



## Effect of vitamin C premedication on dexmedetomidine-ketamine anesthesia in cat

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The effect of ascorbic acid premedication on dexmedetomidine-ketamine anaesthesia was evaluated in five cats in two sets of experiments namely dexmedetomidine-ketamine (control) and ascorbic acid /dexmedetomidine/ketamine (test). The control group involved concurrent intramuscular administration of 10 mg/kg ketamine and 10 µg/kg dexmedetomidine to each cat. Selected anaesthetic indices and vital parameters were recorded at ten minutes' interval for a period of 90 minutes using standard methods. A week later, the test experiment was conducted with the same cats used in the control experiment but the trial was preceded with intramuscular injection of 20 mg/kg ascorbic acid 10 minutes before the concurrent administration of the previously used doses of dexmedetomidine and ketamine. Vitamin C premedication did not produce any significant difference on heart and respiratory rates and rectal temperature of the treated cats. Onset of drug action was not influenced by premedication with vitamin C and was the same in both control and test groups ( $3.6 \pm 1.50$  min). The duration of analgesia was also similar for both control ( $45.6 \pm 13.22$  min) and test trials ( $44.4 \pm 10.01$  min). Ascorbic acid premedication produced a longer duration of anaesthesia ( $68.2 \pm 17.96$  min) than the control ( $59.6 \pm 21.51$  min). It also produced a significantly ( $P < 0.05$ ) shorter time to stand ( $2.2 \pm 2.49$  min) than the control ( $4.8 \pm 5.34$  min). It was concluded that vitamin C intramuscular administration at a dosage of 20mg/kg prior to dexmedetomidine-ketamine anesthesia in cats produced a longer duration of anaesthesia but hastened the time to stand from sternal recumbency.

**Keywords:** Anaesthesia, Cat, Dexmedetomidine, Ketamine, Vitamin C

### Introduction

Cats are difficult subjects to restrain physically even for brief non-painful procedures. Ketamine is a popular injectable anaesthetic used for both chemical restraint and surgery in this species (Clarke *et al.*, 2014). Ketamine is popular because of its intramuscular route of administration, ability to stimulate the cardiovascular system and the wide safety margin (Lin, 2007). Although ketamine can be given alone in cats, its sole use may result in side effects such as increased muscle tone, spontaneous movements that are unrelated to surgical stimulation and rough recovery from anaesthesia (Clarke *et al.*, 2014). Ketamine has

therefore been used in combination with various classes of sedatives such as  $\alpha_2$ -adrenergic receptor ( $\alpha_2$ -AR) agonists, phenothiazines and benzodiazepines, (Moens & Fargetton, 1990; Hellyer *et al.*, 1991; Lin, 2007) in order to counteract these undesirable effects. Some of the ketamine-sedative combinations that have been used in the cat include diazepam/ketamine, xylazine/ketamine, acepromazine/ketamine (Clarke *et al.*, 2014), medetomidine/ketamine (Moens & Fargetton, 1990) and most recently, dexmedetomidine/ketamine (Neto, 2009).

Dexmedetomidine has been shown to highly potentiate the anaesthetic effects of ketamine and has balanced the two main disadvantages of this drug which are weak muscle relaxation and poor analgesia in deep organs by providing good muscle relaxation and good analgesia (Verstegen *et al.*, 1989). However, like other  $\alpha_2$  agonists, use of dexmedetomidine is associated with some cardiopulmonary depression which is dose dependent (Pagel *et al.*, 1998; Alvaides *et al.*, 2008).

Vitamin C is a water-soluble vitamin that is necessary for a variety of physiological reactions such as adrenaline production and collagen synthesis (Kim *et al.*, 2013). Previous animal studies have showed that there is a close relationship between extracellular vitamin C levels and recovery from anaesthesia (Crespi *et al.*, 1992). Najafpour & Sadeghi-Hashjin (2007) suggested the possibility of the inclusion of vitamin C for premedication in clinical practice in order to lower the dose of anaesthetics thereby reducing their side effects. There are some studies in rabbits which have combined vitamin C with xylazine (Egwu *et al.*, 2015) and ketamine (Elsa & Ubandawaki, 2005; Hasar & Najafpour, 2009) alone, vitamin C with xylazine and ketamine combination in rats (Najafpour & Sadeghi-Hashjin, 2007) and ketamine alone in cats (Hasar & Najafpour, 2009) with varying results. However, to our knowledge there has been no report on the use of vitamin C as a premedicant with dexmedetomidine-ketamine combination in cats. The aim of this study, therefore, was to evaluate the effect of vitamin C (ascorbic acid) premedication on dexmedetomidine-ketamine anaesthesia in cats not undergoing any surgical procedure.

## Materials and Methods

### Animals

Five domesticated, home bred, short haired local cats of both sexes (4 intact males and 1 intact female) in the age range of one to two years and mean body weight of  $1.5 \pm 0.0$  (Mean  $\pm$  SD) kg were used for the study.

### Housing

The cats were housed in indoor locker-type cages built of concrete and iron doors. The floor of the cages were provided with bedding, and plastic litter trays (sand box) to keep them warm and enhance hygienic cage maintenance.

### Stabilization

The cats were clinically evaluated, dewormed with 250mg/ml Pyrantel pamoate suspension

(Pyranthrin<sup>®</sup>, Neimeth pharmaceuticals, Oregon, Nigeria) at a dosage of 5mg/kg body weight, and allowed two-week acclimatization period with their new environment, feeding regimen and handling. They were fed with rice and fish, provided with drinkable water *ad-libitum* and were adjudged to be in good health following complete physical examination before commencement of the study.

### Drugs

The drugs used for this study were: Ascorbic acid (Vitamin C; Anhui Medipharm Co., Ltd. China) supplied as a 500mg/5ml solution for injection in a 5-ml ampoule. Dexmedetomidine (Dexdomitor<sup>®</sup>; Orion Corporation, Orionintie 1 FI-02200 Espoo, Finland) supplied as a 0.1mg/ml solution for intramuscular or intravenous injection in a 15-ml multi dose vial, and Ketamine hydrochloride (Ketalor<sup>®</sup>; Kwaliti Pharmaceuticals Pvt. Ltd, Amritsar-India) was supplied as a 50 mg/ml aqueous solution for intramuscular or intravenous injection in a 10-ml multi-dose vial.

### Study design

A simple randomized controlled crossover design was employed. Each cat (n=5) was induced by a concomitant administration of ketamine and dexmedetomidine and vital parameter measurements taken. After a wash out period week, a second experiment was done with administration of ascorbic acid 10 minutes before simultaneous administration of ketamine and dexmedetomidine and measurements repeated and compared.

### Experimental procedure

Prior to the experiment, food was withheld from the cats for 12 hours but they were allowed free access to drinking water until the time of drug administration.. The weights of the cats were determined using a top loading weighing balance. The first series of experimental trial (control) involved the concurrent intramuscular administration of ketamine and dexmedetomidine (DK) at a dosage of 10 mg and 10  $\mu$ g per kg body weight respectively.

The second series of experimental trial (test) involved intramuscular administration of 20 mg/kg bodyweight of ascorbic acid followed 10 minutes later by concurrent intramuscular administration of ketamine and dexmedetomidine (ADK) at the dosage of 10 mg and 10  $\mu$ g per kg body weight respectively.

Following loss of righting reflex by the anaesthetized cats, they were placed on right lateral recumbency and allowed to cycles in room air for the duration of the experiment. Analgesia was tested using paw-pinch withdrawal reflex as

previously described (Cruz *et al.*, 1997). Baseline readings of the heart rate (HR), respiratory rate (RR) and rectal temperature (RT) were determined and thereafter at 10 minutes interval over a 90 minute period. The heart rate (in beats per minute) was determined with the aid of a precordial stethoscope. Respiratory rate (in breaths per minute) was determined by counting the cat's thoracic movements while rectal temperature was determined using a digital clinical thermometer.

#### Calculations

The anaesthetic indices were calculated:

- Onset of drug action (ODA):** Time interval (in minutes) between concurrent drug administrations of dexmedetomidine-ketamine and loss of righting reflex by the anaesthetized rabbits.
- Duration of analgesia (DA):** Time interval (in minutes) between the loss and return of pedal reflex.
- Duration of recumbency (DR):** Time interval (in minutes) between loss of righting reflex by the rabbits and their assumption of sternal posture.
- Time to standing (TS):** Time interval (in minutes) between assumption of sternal posture and time to stand.

#### Statistical analysis

All data were expressed as means  $\pm$  standard deviation (means  $\pm$  SD). The means of the anaesthetic indices and vital parameters were compared using student's t-test for paired data followed as appropriate by Tukey-Kramer multiple comparisons. A value of  $P < 0.05$  was considered statistically significant for all the comparisons (Dawson & Trapps, 2004).

## Results

### Observation

All cats reacted to pain on intramuscular injection. Two cats, one each in the

dexmedetomidine/ketamine (DK) and the ascorbic acid/dexmedetomidine/ketamine (ADK) groups vomited some minutes after drug administration.

**Onset of drug action (ODA):** Time of onset of drug action with DK ( $3.6 \pm 1.50$ ) min was the same with ADK.

#### Duration of analgesia (DA)

Duration of analgesia with DK group ( $45.6 \pm 13.22$  min) was not significantly ( $p > 0.05$ ) different with ADK ( $44.4 \pm 10.01$  min) (Table 1).

#### Duration of Recumbency (DR)

The duration of recumbency achieved with DK ( $59.6 \pm 21.51$  min) was not significantly ( $p > 0.05$ ) different with ADK ( $68.2 \pm 17.96$  min). (Table 1)

#### Time to standing (TS)

The time to standing with DK group ( $4.8 \pm 5.34$  min) was significantly ( $p < 0.05$ ) longer than with ADK group ( $2.2 \pm 2.49$  min) (Table 1).

#### Heart rate (HR)

The mean heart rates obtained after DK injection ranged from  $104.8 \pm 6.48$  to  $158.8 \pm 32.87$  beats/min while that of ADK ranged between  $107.2 \pm 16.32$  and  $158.0 \pm 52.55$  beats/min. Heart rates fell below the base line values for the first 40 minutes of anaesthesia in both treatment groups and began to increase at the 50<sup>th</sup> minute. The ascorbic acid treated group had lower heart rates than the DK group in this first 40 minutes of anaesthesia. This difference was not significant ( $p = 0.05$ ) (Figure 1).

#### Respiratory rate (RR)

The mean RR of the DK group ranged from  $10.6 \pm 5.81$  to  $41.2 \pm 8.94$  breaths/min while that of ADK ranged from  $15.2 \pm 1.79$  to  $38.4 \pm 8.27$  breaths/min. RR fell below baseline values in both treatment groups in the first 20<sup>th</sup> minute of anaesthesia. The RR became faster in both groups from the 30<sup>th</sup> minute but the values were significantly lower with ADK than with DK. There was no significant difference between

**Table 1:** Anaesthetic indices of cats anaesthetized with either concurrent intramuscular administration of ketamine and dexmedetomidine alone <sup>a</sup> or following premedication with intramuscularly administered ascorbic acid <sup>b</sup>

Indices (Min)	Treatment Groups	
	DK	ADK
ODA	$3.6 \pm 1.50$ min	$3.6 \pm 1.50$ min
DA	$45.6 \pm 13.22$ min	$44.4 \pm 10.01$ min
DAN	$59.6 \pm 21.51$ min	$68.2 \pm 17.96$ min
TS	$*4.8 \pm 5.34$ min	$2.2 \pm 2.49$ min

Data are expressed as means  $\pm$  standard deviation (SD)

a - 10mg/kg of dexmedetomidine / 10  $\mu$ g/kg of ketamine

b - 20mg/kg of ascorbic acid / 10 mg/kg of dexmedetomidine / 10  $\mu$ g/kg of ketamine

\*  $p < 0.05$

RR in the groups as from the 60<sup>th</sup> minute (P>0.05) (Figure II).

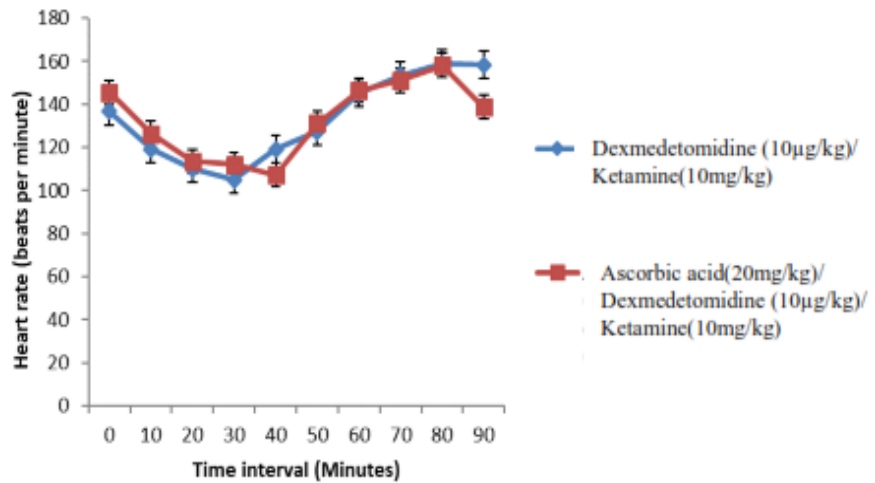
**Rectal temperature (RT)**

The mean rectal temperatures obtained in the ADK group ranged between 36.1 ± 0.45 and 38.2 ± 0.45°C while RT of DK group ranged between 36.4

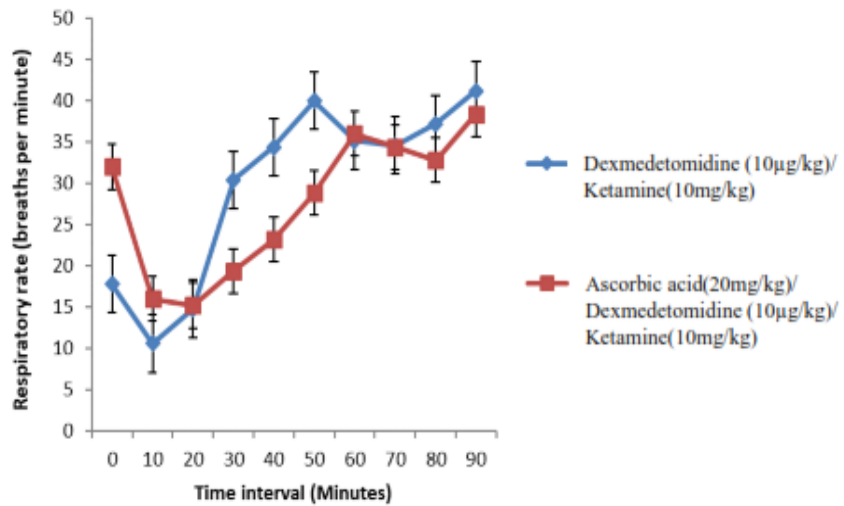
± 0.22 to 38.1 ± 0.45°C. There were no significant differences in mean RT between the two groups but the values fell below base line values gradually from the 20<sup>th</sup> minute and the cats were subsequently hypothermic (Figure III).

**Discussion**

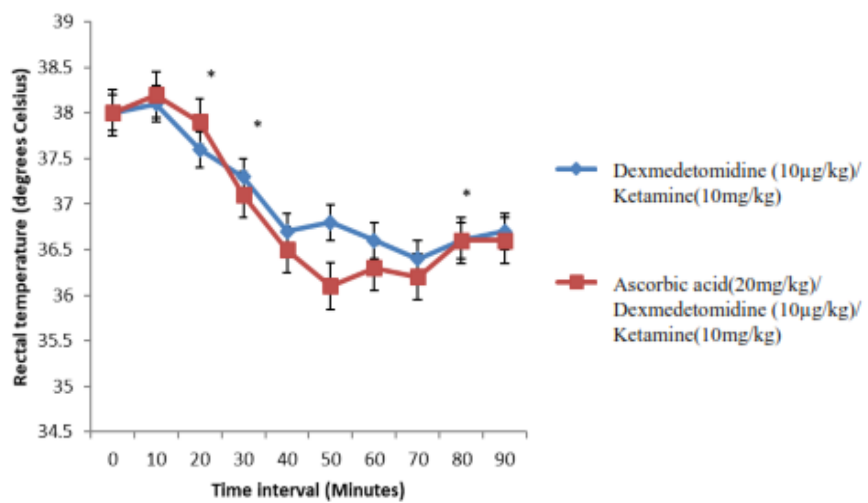
The result of this study showed that vitamin C at the dosage of 20mg/kg body weight for premedication did not have a profound effect on dexmedetomidine-ketamine anaesthesia in cats. The observed vomiting following administration of dexmedetomidine was consistent with emetic properties of α2 agonists (Granholm *et al.*, 2006). The intramuscular route was favoured for drug administration in this study for ease of drug administration as cats resent being held for too long and may not cooperate well with venipuncture (Mc Curnin & Bassert, 2006). A non-significantly longer duration of recumbency was recorded in the ADK (68.2 ± 17.96 minute) group compared with the DK (59.6 ± 21.51 minute). In a similar study in dogs, vitamin C premedication,



**Figure I:** Heart rate responses of cats to the intramuscular administration of dexmedetomidine/ketamine alone and that of ascorbic acid/dexmedetomidine/ketamine



**Figure II:** Respiratory rate responses of cats to the intramuscular administration of dexmedetomidine/ketamine alone and combined with ascorbic acid



**Figure III:** Rectal temperature responses of cats to the intramuscular administration of dexmedetomidine/ketamine alone and combined with ascorbic acid

\* p<0.05

and ketamine anaesthesia produced a significantly longer duration of anaesthesia in experimental group compared with the control (Sanni *et al.*, 2016). The slight difference in result may be due to the lower dose of Vitamin C (20mg/kg) used in this study as against 30mg/kg used in the previous study. A significantly shorter time to stand from sternal recumbency recorded in the ADK group was also similar to findings in dogs and rabbits (Sanni *et al.*, 2016; Yanmaz *et al.*, 2016). The observed quicker time to stand may be due to vitamin C psycho-stimulatory influence on the central nervous system which is similar physiologically to amphetamine effects on central nervous system (Elsa & Ubandawaki, 2005). Amphetamine lessens the degree of central depression effects caused by various drugs, through stimulation of cortical and reticular activating system (Brunton *et al.*, 2011). There was no significant difference in the HR values between the two groups). However the heart rates values fell below the acceptable rate of 140-220 beats/minute for cats (Mc Curnin & Bassert, 2006) from the 10<sup>th</sup> minute to the 50<sup>th</sup> minute. The bradycardia observed could be attributed to dexmedetomidine's  $\alpha_2$  agonists effects.

Dexmedetomidine causes bradycardia and bradypnoea, due to decreased sympathetic tone and CNS depression (Sinclair, 2003).

The mean respiratory rates of the two groups of cats fell below the normal range of 24-48 breaths/minute (Mc Curnin & Bassert, 2006) in the first 20 minutes. The ADK group had a prolonged respiratory depression shown by a slower rise in respiratory rate that was prominent between 20 and 50 minutes. The non-significant respiratory depression of ADK synchronizes with the observed duration of recumbency associated with vitamin C influence on dexmedetomidine associated cardio-respiratory depression (Sinclair, 2003). A significant fall in temperature was observed in both DK and ADK at 20, 30 and 80 minutes. The fall in temperature is due to compromised basal metabolic rate caused by the combined CNS depressant effects of the anaesthetic drugs (Clarke *et al.*, 2014). Cats should be provided with warm water blankets or other heat source to treat hypothermia whenever these drug combinations are employed.

It was concluded that vitamin C intramuscular administration at a dosage of 20mg/kg prior to dexmedetomidine-ketamine anaesthesia in cats produced a longer duration of anaesthesia but hastened the time to stand from sternal recumbency.

### Conflicts of Interest

The authors declare no conflicts of interest.

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