



## Effects of Combination of Ketamine–Medetomidine Anaesthesia on Haematology and Some Serum Chemistry Parameters In Dogs

UMAR, M.A. and ADAM, M.K.

Department of Veterinary Surgery and Theriogenology, Faculty of Veterinary Medicine, University of Maiduguri, PMB 1069, Maiduguri, Borno State, NIGERIA. Correspondence: E-mail: ahmedtjumar@gmail.com, Tel. no. +234 80 3349 9693

### SUMMARY

The effects of combination of ketamine-medetomidine intravenous anaesthesia on haematological parameters and serum chemistry were evaluated in six dogs weighing  $12.75 \pm 2.7$  kg comprising 4 females and 2 males. Each dog was given recommended dose of the drugs combination: medetomidine at 0.04mg/kg body weight IV and ketamine at 5mg/kg body weight IV. Pre injection blood samples were taken and at 30mins interval during anaesthesia in plain and EDTA bottles and later analyzed. The parameters evaluated were Packed Cell Volume (PCV), Haemoglobin (Hb), Red Blood Cell (RBC), White Blood Cell (WBC) and Differential Leucocyte Count (DLC: neutrophil, eosinophils basophils lymphocytes and monocytes) and serum chemistry: creatinine (CRE), blood urea nitrogen (BUN), alanine amino transferase (ALT).

The ketamine-medetomidine combination produced significant decreases in PCV and RBC at 90mins ( $32 \pm 6.2\%$ ) and ( $4.96 \pm 1.4 \times 10^6/\mu\text{l}$ ) and haemoglobin ( $12 \pm 1.9\text{g/dl}$ ) while WBC values showed significant increase at 60 minutes ( $15.4 \pm 0.5 \times 10^3/\mu\text{l}$ ) compared with pre injection values. BUN values did not differ significantly compared with pre value while CRE increase significantly at 60 minutes ( $71.8 \pm 23.7\mu\text{mol/l}$ ) and ALT values showed no significant difference. Neutrophils increased as compared to the base line value, lymphocytes showed significant decrease while monocytes

and eosinophils did not differ significantly.

Ketamine-medetomidine anaesthesia in dogs produced transient decrease in PCV, Hb, RBC and lymphocytes and significant increase in WBC, neutrophils and CRE. There was no significant effect on BUN and ALT. The dogs recovered uneventfully from anaesthesia.

**Key words:** Haematology, serum chemistry, ketamine, medetomidine, anaesthesia

### INTRODUCTION

In veterinary anaesthesia, ketamine is often used for its anaesthetic and analgesic effects in cats, dogs, rabbits, rats and other animals. Ketamine is used to manage pain in large animals, it is the primary anaesthetic agent used in equine surgery, often in conjunction with detomidine and thiopental or sometimes guaifenesin (Hijazi and Boulieu, 2002; Umar *et al*, 2006; Yamashita *et al*, 2007). Ketamine has been the drug of choice because of its rapid effects on cats, dogs, rabbits, rats and other small animals. Veterinarians often use ketamine with sedative drugs to produce balanced anaesthesia and analgesia and constant rate infusion to help prevent pain wind-up (Lynch *et al.*, 2005).

Medetomidine is an alpha 2- adrenoreceptor agonist drug used as both a sedative and analgesic. Medetomidine is a relatively new

sedative analgesic drug. It is the most potent alpha 2-adrenoreceptor agonist available for clinical use in veterinary medicine and stimulates receptors centrally to produce dose-dependent sedation and analgesia. Significant dose sparing properties occur when medetomidine is combined with other anesthetic agents correlating with the high affinity of this drug to the alpha 2-adrenoreceptor (Sinclair, 2003). Medetomidine is often used in combinations with opioids as premedication in healthy cats and dogs.

The beneficial effects of medetomidine are the same as those of other alpha 2-agonists and include reliable sedation, analgesia, muscle relaxation, and anxiolysis, as well as a decrease in the anesthetic requirements of injectable and inhalant agents (anesthetic sparing). It is not a controlled substance and, therefore, does not require extensive record keeping. These qualities make medetomidine a viable option in small animal anesthesia (Sinclair, 2003). Due to its potent sedative effect it is commonly used in more aggressive animals. It is sometimes used in combination with butorphanol and ketamine to produce general anaesthesia for short period in healthy but fractious felines that will not allow an intravenous induction agent to be given (Harrison and Simmonds, 1985; Sinclair, 2003). Medetomidine has been shown to produce reliable state of sedation, muscle relaxation and recumbency suitable for small animal practice (Hijazi and Boulieu, 2002).

Kilic (2008) similarly reported a significant decrease in PCV, Hb and RBC for a short time in calves following detomidine-midazolam-ketamine anaesthesia for umbilical surgery. In a study to determine effects of intravenous ketamine-midazolam and intramuscular buprenorphine on haematologic variables in cats, Dhumeaux et al (2012) reported significant decreases in red blood cell counts, haemoglobin concentration and haematocrits after the induction of anaesthesia. Similarly, Biermann et al (2012) reported significant decreases in packed cell volume using different

drug combinations administered intramuscularly in cats.

Because of cardiovascular effects of anaesthetic agents during anaesthesia there is need to also determine their effects on haematology and serum chemistry in animals.

The aim of the study is to evaluate the effect of the combination of ketamine-medetomidine anaesthesia on haematology and some serum chemistry parameters in dogs.

## **MATERIALS and METHODS**

### **Animals**

Six (6) local dogs comprising of four females and two males with a mean ( $\pm$ SD) body weight of  $13.0 \pm 3.0$  kg (Range, 10-18kg) aged 1-2 years were used for the study. The dogs were judged to be in good to excellent health based upon the results of a physical examination, complete blood cell count, and serum biochemical analysis. The dogs were kept for two weeks to stabilize at Department of Veterinary Surgery and Theriogenology pens before the study commenced. Food but not water was withheld from dogs for 12hr before the commencement of each experiment.

### **Anaesthesia**

The drugs used for this study were medetomidine (Dormitor<sup>®</sup>, Meiji Seika Co. Ltd. Tokyo, Japan) and ketamine hydrochloride (ketajex<sup>®</sup> 50mg/ml Chachanwadi-Vasana, Ahmedabad, India).

Each dog was given a recommended dose of the drug combination: medetomidine at 0.04mg/kg body weight and ketamine at 5mg/kg, intravenously. After injecting the drugs the dogs were placed on an intravenous fluid therapy at 10ml/kg/hr during anaesthesia.

The dog's reactions were observed during and after intravenous injection of the drugs, the onset of the drug action was observed after injection and the time to recumbency were noted.

### **Haematological and Serum chemistry Analyses**

Blood samples (2ml) were collected from the cephalic vein before the drugs were

administered and then at 30 minutes interval during anaesthesia (2ml each time, each dog was bled 5 times) into EDTA bottles for haematology and into plain bottles for serum chemistry: creatinine (CRE), blood urea nitrogen (BUN), alanine amino transferase (ALT) that were later analyzed. Packed cell volume (PCV), haemoglobin concentration (Hb), red blood cell (RBC) and white blood cell (WBC) counts were determined using a method described by Dennis and Joanna (2002). Differential leucocyte counts (DLC) were also determined from Giemsa stained slides and Absolute leucocyte counts were calculated using standard formula. The RBC indices (mean corpuscular haemoglobin (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) were calculated using standard formulae (MedlinePlus, 2013).

#### Data analysis

All data were expressed as mean  $\pm$  Standard Deviation (SD). The means of PCV, RBC, WBC, Hb, RBC indices, differential and

absolute leucocytes as well as serum chemistry: CRE, BUN, ALT were assessed using analysis of variance (ANOVA, Graph pad, 2000). Significant differences between means in all cases were declared at probability level of 5 percent ( $p < 0.05$ ).

#### RESULTS

The combination of ketamine–medetomidine anesthesia produced significant decreased in PCV at 90mins ( $32 \pm 6.2\%$ ) as compared to the baseline value, haemoglobin showed significant decrease at 60mins ( $12 \pm 1.9\text{g/dl}$ ) and also RBC decreased at 90 minutes compared to the baseline while WBC increased significantly (TABLE I). Despite the differences in MCV, MCH and MCHC pre injection values compared with values during anaesthesia, the values remained within normal range for dogs except for the decreased MCV value below normal at 120 min and increased MCHC value above normal at 120 min (TABLE I). This implied there was microcytic, hyperchromic anaemia at 120min.

**TABLE I: Effect of intravenous anaesthesia using ketamine (5mg/kg) and medetomidine (0.04mg/kg) on haematological parameters in dogs**

Time interval (min)	PCV (%)	Hb (g/dl)	RBC ( $\times 10^6/\mu\text{l}$ )	MCV (fl)	MCH (pg)	MCHC (g/dl)	WBC ( $\times 10^3/\mu\text{l}$ )
Pre	42.2 $\pm$ 7.5	15.6 $\pm$ 2.3	6.7 $\pm$ 1.6	63.0 $\pm$ 5.9	23.3 $\pm$ 0.7	37.0 $\pm$ 5.2	10.4 $\pm$ 3.2
30	39.2 $\pm$ 5.5	13.1 $\pm$ 1.7	5.6 $\pm$ 1.5	70.0 $\pm$ 3.0	23.4 $\pm$ 0.2	33.4 $\pm$ 3.8	14 $\pm$ 1.42
60	36 $\pm$ 5.9	12 $\pm$ 1.9*	5.3 $\pm$ 2.0	67.9 $\pm$ 3.9	22.6 $\pm$ 0.1	33.3 $\pm$ 4.0	15.4 $\pm$ 0.5**
90	32 $\pm$ 6.2*	10.9 $\pm$ 0.38*	4.96 $\pm$ 1.4*	64.5 $\pm$ 4.8	22.0 $\pm$ 1.0	34.1 $\pm$ 5.8	14.4 $\pm$ 3.2
120	32 $\pm$ 2.2*	12.9 $\pm$ 0.38	5.38 $\pm$ 0.34	59.5 $\pm$ 1.8*	24.0 $\pm$ 0.1	40.3 $\pm$ 1.8	16.8 $\pm$ 0.33**

Data are expressed as mean  $\pm$  SD, n=6; \*Significant decrease ( $p < 0.05$ ) compared with pre injection value. \*\* Significant increase ( $p < 0.05$ ) compared with pre injection value.

**TABLE II: Effect of intravenous anesthesia using ketamine (5mg/kg) and medetomidine (0.04 mg/kg) on serum chemistry in dogs**

Time interval (min)	BUN (mmol/l)	CRE (mmol/l)	ALT (u/l)
Pre	5.6 $\pm$ 1.5	66.8 $\pm$ 18.12	12.5 $\pm$ 5.2
30	5.3 $\pm$ 1.4	61.6 $\pm$ 14.2	11.8 $\pm$ 4.6
60	5.5 $\pm$ 1.3	71.8 $\pm$ 23.7**	10.7 $\pm$ 7.3
90	5.2 $\pm$ 1.3	62.3 $\pm$ 22.9	12.2 $\pm$ 5.2
120	4.5 $\pm$ 0.7	64.3 $\pm$ 15.5	14.5 $\pm$ 6.9

Data are expressed as mean  $\pm$ SD, n=6; \*\* Significant increase ( $p < 0.05$ ) compared with pre injection value.

The BUN value did not differ significantly from the baseline value, creatinine values showed significant increase at 60 mins ( $71.8 \pm 23.7$  mmol/l) as compared to the baseline while ALT showed slight decrease but return to baseline value at 90mins ( $12.2 \pm 5.2$ ) (TABLE II).

The absolute leucocytes count calculated showed neutrophils increased significantly throughout anaesthesia while DLC determined

showed neutrophils increased significantly reaching ( $72 \pm 0.82\%$ ) at 120mins compared to the baseline value of ( $60.5 \pm 4.0\%$ ), lymphocytes showed significant decrease reaching lowest value ( $15.7 \pm 2.2\%$ ) at 120mins as compared to the baseline value ( $29.3 \pm 2.5\%$ ), while eosinophils and monocytes did not differ significantly (TABLE III). Despite the variations in absolute leucocytes count calculated and DLC, these values remained within normal range for dogs.

**TABLE III: Effect of intravenous anesthesia using ketamine (5mg/kg) and medetomidine (0.04 mg/kg) on absolute leucocytes count (differential, %) in dogs**

Time interval (min)	Neutrophils (%)	Lymphocytes (%)	Eosinophils (%)	Monocytes (%)
Pre	6292±416 (60.5±4.0)	3047±260 (29.3±2.5)	437±364 (4.2±3.5)	551±198 (5.3±1.9)
30	8960±294** (64±2.1)	3360±322 (24±2.3)	658±224 (4.7±1.6)	882±266 (6.3±1.9)
60	10195±477** (66.2±3.1)	3388±308 (22±2.0)	816±308 (5.3±2.0)	878±354 (5.7±2.3)
90	9576±1166** (66.5±8.1)	2909±706* (20.2±4.9)	936±418 (6.5±2.9)	821±230 (5.7±1.6)
120	12096±138** (72±0.82)	2638±370* (15.7±2.2)	1008±302 (6.0±1.8)	890±84 (5.3±0.5)

Data are expressed in mean  $\pm$  SD, n=6; \* Significant decrease ( $p < 0.05$ ) compared with pre injection value. \*\* Significant increase ( $p < 0.05$ ) compared with pre injection value.

## DISCUSSION

Total intravenous anesthesia was achieved with combination of ketamine -medetomidine intravenous injection in the dogs and effects were observed during the drug treatment on haematological parameters and serum chemistry.

Following intravenous injection of medetomidine-ketamine, there was rapid lateral recumbency in all the dogs in this study. Kilic (2008) reported sedation after intravenous anaesthesia in dogs. Bennett *et al.*, (1992) reported that there was sedation after intravenous injection of medetomidine-midazolam and ketamine in dogs. The sedation observed in this study is due to medetomidine in combination. Medetomidine and ketamine combination induced deep sedation that proved useful for minor operation and clinical work

(Ueyama *et al* 2008).

Ketamine can redistribute out of the CNS and into all body tissue (Plumb, 2005) which can be influential factor in the resulting duration of anaesthesia. Ketamine can have several effects on serum biochemistry and haematological values, which have been previously reported including decreased leucocyte count due to a decrease in lymphocytes, anaemia, hypoproteinaemia and elevation of aspartate amino transferase, creatinine kinase and lactase dehydrogenase-5-isoenzyme levels (Bennet *et al.*, 1992).

Bennett *et al.*, (1992) also reported a significant decrease in PCV, hemoglobin and RBC for a short time in all the dogs after using medetomidine- midazolam-ketamine for umbilical surgery. However the values of the

Hb, RBC returned to the base line and the values of WBC showed a non-significant increase at 24 hours. Similarly in the present study decrease in PCV, Hb and RBC were observed. Also in this study, despite the differences in MCV, MCH and MCHC pre injection values compared with values during anaesthesia, the values remained within normal range for dogs (Plumb, 2005). However there was increase in WBC similar to the findings of Bennette *et al*, (1992). Gweba *et al* (2010) similarly reported decrease in PCV and Hb with slight increase in WBC following xylazine sedation in goats. Leukocytosis is frequently a sign of inflammatory response (Port, 2011) due to infection and it may also follow anaesthesia administration, after strenuous exercise, pregnancy and labour (Rogers, 2011). Despite the variations in absolute leucocytes count calculated and DLC in this study, these values remained within normal range for dogs (Plumb, 2005).

Kilic (2008) similarly reported a significant decrease in PCV, Hb and RBC for a short time in calves following detomidine-midazolam-ketamine anaesthesia for umbilical surgery. This observed decrease was suggested to be due to pooling of circulatory blood cells in the spleen and other reservoirs secondary to decreased sympathetic activity (Kilic, 2008).

In a study to determine effects of intravenous ketamine-midazolam and intramuscular buprenorphine on haematologic variables in cats, Dhumeaux *et al* (2012) reported significant decreases in red blood cell counts, haemoglobin concentration and haematocrits after the induction of anaesthesia. Similarly, Biermann *et al* (2012) reported significant decreases in packed cell volume using different drug combinations administered intramuscularly in cats. The results of the present study agree with these findings.

Decrease in the values of PCV, Hb and RBC may also be due to repeated bleeding during this study. Research protocols require repeated

bleeding of animals during experiments; haematologic response to such procedure might affect interpretation of data. The effects of bleeding animals on haematology have been reported by several authors and it is said to be slight and insignificant (Wall *et al*, 1985).

In the present study there was no significant effect of ketamine-medetomidine anaesthesia on BUN and ALT. This is similar to the report of Lugo-Roman *et al* (2010) who reported non-significant effects on BUN and CRE but with significant decrease of ALT following ketamine-medetomidine anaesthesia in rhesus macaques. In contrast to that study there was increase in CRE at 60 min in this study. This agrees with the report in calves by Kilic (2008). The increase in plasma CRE has been attributed to temporary inhibitory effect of these drugs on renal blood flow that could have produced an increase in plasma creatinine values (Kilic, 2008).

In conclusion, ketamine-medetomidine anaesthesia in dogs produced transient decrease in PCV, Hb, RBC and lymphocytes and increase in WBC, neutrophils and CRE. There was no significant effect on BUN and ALT. The dogs recovered uneventfully from anaesthesia.

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