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Research Article

Xylazine-Ketamine Anesthesia Following Premedication of New Zealand White Rabbits with Vitamin C

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Abstract

This study was aimed out to evaluate the effects of vitamin C premedication on xylazine-ketamine anesthesia in New Zealand white rabbits. Twelve New Zealand white rabbits were divided into two groups (Group XK and Group VCXK) that each had 3 males and 3 females. The animals in group XK were treated with 10 mg/kg Xylazine HCl and 50 mg/kg Ketamine HCl. The animals in group VCXK were pre-treated with 60 mg/kg Vitamin C prior to xylazine-ketamine combination. The onset of anesthesia, the length of surgical anesthesia and the recovery time were recorded. Body temperature, heart and respiratory rates were recorded at 0, 5, 10, 15, 30, 45, 60 min. In XK group onset of action and length of surgical anesthesia were 5.81±0.19 min and 55.00±2.81 min, respectively. Premedication of rabbits with 60 mg/kg vitamin C resulted in significant decrease in the onset of action (3.93±0.13 min) and increase in the duration of xylazine-ketamine anesthesia (77.50±6.15 min). The body temperature change between treatment groups were significant at 30, 45 and 60 min. This study shows that vitamin C administration prior to xylazine-ketamine anesthesia in New Zealand white rabbits decreases the time for onset of action and prolonged the length of surgical anesthesia.

Keywords: *Xylazine, Ketamine, Anesthesia, Vitamin C, Recovery, New Zealand white rabbit*

Beyaz Yeni Zelanda Tavşanlarında Vitamin C Premedikasyonu Sonrasında Ksilazin-Ketamin Anestezisi

Özet

Bu çalışma, beyaz Yeni Zelanda tavşanlarında xylazine-ketamine anestezisi üzerine vitamin C premedikasyonunun etkilerini değerlendirmeyi amaçladı. On-iki beyaz Yeni Zelenda tavşanı her grupta 3 erkek ve 3 dişi olacak şekilde iki gruba (Grup XK ve Grup VCXK) ayrıldı. Grup XK'daki hayvanlara 10 mg/kg Xylazine HCl ve 50 mg/kg Ketamin HCl uygulandı. Grup VCXK'daki hayvanlara Xylazine-Ketamine kombinasyonu öncesinde, 60 mg/kg Vitamin C verildi. Anestezi başlangıcı, cerrahi anestezi süresi ve uyanma zamanı kaydedildi. Vücut sıcaklığı, kalp frekansı ve solunum oranları 0, 5, 10, 15, 30, 45 ve 60. dakikalarda kaydedildi. XK grubunda anestezi başlangıcı ve cerrahi anestezi süresi sırasıyla 5.81±0.19 dk ve 55.00±2.81 dk'idi. Tavşanların 60 mg/kg vitamin C ile premedikasyonu anestezi başlangıcında önemli bir azalma (3.93±0.13 dk) ve ksilazin-ketamin anestezi süresinde artış (77.50±6.15 dk) ile sonuçlandı. Gruplar arasında vücut sıcaklığı değişimi 30, 45 ve 60. dakikalarda anlamlıydı. Bu çalışma beyaz Yeni Zelanda tavşanlarında ksilazin-ketamin anestezisi öncesinde vitamin C uygulamasının anesteziye giriş süresini kısalttığını ve cerrahi anestezi süresini uzattığını göstermektedir.

Anahtar sözcükler: *Xylazine, Ketamine, Anestezi, Vitamin C, Rekover, Beyaz Yeni Zelanda tavşanı*

INTRODUCTION

Anesthesia is loss of the sensations which allows medical and surgical procedures to be undertaken without causing discomfort. Premedication prior to the anesthesia provides reduction of anxiety, pain and the dosage needed for anesthetic agents [1]. Xylazine is one of the most commonly used premedicant drug in veterinary medicine. It is a sedative, analgesic, muscle relaxant and has been used safely with other drugs for anesthesia [2-4].

Ketamine is a drug in a group of cyclohexylamines and it is routinely used for induction and maintenance of anaesthesia. It is used in rabbits due to rapid onset

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of action with minimal respiratory and cardiovascular effects [3]. Because the sole use of ketamine is not sufficient for anaesthesia, it is commonly combinated with preanesthetic drugs such as xylazine. Xylazine and ketamine combination has been reported to be more effective in rabbits and used with wide margins of safety [4].

Vitamin C is a water-soluble vitamin that is necessary for a variety physiological reactions such as adrenaline production and collagen synthesis [5]. Previous animal studies have showed that there is a close relationship between extracellular vitamin C levels and recovery from anesthesia [6].

There are some studies in rabbits which combined vitamin C with xylazine [1] and ketamine [7] alone. Moreover, one research has been used vitamin C with xylazine and ketamine combination in rats [8]. However, to the authors' knowledge, there is no study about using vitamin C as a premedicant with xylazine-ketamine combination in New Zealand white rabbits. Based on this premise, this study was aimed to evaluate the effects of vitamin C on xylazine-ketamine anesthesia in New Zealand white rabbits.

MATERIAL and METHODS

Animals

Twelve New Zealand white rabbits, 6 males and 6 females, 8-11 months old and weighing between 2.15 and 3.50 kg, were used. The rabbits were healthy, according to physical examinations and biochemistry results within reference range for the species. The animals were divided randomly into two experimental groups (Xylazine-Ketamine: Group XK; Vitamin C-Xylazine-Ketamine: Group VCXK) that each had 3 males and 3 females. They were maintained in individual cages, where they were fed with commercial pellet food and water *ad libitum*. The rabbits were acclimatized for a period of 14 days prior to the start of the study. Animals were not fasted before anesthesia. Atatürk University Local Board of Ethics Committee for Animal Experiments has approved the study protocol of this research (HADYEK decision no: 2015/115).

Study Design

The baseline vital parameters including body temperature, respiratory rate and heart rate were taken prior to the treatment. In group XK; 10 mg/kg Xylazine HCl (2% Rompun, Bayer, Istanbul, Turkey) and 10 min later 50 mg/kg Ketamine HCl (10% Ketasol, Interhas, Richter Pharma, Austria) were administered intramuscularly. Whereas, in group VCXK; 60 mg/kg Vitamin C (20% Injacom C, Ceva, Istanbul, Turkey) was administered intramuscularly 20 min prior to xylazine-ketamine combination. All drugs were injected into the quadriceps femoris muscle. All injections were performed by the same anesthetist who was unaware of the experimental design and all recordings were taken by other researchers who were unaware of the performed injections.

The onset of anesthesia was evident by decrease respiratory rate, recumbency, loss of pedal reflexes and loss of pinprick sensation on skin. The length of surgical anesthesia was evaluated by loss of withdrawal and ear-pinch reflexes [9]. The recovery was assessed by the existence of righting reflex (able to return sternal position by own after being placed on its back) [9,10] and excitement signs (apperance of vocalization, growling, thumping and convulsion). The heart and respiratory rate values were recorded with a veterinary vital signs monitor (Cardell, 9404, Sharn Veterinary Inc, USA) and stethoscope, respectively. The body temperature was measured with a digital rectal thermometer from the rectum. All rates were recorded at preinduction (-1), immediately following induction (0 h) and at 5, 10, 15, 30, 45, 60 min. Complications such as bradypnoea, bradycardia and excessive secretion were recorded.

Statistical Analysis

The generated data were analyzed by analysis of variance (ANOVA). As the data were normally distributed, differences among mean values were treated with paired sample t-test. Statistical significance was considered at *P* value below 0.05. The results are presented as means±standard error (SE). All data were analyzed using the SPSS19 (IBM Company, Version 19.0, SPSS Inc, USA, 2010) statistical package.

RESULTS

The results of the effects of vitamin C administration on xylazine-ketamine anesthesia at different time intervals are presented in *Table 1*. There were no significant differences in heart and respiratory rates between two groups at all time intervals. The body temperature change between treatment groups were significant at 30, 45 and 60 min ($P<0.05$).

The mean heart rate change before and after xylazine-ketamine treatment showed a significant depression ($P<0.05$) at 0, 45 and 60 min. However, in VCXK group mean heart rate depression was significant at 0, 5, 10, 15, 30, 45 min. The mean respiratory rate was significantly decrease at 0, 5, 10, 15, 30, 45 min XK group. In VCXK group, significant respiratory decrease was observed at all time intervals. In XK group, there were no significant differences in body temperature at all time intervals. However, significantly increase were detected in VCXK group at all time intervals.

The effect of vitamin C on onset of action, length of surgical anesthesia and recovery time are shown in *Table 2*.

Table 1. *The mean heart rate, respiratory rate and body temperature (mean±SE) differences in XK (xylazine-ketamine) and VCXK (Vitamin C- Xylazine-ketamine) groups at different measurement times*

Tablo 1. *Farklı ölçüm zamanlarında XK (xylazine-ketamine) ve VCXK (Vitamin C- Xylazine-ketamine) gruplarındaki ortalama kalp frekansı, solunum sayısı ve vücut sıcaklığı farklılıkları (ortalama±standart hata)*

Paremeter	Groups	Measurement Time							
		-1thmin	0thmin	5thmin	10thmin	15thmin	30thmin	45thmin	60thmin
HR	XK	216.00±21.46	186.67±9.00**	192.67±24.71	184.00±24.39	186.00±20.04	183.33±31.94	171.33±24.96**	180.67±17.04**
	VCXK	216.00±21.46	186.00±12.58**	180.67±9.93**	180.67±10.55**	177.33±14.01**	183.33±12.75**	179.33±13.95**	186.33±14.50
RR	XK	144.66±36.52	46.66±10.93**	46.00±10.95**	44.00±10.43**	44.66±10.85**	57.33±12.56**	57.00±6.66**	111.00±9.27
	VCXK	146.00±26.13**	39.33±9.60**	38.00±9.38**	38.66±7.86**	39.33±9.93**	48.66±12.75**	53.33±12.56**	115.33±5.88**
BT	XK	38.93±0.51	39,38±0.29	39.25±0.34	39.20±0.47	39.08±0.45	38.92±0.53	38.75±0,65	38.75±0.65
	VCXK	38.85±0.26	39.81±0.43*	39.76±0.58*	39.71±0.59*	39.71±0.53*	39.80±0.52*	39.78±0.48*	39.86±0.39*

HR: *Heart rate,* ***RR:*** *Respiratory rate,* ***BT:*** *Body temperature,* ***-1:*** *Preinduction,* ***0:*** *Immediately following anesthesia induction, * Significantly increase (P<0.05), ** Significantly decrease (P<0.05)*

Table 2. *Effects of vitamin C on anesthesia parameters*

Tablo 2. *Vitamin C'nin anestezi parametreleri üzerine etkisi*

Groups	Onset of Action (min)	Length of Surgical Anesthesia (min)	Recovery Time (min)
XK	5.81±0.19	55.00±2.81	117.83±5.64
VCXK	3.93±0.13**	77.50±6.15*	110.50±3.93

XK: *Xykazine-ketamine;* ***VCXK:*** *Vitamin C-xylazine-ketamine; * Significantly increase (P<0.05); ** Significantly decrease (P<0.05)*

DISCUSSION

All rabbits were not experience any complications due to anesthesia. Anesthesia induction and recovery from anesthesia were smooth in both groups. The present study shows that vitamin C premedication prior to xylazine-ketamine anesthesia decreases the time needed to induce and increases duration of surgical anesthesia in New Zealand white rabbits. It has been reported in the literature that using vitamin C for premedication can accelerate the onset of action and increase the recovery time [11]. Although in this study we did not use different ratios of xylazine-ketamine combinations to detect whether the vitamin C administration could minimize the anesthetic needs, our results supported that administration of vitamin C can reduce the dose of anesthetics required for general anesthesia [7]. We hypothesized that using Vitamin C as a premedicant might accelerate the effects of xylazine and ketamine without prolonged the recovery time, which is desirable for anesthesia [12,13].

In this study, there were no significant differences in heart rates among groups, but heart rate decreased significantly in XK group at 0, 45 and 60 min, and in VCXK at all intervals except for 60 min. The current findings appear to be in agreement with Elsa and Ubandawaki [7] who reported that ketamine and vitamin C combination in rabbits cause decreasing in heart rate. The reason of this decrease is probably due to vitamin C induced central nervous system depression activity [8]. The main disadvantage of xylazine on the cardiovascular system may have contributed the decreased heart rate in anesthesia [14]. In current study, the heart rate also decreased in XK group at some time intervals. This could be the reason that although ketamine may increase the heart rate by stimulating the sympathetic activity and decreased vagal tone, xylazine overrides these effects by hypotension and decreased sympathetic and increased vagal activity [15]. Moens and Fargetton [16] also found decrease in the heart rate at 45 min in dogs. The same results in cats had been reported previously by Allen et al.[17].

Tachypnoea may observed due to xylazine administration. On the other hand, ketamine may produce mild respiratory depression [18]. A change in respiratory rate is usually an indicator to some physiologic changes [19]. In the current study, there were no significant differences in respiratory rates among groups. However, the mean respiratory rate was significantly decrease after anesthesia induction. Previous studies have reported that xylazine-ketamine anesthesia decrease the respiratory rate [20,21]. Furthermore, more recent study has showed that ketamine at 40 mg/kg in rabbits with or without vitamin C induced significant respiratory depression [7], which is similiar to our results.

Body temperature is expected to decline following the anesthesia by reduction of muscular activity and depression of thermoregulatory center [22]. In our study, however, xylazine-ketamine anesthesia, with our without vitamin C premedication, did not significantly reduce the body temperature. This is in agreement with Kul et al.[14] and Wyatt et al.[23]. On the contrary, in this study, vitamin C premedication prior to xylazine-ketamine anesthesia increased the body temperature. This increasement has

been observed in rabbits due to a possible modulating effect of vitamin C [1].

This study showed that vitamin C administration prior to xylazine-ketamine anesthesia in New Zealand white rabbits decreases the time for onset of action and prolonged the length of surgical anesthesia. Moreover, vitamin C administration did not cause any changement in recovery time. The exact mechanism of vitamin C on anesthesia will require further investigations, thus the anesthetics needed in general anesthesia could decrease and it minimizes their side effects on patients.

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