.* (2014) reported the decrease in enzyme concentration 20 minutes post administration of medetomidine and also reported that the SGOT enzyme response was anesthetic dose dependent.

The values of hemoglobin and PCV values decreased non- significantly after pre-medication and remained non-significantly lower at various intervals in comparison to respective base values during observation periods except at recovery in group II. Comparison between the groups showed that hemoglobin and PCV values non-significantly (p>0.05) changes at various intervals of time during the observation period. The values of TEC in all groups changed non-significantly (p>0.05) at various time intervals in comparison to respective base values during the observation period. Comparison between the groups showed that TEC non-significantly (p>0.05) change at various intervals of time during the observation period. The decrease in the TLC values could be probably due to the pooling of circulating erythrocytes in the spleen or other reservoirs secondary to the decreased sympathetic stimulation (Kinjavdekar *et al.* 2000). Khan *et al.* (2006) reported a decrease in TLC following administration of propofol alone. Similar findings

Table 1: Anesthetic drug combination used in dogs of different groups.

Group	No. of animals	Pre-medication	Induction (I/V)	Maintenance (CRI)
Group I	6	Glycopyrrolate @ 0.01 mg/kg b.wt I/M + Butorphanol @ 0.2 mg/kg b.wt I/M+Xylazine @ 1 mg/kgb.wt I/M	As per requirement with propofol	Ketamine@ 300 µg/kg/min
Group II	6	Glycopyrrolate @ 0.01 mg/kg b.wt I/M + Butorphanol @ 0.2 mg/kg b.wt I/M+ Xylazine @ 1 mg/kgb.wt I/M	As per requirement with propofol	Propofol @300 µg/kg/min
Group III	6	Glycopyrrolate @ 0.01 mg/kg b.wt I/M + Butorphanol @ 0.2 mg/kg b.wt I/M+ Xylazine @ 1 mg/kgb.wt I/M	As per requirement with propofol	Ketofol 1:1 ratio @300 µg/kg/min volume (1: 5 ml)

were reported by Bayan *et al.* (2002) in dogs. In contrast, Akbar *et al.* (2014) reported increasing alteration in TLC upon administration of medetomidine in dogs.

CONCLUSION

The present clinical study haemodynamic and haemato-biochemical observation revealed that pre-medication with glycopyrrolate, butorphanol and xylazine followed induction with propofol and maintenance with CRI propofol was better in comparison to other groups.

Conflict of interest: None.

REFERENCES

Ahmad, R.A. (2009). Evaluation of halothane anaesthesia following induction with propofol or thiopental in acepromazine/ medetomidine-butorphanol premedicated buffaloes. M.V.Sc. Thesis submitted to Deemed University, Indian Veterinary Research Institute, Izatnagar, India.

Ahsam, M.Z., Khan, F.U., Zhao, M.J. and Wang, Y.X. (2020). Synergistic interaction between butorphanol and dexmedetomidine in antinociception. European Journal of Pharmaceutical Sciences. 149: 105322. doi: 10.1016/ j.ejps.2020.105322.

Akbar, H., Khan, M.A., Khan, M.S., Aslam, S., Nasir, A. and Anjum, A.A. (2014). Effects of different doses of medetomidine on clinical and hematological parameters in dogs. Journal of Animal and Plant Science. 24: 730-737.

Bayan, H., Sarma, K.K. and Charkravarty, P. (2002). Biochemical and haematological changes during propofol anaesthesia in canines. Indian Journal of Veterinary Surgery. 23: 9-96.

Branson, K.R. and Gross, M.E. (1994). Propofol in veterinary medicine. Journal of the American Veterinary Medical Association. 204: 1888-1890.

Burton, S., Lemke, K.A., Ihle, S.L. and Mackenzie, A.L. (1997). Effects of medetomidine on serum insulin and plasma glucose concentration in clinically normal dogs. American Journal of Veterinary Research. 58: 1440-1442.

Cima, D.S., Sato, K., Torrecilla, J.S., Iwata, V.T. and Futenma, F. (2016). Comparative study between propofol and propofol-ketamine for induction of anaesthesia in dogs. Brazilian Journal of Veterinary Research and Animal Science. 53: 146-152.

Furuya, A., Matsukaw, T., Ozaki, M., Nishiyama, T., Kume, M. and Kumazawa, T. (2001). Intravenous ketamine attenuates arterial pressure changes during the induction of anesthesia with propofol. European Journal of Anaesthesiology. 18: 88-92.

Gasthuys, F., Terptra, P., Hende, C.V. and DeMoor, A. (1987). Hyperglycaemia and diuresis during sedation with detomidine in the horse. Journal of Veterinary Medical Association. 34: 641. doi: 10.1111/j.1439-0442.1987.

Hikasa, Hokushin, S., Takasa, K. and Ogawamara, S. (2002). Cardiopulmonary, haematological, serum biochemical and behavioral effects of sevoflurane compared with isoflurane or halothane in spontaneously ventilating goats. Small Ruminant Research. 43: 3. DOI: 10.1016/ s0921-4488(99)00121-2.

Intelisano, T.R., Kitahara, F.R., Otsuki, D.A., Fantoni, D.T., AulerJr, J.O. and Cortopassi, S.R. (2008). Total intravenous anesthesia with propofol-racemic ketamine and propofol-S-ketamine: A comparative study and haemodynamic evaluation in dogs undergoing ovariohysterectomy. Brazilian Veterinary Research. 28: 216-222.

Jena, B., Das, J., Nath, I., Sardar, K.K., Sahoo, A., Beura, S.S. and Painuli, A. (2014). Clinical evaluation of total intravenous anaesthesia using xylazine or dexmedetomidine with propofol in surgical management of canine patients. Veterinary World. 7: 59-63.

Kastner, E., Verma, V., Lowry, D. and Perrie, Y. (2015). Microfluidic-controlled manufacture of liposomes for the solubilization of a poorly water-soluble drug. International Journal of Pharmaceutics. 485: 122-130.

Khan, K.M., Mehsare, S.P., Pawshe, D.B., Patil, R.B. and Rahman, S. (2006). Effect of midazolam as a preanesthetic to propofol anesthesia in canines on hematological and biochemical parameters. Veterinary World. 5: 77-80.

Kennedy, M.J. and Smith, L.J. (2015). A comparison of cardiopulmonary function, recovery quality and total dosages required for induction and total intravenous anesthesia with propofol versus and propofol-ketamine combination in healthy Beagle dogs. Veterinary Anesthesia and Analgesia. 42: 350-359.

Kinjavdekar, P., Singh, G.R., Amarpal, Aithal, H.P. and Pawde, A.M. (2000). Physiologic and biochemical effects of subarachnoidally administered xylazine and medetomidine in goats. Small Ruminant Research. 38: 217-28.

Kumar, A., Thurmon, J.C., Nelson, D.R., Benson, G.J. and Tranquilli, W.J. (1983). Response of goats to ketamine hydrochloride with and without premedication of atropine, acetylpromazine, diazepam, or xylazine. Veterinary Medicine and Small Animal Clinician. 78: 955-960.

Link, R.E., Desai, K., Hein, L., Stevens, M.E., Chruscinski, A., Bernstein, D. and Kobilka, B.K. (1996). Cardiovascular regulation in mice lacking α2-adrenergic receptor subtypes b and c. Science. 273: 803-805.

Mahmud, M.A., Shaba, P., Yisa, H.Y., Gana, J., Ndagimba, R. and Ndagi, S. (2014). Comparative efficacy of Diazepam, Ketamine and Diazepam-Ketamine combination for sedation or anesthesia in cockerel chickens. Journal of Advanced Veterinary and Animal Research. 1: 107-113.

Mair, A.R., Pawson, P., Courcier, E. and Flaherty, D. (2009). A comparison of the effects of two differences does of ketamine used for co-induction of anesthesia with a target-controlled infusion of propofol in dogs. Veterinary Anesthesia and Analgesia. 36: 532-538.

Musk, G.C., Pang, D.S., Beths, T. and Flaherty, D.A. (2005). Target-controlled infusion of propofol in dogs-evaluation of four targets for induction of anaesthesia. The Veterinary Record. 157: 766-770.

Nagashima, Y., Furukawa, Y. and Chiba, S. (2000). Propofol decreases contractility of isolated blood-perfused left ventricular muscle in the dog. Journal of Anesthesia. 14: 45-47.

Njoku, N.U. (2015). Effects of maintenance of propofol-ketamine anesthesia with repeat bolus and constant rate infusion of propofol on physiological, biochemical, anesthetic and analgesic indices in dogs. Journal of Advanced Veterinary and Animal Research. 2: 427-434.

O'Connor, C.J., Rothenberg, D.M. and Tuman, K.J. (2010). Anesthesia and the Hepatobiliary System. In: Miller's Anesthesia. 7th ed. Edited by [Miller, RD]: Philadelphia, Elsevier Churchill Livingstone. Pp: 2135-49.

Özkan, F., Çakır-Özkan, N., Eyibilen, A., Yener, T. and Erkorkmaz, Ü. (2010). Comparison of ketamine-diazepam with ketamine-xylazine anesthetic combinations in sheep spontaneously breathing and undergoing maxillofacial surgery. Bosnian Journal of Basic Medical Sciences. 10: 297-302. doi: 10.17305/bjbms.2010.2675.

Pablo, L.S. (2011). How's and Whys of CRI analgesia in small animals? America College of Veterinary Surgeons Veterinary Symposium, the surgical summit proceedings, Chicago, Illinois, USA. p.157.

Robertson, J.T. and Muir, W. (1983). A new analgesic drug combination in the horse. American Journal of Veterinary Research. 44: 1667-1669.

Singh, S. (2011). Evaluation of epidural effect of bupivacaine, Bupivacaine-ketamine and bupivacaine tramadol in Buffalo calves MVSc. Thesis (Surgery and Radiology), Nanaji Deshmukh Veterinary Science University, Jabalpur.

Snedecor, G.W. and Cochran, W.G. (1994). Statistical Analysis. Iowa State University Press, Ames.

William, W.M., John A.E., Richard, M.B. and Roman, T.S. (2007). Hand Book of Veterinary Anesthesia, 4th edn. Mosby Elsevier USA, Columbus, USA.

Willman, E.V. and Andolfatto, G. (2007). A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. Annals of Emergency Medicine. 49: 23-30.