COMPARATIVE EVALUATION OF XYLAZINE AND MIDAZOLAM ON PROPOFOL-HALOTHANE ANAESTHESIA IN DOGS: A HAEMATO-BIOCHEMICAL STUDY

Tejveer Singh[1], V. Malik[2] and B. Singh[3]

[1] PG Scholar, [2] Assistant Professor, [3] Professor, Department of Surgery and Radiology, College of Veterinary Sciences and Animal Husbandry, U.P. Pandit Deen Dayal Upadhayay Pashu-Chikitsa Vigyan Vishwavidyalaya Evam Go-Anusandhan Sansthan (DUVASU), Mathura (Uttar Pradesh)- 281001 India.

[Received: 30.05.2014; Accepted: 30.11.2014]

The present study was conducted on 24 clinical cases of dogs of either sex and of different breeds to test effects of xylazine and midazolam to propofol-halothane anaesthesia in dogs. The dogs were divided in to three groups viz. A, B, C. All the animals were administered with atropine sulphate (0.04mg/kg i.m.).Xylazine (0.5mg/kg i.m.) in A group, midazolam (0.5mg/kg i.m.) in B group and xylazine (0.25mg/kg i.m.) + midazolam (0.25mg/kg i.m.) in C group. Anaesthesia was induced with 1% propofol (i.v., to effect) and maintained with halothane in 100% oxygen in all animals. Effect of these combinations were recorded on viz. Haemoglobin, PCV, TLC, DLC, plasma urea nitrogen, plasma glucose, plasma the depth of anaesthesia and facilitate early recovery. Xylazine is an alpha-2 adrenoceptor agonist creatinine, plasma aspartate amino transferase, plasma Sodium and potassium. All the combinations in this study were found suitable for propofol-halothane anaesthesia in clinical cases of dogs.

Keywords: anaesthesia, dogs, halothane, midazolam, propofol, xylazine

Introduction

Total intravenous anaesthesia is associated with prolonged recovery and recumbency time. These disadvantages can be overcome by intravenous bolus administration of drugs for induction and then maintenance with inhalant anaesthetics. Inhalant anaesthetics offer comparative safety as they provide better control over with sedative and analgesic properties and midazolam, a water-soluble benzodiazepine has been used as sedative and induction agent in dogs. Midazolam has been reported to be used in combination with α_2-agonists to improve the quality of sedation, analgesia and muscular relaxation with lesser cardiopulmonary depression (Machin and Caulkett, 1998). Propofol is a nonbarbiturate hypnotic with noncumulative properties has been used for induction and maintenance of anaesthesia in dogs (Pottie *et al*., 2008). Halothane is a commonly used clear and colourless volatile anaesthetic. There are few studies where propofol in combination with xylazine and midazolam has been used to study their effect on halothane anaesthesia in dogs (Topal *et al*., 2003). The objective of this study is to compare the haematological effects of xylazine, midazolam and xylazine-midazolam combination to propofol-halothane anaesthesia in dogs.

Materials and Methods

The present study included twenty four dogs of different age groups, breeds and body weight, reported for diagnosis and treatment to Teaching Veterinary Clinical Complex (TVCC) of the university. These dogs were divided into three groups. The animals were kept off feed for 12 hours and water was withheld 6 hours prior to the start of the experiment.

The dogs were divided in to three groups viz. A, B, C. All the animals were administered with atropine sulphate (0.04mg/kg i.m.). Xylazine (Xylazine-xylaxin (20mg/ml), (0.5mg/kg i.m.) in A group, midazolam (0.5mg/kg i.m.) in B group and xylazine (0.25mg/kg i.m.) + midazolam (Midazolam- Mezolam (1mg/ml), (0.25mg/kg i.m.) combination in C group were used. The animals were restrained in lateral recumbency

and during this period the animals were prepared for diagnosis and operative procedures as per the case. After 15 minutes of premedication anaesthesia was induced with 1% propofol (i.v., to effect) over a period of approximately 30-60 seconds. General anaesthesia was maintained with halothane (Halothane I.P. 85) in 100% oxygen via a semi closed rebreathing system of small animal anaesthesia machine. The vaporizer was set and regulated to maintain adequate depth of anaesthesia after monitoring the animal's response to noxious stimulus. The blood samples (1.5 ml) were collected in clean dry test tubes, at time 0 (base line) and after 15, 30, 60 and 120 minutes of the administration of preanaesthetic agents for separation of plasma. The plasma samples were subjected to the estimation of Haemoglobin, PCV, TLC, DLC, plasma urea nitrogen (mmol/L), plasma glucose (mmol/L), plasma creatinine (µmol/L),
plasma aspartate amino transferase (IU/L), plasma sodium (Na^+) and potassium (K^+) (mmol/L) by using semi auto chemistry analyzer **(**Model –CHEM-400, Version V5.1P E I. product Parwanoo) and digital clinical flame photometer (Model no.-391. manufactured by Cisco Pvt. India Ltd). ANOVA (Analysis of variance) and Duncan's multiple range test (DMRT) were used to compare the means at different time intervals among different groups. Paired "t" test was used to compare the mean values at different intervals with their base values in each group (Snedecor and Cochran, 1980).

Results and Discussion

Haemoglobin (Hb), packed cell volume (PCV) and total leucocytes count (TLC) decreased significantly in all groups, which remained so till the end of observation period (Table 1). Pooling of circulatory blood cells in the spleen or other reservoir secondary to sympathetic activity may explain the decrease in Hb, PCV and TLC recorded and this has also been suggested by Wagner *et al.* (1991). The decrease in Hb and PCV during the period of anaesthesia or sedation may be due to the shifting of fluid from extra vascular compartment to intravascular compartment to maintain cardiac output in the animals (Wagner *et al.,* 1991). Similar findings were also noted after propofol administration in dogs, xylazine administration in dogs (Cwiek *et al*., 2009), midazolam administration in dogs, midazolam- ketamine administration in dogs (Butola and Singh., 2003), and during continuous infusion of propofol in buffaloes (Malik *and Singh,* 2008) and after administration of propofol in dogs premedicated with midazolam (Bayan *et al*., 2007), halothane anaesthesia (Cwiek *et al*., 2009) in dogs.

Significant neutrophilia and lymphocytopenia were observed in all the animals, which might be due to the stimulation of adrenal gland and restoration of ACTH level. Similar observations have been reported after propofol and xylazine administration in dogs (Mukati *et al.,* 2006), midazolam administration in dogs (Butola and Singh 2003), and xylazine, midazolam, propofol and halothane anaesthesia in dogs (Cwiek *et al*., 2009).

An increase in plasma glucose was observed in all the animals; however, the values returned to the base line at the end of the anaesthesia and remained lower than the base line for rest of the observation period. The values obtained during restraint of the animals were much higher. The high glucose was probably due to increased muscular activity and sympathetic stimulation caused by restraining the animals on table resulting into increased secretion of adrenocortical hormone. Similar findings were also recorded by Singh *et al*. (1994) in dogs. Hyperglycemia observed in the present study might be attributed to an alpha-2 adrenergic inhibition of insulin released from beta pancreatic cells and to an increased glucose

production in the liver (Gasthuys *et al*., 1987). Increased blood glucose level were reported during anaesthesia with propofol, diazepam and midazolam alone or in combinations in dogs (Butola and Singh., 2003). Similarly, administration of xylazine in dogs (Cwiek *et al.,* 2009) has also been reported to cause hyperglycemia. Halothane has been demonstrated to decrease insulin secretion without altering the glucose oxidation (Gingerich *et al.,* 1980). Halothane may cause slight increase in glucose in dogs (Redondo *et al.,* 1999). Singh (1988) also observed hyperglycemia after thiopental-halothane anaesthesia in calves but some of the workers have observed that halothane anaesthesia has got no effect on blood glucose levels (Sobti *et al.,* 1990).

The increase in plasma creatinine might be attributed to the temporary inhibitory effects of these anaesthetic drugs on the renal blood flow, which in turn might have caused a rise in plasma creatinine (Kinjavdekar *et al*. 2000). In present study all the groups showed significant increasing trend of serum creatinine but the values were within physiological limit. Similar findings were observed with midazolam and midazolam - kitamine anaesthesia in dogs and by Jain *et al.* (2007) with atropine sulphate, diazepam and propofol with ether in dogs.

In this study non significant increase of AST was observed in all groups. Similar observations were also recorded with xylazine and propofol by Mukati *et al.* (2006) in dogs. Similar observations were also recorded by Topal *et al.* (2003) after xylazine with propofol

Table 1. Mean±SE values of different haematologic parameters at different time intervals in different groups of animals

Time interval	**Haemoglobin (%)**			**Packed Cell Volume (%)**			**Total Leucocyte Count ($x10^9$/L)**		
	Group A	Group B	Group C	Group A	Group B	Group C	Group A	Group B	Group C
At 0 min	13.83 ±0.336	13.88 ±0.513	13.15 ±0.289	42.35 ±1.105	42.75 ±1.602	40.40 ±0.588	10.357 ±0.123	10.362 ±0.112	10.588 ±0.095
At 15 min	13.51* ±0.333	13.59* ±0.508	12.83* ±0.278	41.55* ±1.112	41.80* ±1.579	41.80* ±1.579	10.127* ±0.108	10.123* ±0.120	10.262* ±0.043
At 30 min	12.68 ±0.331	12.88* ±0.500	12.183 ±0.122	35.35** ±3.793	39.40* ±1.512	34.01** ±3.397	9.852* ±0.114	9.865* ±0.121	10.055* ±0.040
At 60 min	12.73* ±0.356	12.75* ±0.487	12.01* ±0.174	39.15* ±0.977	39.83* ±1.115	35.66* ±0.792	9.648* ±0.133	9.757* ±0.129	9.937* ±0.032
At 120 min	13.55* ±0.367	13.38* ±0.467	12.71* ±0.156	41.98* ±0.825	41.31* ±1.273	37.35* ±5.069	10.127* ±0.123	10.138* ±0.095*	10.282* ±0.059

*significantly different from base value

Values with different superscripts differ significantly

Table.2. Mean±SE values of different haematologic parameters at different time intervals in different groups of animals

Time interval	Neutrophils (%)			Lymphocyte (%)			Eosinophils (%)		
	Group A	Group B	Group C	Group A	Group B	Group C	Group A	Group B	Group C
At 0 min	70.00_{b} ±0.931	65.33_{a} ±0.615	68.16_{b} ±0.946	26.50_{a} ±0.991	$31.33b_{c}$ ±0.333	29.33_{ab} ±1.256	2.333 ±0.333	2.167 ±0.307	1.833 ±0.167
At 15 min	$72.16*_{c}$ ±0.872	$67.16*_{ab}$ ±0.703	69.50_{bc} ±1.455	$24.83*_{a}$ ±0.872	$29.83*_{a}$ ±0.543	$28.00*_{ab}$ ±1.483	2.167 ±0.167	1.500 ±0.224	2.000 ±0.000
At 30 min	$74.00*_{b}$ ±0.730	$70.16*_{ab}$ ±0.601	$72.16*_{ab}$ ±1.621	$23.33*_{a}$ ±0.667	$26.83**_{b}$ ±0.307	$25.50**_{ab}$ ±1.057	2.500 ±0.341	1.833 ±0.167	2.667 ±0.211
At 60 min	$73.66*_{b}$ ±0.615	$72.50**_{b}$ ±0.671	$72.50*_{b}$ ±0.719	23.83* ±0.703	24.16** ±0.401	24.83** ±0.601	2.167 ±0.167	1.667 ±0.211	2.000 ±0.000
At 120 min	$73.00*_{c}$ ±0.816	$68.83*_{ab}$ ±0.477	$71.00*_{bc}$ ±1.033	$24.50*_{a}$ ±0.619	$28.16*_{a}$ ±0.477	$25.83*_{b}$ ±0.872	1.500 ±0.224	2.167 ±0.307	1.667 ±0.211

*significantly different from base value
Values with different superscripts differ significantly

Table.3 Mean±SE values of different biochemical parameters at different time intervals in different groups of animals

Time intervals	Glucose (mmol/L)			Creatinine (µmol/L)			Blood Urea Nitrogen (mmol/L)		
	Group A	Group B	Group C	Group A	Group B	Group C	Group A	Group B	Group C
At 0 min	93.66_{c} ±3.333	89.66_{b} ±4.506	94.83_{c} ±2.46	1.010_{a} ±0.094	1.35_{c} ±0.089	1.21_{b} ±0.110	13.220 ±1.013	14.078 ±1.612	12.267 ±0.726
At 15 min	103.33 $**_{c}$ ±3.546	96.00* $*_{b}$ ±5.052	102.33 $**_{c}$ ±2.216	$1.08*_{a}$ ±0.090	$1.43*_{c}$ ±0.073	$1.27*_{b}$ ±0.108	13.418 ±0.975	12.463 ±0.738	12.463 ±0.738
At 30 min	112.16 $**_{c}$ ±3.259	102.50 $**_{b}$ ±5.376	110.33 $**_{c}$ ±2.679	$1.10*_{a}$ ±0.085	$1.47*_{c}$ ±0.070	$1.33*_{b}$ ±0.095	13.823 * ±1.076	14.672 * ±1.639	12.770 * ±0.728
At 60 min	121.33 $**_{c}$ ±3.179	110.00 $**_{b}$ ±5.685	119.16 $**_{c}$ ±2.271	$1.15*_{a}$ ±0.083	$1.52*_{c}$ ±0.063	$1.40*_{b}$ ±0.077	14.208 * ±1.071	14.978 * ±1.633	13.035 * ±0.717
At 120 min	103.83 $**_{c}$ ±3.004	98.50* $*_{b}$ ±5.413	102.66 $**_{c}$ ±2.108	$1.10*_{a}$ ±0.088	$1.46*_{c}$ ±0.064	$1.31*_{b}$ ±0.090	13.962 * ±1.063	14.807 * ±1.649	12.858 * ±0.721

*significantly different from base value
Values with different superscripts differ significantly

Table.4. Mean±SE values of different biochemical parameters at different time intervals in different groups of animals

Time interval	AST (U/L)			Plasma Sodium (mmol/L)			Plasma Potassium (mmol/L)		
	Group A	Group B	Group C	Group A	Group B	Group C	Group A	Group B	Group C
At 0 min	29.667_{b} ±1.453	31.667_{c} ±1.498	26.833_{ab} ±1.661	142.0 ±2.11	140.5 ±2.93	145.2 ±2.01	4.842 ±0.163	4.503 ±0.177	4.878 ±0.220
At 15 min	31.167_{b} ±1.579	33.333_{c} ±1.406	28.333_{ab} ±1.744	144.3 ±2.15	142.2 ±2.81	147.0 ±2.14	4.693 ±0.167	4.430 ±0.160	4.758 ±0.219
At 30 min	32.667_{b} ±1.563	35.000c ±1.633	30.000_{ab} ±1.732	146.0 ±2.31	144.3 ±2.65	149.2 ±1.92	4.555 ±0.162	4.380 ±0.153	4.620 ±0.208
At 60 min	34.500_{b} ±1.455	36.667c ±1.563	31.500_{ab} ±1.784	147.3 ±2.23	146.2 ±2.82	133.8 ±17.81	4.420 ±0.172	4.302 ±0.162	4.522 ±0.220
At 120 min	31.333_{b} ±1.282	34.000c ±1.460	29.000_{ab} ±1.897	145.7 ±2.38	144.2 ±2.75	148.5 ±1.82	4.570 ±0.176	4.408 ±0.158	4.658 ±0.228

*significantly different from base value
Values with different superscripts differ significantly

anaesthesia in dogs. Similar observations i.e. non significant increase in the level of plasma transaminases (ALT and AST) have been recorded by Cwiek *et al*., (2009) in dogs.

In this study a non significant increase in plasma urea nitrogen in the animals of different groups was recorded. Similar finding have also been reported by Mukati *et al*., (2006) and Cwiek *et al*., (2009) after administration of xylazine and propofol in dogs. The increased hepatic urea production from amino acids degradation could also be account for the observed increase in plasma urea nitrogen values (Eichner *et al*., 1979). Increase in plasma urea nitrogen might be due to hypotension and reduced renal flow. However, all the reported values in the present study were within the normal physiological limits.

In the present study non significant increase in plasma sodium level was observed in all the groups of animals, but it remained within normal physiological limits which correlates with the findings of Kumar (2006), after administration of propofol in xylazine premedicated dogs. Increase in plasma sodium level in the present study might be due administration of NSS fluid during general anaesthesia which has also been reported by Khanna *et al.,* (1997). Halothane has also been reported not to cause any significant alteration in the level of plasma sodium and potassium in dogs (Steffey and Holand Jr., 1979).

A decrease in serum potassium level was observed in all the groups but these values were within normal physiological limit (Singh *et al.,* 2005), however, the decreased level of potassium might be associated with the traslocation of potassium from extracellular to intracellular space or may be related to administration of potassium free parental fluid (Mathews, 2004) and these change might also be due to haemodilution in response to vasodilation, that is in conformity with the findings of Butola and Singh (2003) after ketamine-midazoalm administration in dogs. Halothane has also been reported not to cause any significant alteration in the level of plasma potassium with xylazine, midazolam, propofol and halothane anaesthesia in dogs.

References

Bayan, H. Sharma, K.K. and Thomas, S. (2007). Studies on midazolam –propofol anaesthesia in canine. Indian J. Anim. Sci.

77(5): 385-386.
Butola, V. and Sing, B. (2003) Biochemical effects of midazolam and ketamine anaesthesia in dogs. Indian J. Vet. Surg. **24**: 44-45.
Cwiek, A., Balicki, I., Rozanska, D., Poklowska, I and Orzelski, M. (2009). Propofol-induced inhalation anaesthesia in dogs after xylazine or xylazine and midazolam premedicated . Medyeyna-Weterynaryzna **65(1)**: 29-32.
Eichner, R.D., Proir, R.L. and Kvascnicka, W.G. (1979). Xylazine induced hyperglycemia in beef cattle. Am. J. vet. Res. **40**: 127-129.
Gasthuys, F., Terpstra, P., Hende, C.V. and DeMoor, A. (1987). Hyperglycemia and diuresis during sedation with detomidine in the horse. J. Vet. Med. Assoc. **34**: 641.
Gingerich, R., Wright, P.H. and Paradise, R.R. (1980). Effects of halothane on glucose stimulated insulin secretion and glucose oxidation in isolated rat pancreatic islets. Anaesthesiology **53**: 219-222.
Jain, R., Bhargava, M.K., Chandrapuria, V.P., Shahi, A. and Gehlout, B.S. (2007). Propofol ether anaesthesia in dogs; biochemical studies. Indian. J. Vet. Surg. **28(1)**: 35-36.
Khanna, C. (1997). Fatal hyperntremia in dogs from salt indigestion. J. Am. Anim. Hosp. Assoc. **33**:113.
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 Rum. Res. **38**: 217-228.
Kumar, A. (2006). Evaluation of xylazine – ketamine and xylazine-propofol for clinical surgery in dogs. M.V.Sc. thesis submitted to DUVASU, Mathura (India).
Machin, K.L. and Caulkett, N.A.(1998). Cardiopulmonary effects of propofol and a medetomidine-midazolam-ketamine combination in mallard ducks. Am. J. Vet. Res. **59**: 598-602.
Malik, V. and Singh, B. (2008). Clinical and haematobiochemical studies on ketamine and its combinations with diazepam, midazolam and xylazine for general anaesthesia in horse. Indian J. Vet. Surg. **28(1)**: 23-26.
Mathews, N.S., Brown, R.M., Barling, K.S., Lovering, S.L., and Herrig, B.W. (2004) Repetitive Propofol Administration in Dogs and Cats. J. Am. Anim. Hosp. Assoc. **40**:255-260.
Mukati, B.D., Singh, V. and Chauhan, A.R. (2006). Clinico-biochemical effects of propofol alone and in combination with xylazine or acepromazine in dogs. J. Bombay Vet. College 14: 108-113.
Pottie, R.G, Dart, C.M and Perkins, N.R (2008) Speed of induction of anaesthesia in dogs administered halothane, isoflurane and sevoflurane or propofol in clinical setting. Australian Vet. Journal **83(1/2)**: 26-31.
Redondo-Garcia, I.J., Gomez-Villamandos, R.J, Santisteban, J.M., Ruiz, I., Galka, M. and Avila, I. (1999). Propofol-halothane and thiopental-halothane anesthesia in three dogs. Canine Pract. **24**: 10–13.
Singh, H. (1988). Studies on diazepam, chloral hdrate and halothane anaesthesia in relation to different surgical operations in bovine. M.V.Sc. thesis submitted to Punjab Agriculture university.
Singh, R., Peshin, P.K, Patil, D.B., Sharda, R., Singh, J., Singh, A.P., Sharifi, D. (1994). Evaluation of halothane as an anaesthetic in camels. J. Vet. Med. A. **41**: 359-368.
Singh, V., Kinjavdekar, P., Aithal, H.P., and Pratrap, K (2005). Hematobiochemical changes following epidural administration of xylazine and ketamine in buffalo calves. Indian J. Anim. Sci. **75**: 178-181.
Snedecor G.W, Cochran W.G. (1980) Statistical methods. 9th edn, Iowa state university, Press, USA.
Sobti, V.K., Singh, K., Bansal, P.S., Singh, N. and Rathor, S.S. (1990). Haloperidol as a

premedicant for thiopental anaesthesia in the dog. J. Vet. Med. Series-A, 37: 170-173.

Steffey, E.P., Howland, D. (1979). Halothane anaesthesia in calves. Am. J. Vet. Res. **40 (3)**:372-376.

Topal, A., Gul, N., Heol, Y. and Gorgul, O. S. (2003). Hepatic effect of halothane, isoflurane and sevoflurane. J. Vet. Med. A. **50(10)**: 530-533.

Wagner, A.E. and Muir, W.W. (1991) comparison of arterial and ligual venous blood gases in anaesthetized dogs. J. Vet. Emerg. Crit. Care **1**:14.