



Asian Journal of Scientific Research

ISSN 1992-1454

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Evaluation of Use of Ketamine Hydrochloride for Induction of Anaesthesia in Rabbits with Experimentally Induced Unilateral Ureteral Obstruction

Rita I. Udegbumam, Kenneth C. Ogbanya, Sunday O. Udegbumam and Austin C. Onuba
Department of Veterinary Surgery, Faculty of Veterinary Medicine, University of Nigeria, Nsukka, Enugu State, Nigeria

Corresponding Author: Rita I. Udegbumam, Department of Veterinary Surgery, Faculty of Veterinary Medicine, University of Nigeria, Nsukka, Enugu State, Nigeria

ABSTRACT

This study investigated the anaesthetic characteristics of ketamine hydrochloride in rabbits with Unilateral Ureteral Obstruction (UUO). Two groups of rabbits (B and C) were anaesthetized with 30 mg kg⁻¹ ketamine intravenously (IV) on days 7 and 14 respectively post UUO. Healthy rabbits in group A (control) were anaesthetized with ketamine (30 mg kg⁻¹, IV). Post Ketamine Injection (PKI), anaesthetic indices, quality of anaesthesia, vital parameters and haematocrit of rabbits were studied. Duration of anaesthesia was significantly ($p < 0.05$) shorter in groups B and C with the shortest duration recorded in group C. Time of recovery was significantly ($p < 0.05$) shortest in group C. Quality of induction was good in 100% rabbits in groups A and C and good in 83.3% rabbits in group B. Recovery quality was good in 50% rabbits in groups A and C and in 60% rabbits in group B. Depth of anaesthesia was poor in all rabbits in groups A, B and C. Heart rates (HR) of rabbits in group A were significantly ($p < 0.05$) higher at 20 and 50 min PKI compared to HR of groups B and C. Respiratory rates of rabbits in group C were significantly ($p < 0.05$) lower than those of rabbits in groups A and B at 20, 30, 40 and 50 min PKI. Rectal temperature of group C was significantly ($p < 0.05$) lower compared to those of groups A and B at 40 and 50 min PKI. Haematocrit of rabbits in all the groups decreased though not significantly ($p > 0.05$) PKI. Serum potassium and chlorine of all the study groups increased though not significantly ($p > 0.05$) while serum sodium level of all groups increased significantly ($p < 0.05$) PKI. This study showed that duration of ketamine anaesthesia was shortened in rabbits with UUO. Also cardiopulmonary depression was observed in rabbits anaesthetized post UUO and this may further compromise renal function as well as tissue oxygenation in these patients. We therefore conclude that ketamine hydrochloride is not a choice anaesthetic for use in patients with UUO.

Key words: Ketamine, anaesthesia, rabbits, ureteral obstruction, respiration

INTRODUCTION

The kidney functions in filtration, re-absorption and secretion and to accomplish these functions, it receives about twenty-five percent (25%) of the cardiac output. Renal Blood Flow (RBF) is regulated by extrinsic (neuronal, hormonal and pharmacological) and intrinsic (renal insufficiency/failure) auto regulation factors. Any alteration in these aforementioned auto regulatory factors can bring about changes in RBF and glomerular filtration rate (Green and Grauer, 2007).

Obstructive uropathy especially ureteral obstruction remains an important cause of renal insufficiency (Chevalier *et al.*, 1999). This clinical condition is characterized by reduction in urine flow, renal blood flow and glomerular filtration rate (Cochrane *et al.*, 2005). In long standing cases, interstitial inflammation, tubular atrophy, fibrosis and hydronephroses occurs (Abd El-Hakim *et al.*, 2011). These derangements may pose great challenges during anaesthesia of patients with unilateral ureteral obstruction (UUO) since nearly every anaesthetic agent decreases renal blood flow and glomerular filtration rate (Green and Grauer, 2007; Weils, 2010). Thus patients with renal insufficiency are to be anaesthetized with drugs such as ketamine and propofol which optimize cardiac output with minimal hemostatic alteration (Weils, 2010).

Ketamine hydrochloride is a dissociative drug which has anaesthetic and analgesic properties (Shekidif *et al.*, 2013). Ketamine have been extensively used in rabbits alone or in combination with sedatives (Borowski *et al.*, 1990; Orr *et al.*, 2005; Grint and Murison, 2008; Amarpal *et al.*, 2010). Ketamine when used alone is associated with increase in cardiac output, heart rate and blood pressure due to increased sympathetic activity (Jacobson and Hartsfield, 1993; Jacobson *et al.*, 1994). According to Green and Grauer (2007), after ketamine hydrochloride injection, renal blood flow and glomerular filtration rate may decrease or remain unchanged.

We are not aware of any empirical study carried out to investigate the effect of ketamine hydrochloride on patients with unilateral ureteral obstruction thus the need for this study. In this study, we investigated the anaesthetic characteristics of ketamine hydrochloride in patients with existing unilateral ureteral obstruction. The effects of ketamine hydrochloride in these patients were compared with effects observed in non obstructed rabbits.

MATERIALS AND METHODS

Experimental animals: Eighteen New Zealand white male rabbits of mean (SEM) body weight 1.2 ± 0.5 kg, were used in this study. These rabbits were housed in stainless steel cages (1.5 ft^2) in the experimental animal house in the Department of Veterinary Surgery, University of Nigeria, Nsukka. During the period of study, rabbits were fed with growers mash supplemented with fresh grass (*Centrosima pubescens*) while water was provided *ad-libitum*.

Prior to the study, rabbits were assigned to 3 groups ($n = 6$) namely group A (control group), group B (unilateral ureteral obstruction anaesthetized on day 7 post surgery) and group C (unilateral ureteral obstruction anaesthetized on day 14 post surgery). Clearance and approval for animal usage were obtained from the University of Nigeria, Nsukka Ethics Committee for Medical and Scientific Research before the commencement of the experiment.

Unilateral ureteral obstruction: The ventral abdominal area of rabbits in groups B and C were shaved from the xiphoid region down to the lower abdomen and prepared for aseptic surgery. Rabbits were premedicated with xylazine hydrochloride (5 mg kg^{-1}) and anaesthesia was induced using ketamine hydrochloride (30 mg kg^{-1}) anaesthesia. Under deep anaesthesia, a ventral midline incision was made 2 cm caudal to the xiphoid region down to 2 cm below the umbilicus cutting through the subcutis, muscle, peritoneum and into the abdomen to expose the right kidney. The ureter was ligated post renally using size 3/0 polyglycolic acid suture (vicryl®). Thereafter, the peritoneum, subcutis and muscles were sutured with simple continuous pattern using size 2/0 chromic catgut suture. The skin was sutured with size 2/0 silk using simple interrupted suture pattern. After surgery, tramadol hydrochloride (10 mg kg^{-1}) was administered intramuscularly once daily for 3 days. Penicillin and streptomycin at the doses of 0.5 and 1 mg kg^{-1} b.wt., respectively, were injected intramuscularly once daily for 5 days post surgery to all the groups.

Induction of ketamine anaesthesia: The rabbits received no premedication and were not deprived of food and water prior to anaesthesia. In group B and C on day 7 and 14, respectively post UUO, anaesthesia was induced with ketamine (30 mg kg⁻¹) administered intravenously into the jugular veins of rabbits. Healthy rabbits (without UUO) in group A served as the control group and were injected intravenously with 30 mg kg⁻¹ ketamine. After induction of anaesthesia the following were studied

Anaesthetic indices

Induction time: Time from end of injection to onset of recumbency.

Duration of anaesthesia: Time from loss of righting reflex to return of righting reflex.

Time of recovery: Time from return of righting reflex to time of maintenance of standing posture unassisted.

Quality of anaesthesia

Quality of induction: This was evaluated and scored “good”, “fair” or “poor” using the criteria (modified) earlier described by Prassinis *et al.* (2005) as shown below:

Good: Smooth induction, rapidly assumes recumbency, no sign of excitement

Fair : Slightly prolonged, mild excitement

Poor : Obvious excitement, jumps or attempts to stand after recumbency

Recovery quality: This was evaluated and scored “good”, “fair” or “poor” using the criteria (modified) earlier described by Prassinis *et al.* (2005) as shown below:

Good: Smooth easy transition to alertness, stands in a reasonable amount of time and is able to walk with minimal ataxia

Fair : Transient excitement or whole body movements, some struggling, hyper-responsiveness that disappears once rabbit stands unassisted with moderate ataxia

Poor : Stereotypical behaviour such as circling, premature attempts to stand, prolonged recovery

Depth of anaesthesia: This was assessed by attempting ‘blind’ endotracheal intubation and pinna reflex testing as described by (Prassinis *et al.*, 2005; Borkowski *et al.*, 1990). Depth of anaesthetic was graded as shown below:

Good: Easy tracheal intubation, no response to ear pinch

Fair : Reflex response to tracheal intubation, sluggish response to ear pinch

Poor : Inability to intubate trachea, brisk response to ear pinch

Side effects: The incidence of side effects such as regurgitation, hypersalivation, tympany, apnoea (no spontaneous breathing for more than 20 sec) and apneustic breathing were recorded.

Vital parameters: Heart rates, respiratory rates and rectal temperatures of rabbits were measured before induction of anaesthesia to obtain their baseline values. These parameters were

re-determined every 10 min after induction of anaesthesia until recovery. Heart rates (beats/min) were measured with a precordial stethoscope and respiratory rates were measured by visual observation of the chest movements of rabbits. Rectal temperatures of rabbits were measured with a digital thermometer.

Haematocrit determination: The jugular area of rabbits were shaved and prepared for aseptic venipuncture by scrubbing with 0.5% chlohexidine hydrochloride. Intravenous cannulas (23 G) were inserted into the jugular veins of rabbits to allow blood collection. For each rabbit, blood (2 mL) was collected into heparinized bottles before ketamine hydrochloride injection and 20 min post ketamine injection for determination of haematocrit (Tvedten, 1994).

Serum electrolytes determination: Blood were collected from rabbits before ketamine injection and 20 min post injection into plain sample bottles and serum was subsequently harvested. Serum sodium, chlorine and potassium were determined using commercial test kits (Randox®). The assay procedures specified on the kits were strictly followed.

Data analysis: Data obtained were summarized as Mean±SEM. The anaesthetic indices, heart rate, respiratory rate and temperature of the three groups of rabbits were compared using One Way Analysis of Variance (ANOVA). Duncan Multiple Range Test (DMRT) was used to separate the variant mean. Mean haematocrit and serum electrolytes values of the respective groups obtained after ketamine injection were compared with their baseline values using T-test. Probability less than 0.05 were considered significant.

RESULTS

Anaesthetic indices: As shown in Table 1, duration of anaesthesia was significantly ($p<0.05$) shorter in the two groups of rabbits (groups B and C) anaesthetized post UUO with the shortest duration recorded in group C. Time of recovery was significantly ($p<0.05$) shortest in group C.

Quality of anaesthesia: As shown in Table 2, quality of induction was good in 100% rabbits in groups A and C and in 85 % of the rabbits in group B. Recovery quality was good in 50% rabbits in groups A and C and in 60% rabbits in group B. Depth of anaesthesia was poor in all rabbits in groups A, B and C. Apneustic breathing was observed in 30% rabbits in groups A and C while 60% rabbits in group B showed apneustic breathing.

Vital parameters: Heart rate of rabbits in group A were significantly ($p<0.05$) higher at 20 and 50 min PKI compared to HR of groups B and C (Fig. 1). Respiratory Rates (RR) of rabbits in group C were significantly ($p<0.05$) lower than those of rabbits in groups A and B at 20, 30, 40 and 50 min PKI (Fig. 2). Rectal temperature of all groups were not significantly different ($p<0.05$) at

Table 1: Anaesthetic indices after injection of ketamine (30 mg kg^{-1})

Time (min)	Groups			p levels
	A	B	C	
Induction time	0.0 ± 0.0^a	2.0 ± 0.0^b	0.0 ± 0.0^a	ab: $p<0.05$
Duration of anaesthesia	32.7 ± 0.3^a	17.7 ± 3.2^b	11.7 ± 0.9^c	ab: $p<0.05$ ac: $p<0.05$
Time of recovery	16.3 ± 3.2^a	16.0 ± 2.1^a	4.0 ± 1.2^b	ab: $p<0.05$

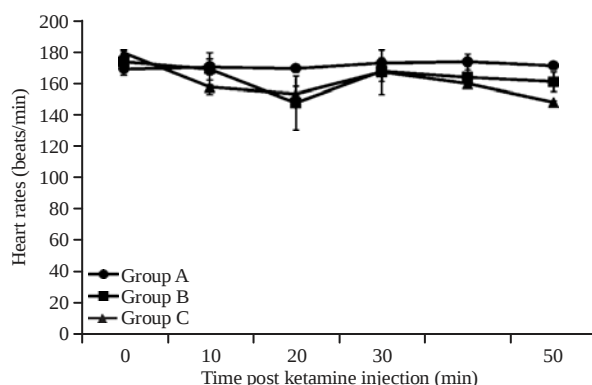


Fig. 1: Heart rates (beats/minute) of rabbits post ketamine injection

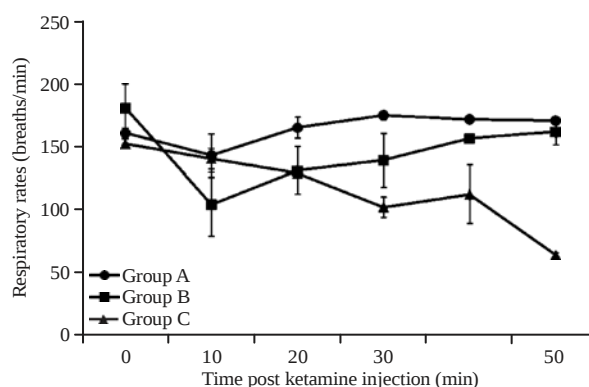


Fig. 2: Respiratory rates (breaths/minute) of rabbits post ketamine injection

Table 2: Summary of induction and recovery quality and occurrence of side effects in rabbits (n = 6) induced with 30 mg kg⁻¹ ketamine

Parameters	Groups		
	A	B	C
Quality of induction	Good (100%)	Good (85%)	Good (100%)
Recovery quality	Good (50%)	Good (60%)	Good (50%)
	Fair (50%)	Fair (40%)	Fair (50%)
Depth of Anaesthesia	Good (0%)	Good (0%)	Good (0%)
	Poor (100%)	Poor (100%)	Poor (100%)
Regurgitation	0	0	0
Hypersalivation	0	0	0
Tympany	0	0	0
Apnoea	0	0	0
Apneustic breathing	30%	60%	30%

10, 20 and 30 min PKI (Fig. 3). Rectal temperature of group C was significantly ($p < 0.05$) lower compared to those of groups A and B at 40 and 50 min PKI.

Haematocrit: As shown in Table 3, haematocrit of rabbits in all the groups decreased though not significantly ($p > 0.05$) post ketamine injection.

Serum electrolytes: Serum potassium and chlorine of all the study groups increased though not significantly ($p > 0.05$) while serum sodium level of all groups increased significantly ($p < 0.05$) PKI (Table 4).

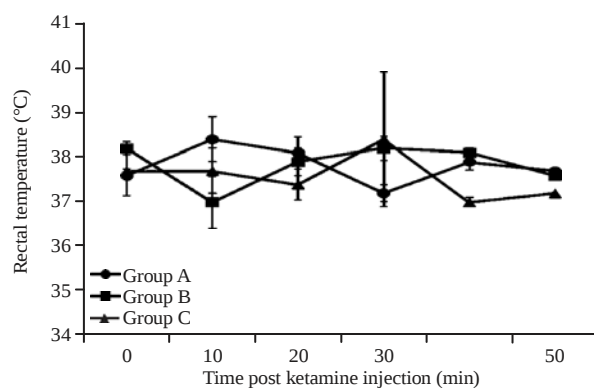


Fig. 3: Rectal temperature (°C) of rabbits post ketamine injection

Table 3: Haematocrit of rabbits anaesthetized using 30 mg kg⁻¹ ketamine

Groups	Haematocrit (%)		p levels
	0 min	20 min	
A	34.0±1.1 ^a	32.7±2.1 ^a	p>0.05
B	28.7±1.7 ^a	26.7±1.1 ^a	p>0.05
C	17.0±0.6 ^a	11.3±3.8 ^a	p>0.05

Table 4: Serum electrolytes of rabbits anaesthetized using 30 mg kg⁻¹ ketamine

Groups	Potassium (mmol L ⁻¹)		Sodium (mmol L ⁻¹)		Chlorine (mmol L ⁻¹)		p levels
	0 min	20 min	0 min	20 min	0 min	20 min	
A	5.7±6.7 ^a	5.8±1.5 ^a	166.6±23.5 ^a	195.9±6.3 ^b	85.9±3.3 ^a	86.4±1.5 ^a	ab:p<0.05
B	5.66±2.3 ^a	6.1±4.4 ^a	154.8±22.7 ^a	166.2±26.7 ^b	93.3±2.7 ^a	94.0±1.7 ^a	ab:p<0.05
C	5.1±1.0 ^a	5.7±0.5 ^a	163.8±25.0 ^a	190.3±14.1 ^b	97.2±2.6 ^a	99.2±5.6 ^b	ab:p<0.05

DISCUSSION

The result of this study showed that the duration of anaesthesia in the UUO groups were shorter compared to that of the control group which constituted of healthy rabbits. A study conducted by Pedraz *et al.* (1985) revealed inhibition of biotransformation of ketamine hydrochloride in renally impaired rabbits due to accumulation of the drug. Also, according to Short (1987) animals with renal dysfunction or obstruction to urine flow may exhibit prolonged sleep time when large doses of ketamine hydrochloride are administered. We are of the opinion that the elimination of ketamine hydrochloride was faster in the rabbits with UUO probably due to the compensatory role of the contralateral kidney.

The study of the anaesthetic quality of ketamine hydrochloride in all groups of rabbit showed that quality of induction, recovery quality and depth of anaesthesia were unsatisfactory in most rabbits. Previously, while studying the use of ketamine hydrochloride for anaesthetic induction in goats, Prassinis *et al.* (2005) noted similar qualities of ketamine hydrochloride. These findings may be explained by the fact that ketamine hydrochloride causes increased myoclonus (spontaneous involuntary muscle movement) and rough recoveries when used alone (Green *et al.*, 1981; Haskins *et al.*, 1985).

Anaesthetics may directly affect Renal Blood Flow (RBF) or indirectly alter renal function through changes in cardiovascular and/or neuroendocrine activity. In general however, most anaesthetics decrease Glomerular Filtration Rates (GFR) as a consequence of decreased RBF (Green and Grauer, 2007). In this study, while heart rate of control rabbits increased PKI, those of rabbits in groups B and C decreased. The finding in the control group was in consonance with

earlier documented effects of ketamine hydrochloride in rabbits (Dhasmana *et al.*, 1984). The recorded cardiovascular depression in the UUO groups suggests that ketamine hydrochloride altered the compensatory cardiovascular response of rabbits to its use. According to Green and Grauer (2007), after ketamine hydrochloride injection, renal blood flow may increase while glomerular filtration rate may decrease or remain unchanged. The finding of this study suggests that contrary to this documentation, renal blood flow and GFR decreased PKI in UUO rabbits. This may further compromise renal function in UUO patients during anaesthesia.

Post ketamine hydrochloride injection, the respiratory rate decreased minimally in the control group while marked respiratory depression was recorded in rabbits in group C. In rabbits, low doses of ketamine hydrochloride decreased respiratory rate and partial pressure of oxygen (Dhasmana *et al.*, 1984). The finding in the UUO groups suggests an adverse reaction since ketamine hydrochloride has minimal effect on respiration (Meyer and Fish, 2008). Furthermore, this study showed that PCV of dogs in group C (anaesthetized on day 14 post UUO) was below normal (PCV: 17%) before ketamine hydrochloride injection (Table 3). This finding showed that rabbits in this group were anaemic, thus severe respiratory depression noted in these rabbits post ketamine hydrochloride injection may affect oxygenation during anaesthesia.

The serum electrolyte assay performed in this study showed that sodium levels of all groups increased significantly PKI. The observed increase in sodium level in the control group was at variance with earlier reported effects of ketamine hydrochloride on serum sodium levels in goats (Kinjavdekar *et al.*, 2007), cynomolgus monkeys (Kim *et al.*, 2005) and Bonnet macaques (Venkatesan *et al.*, 2006). Kinjavdekar *et al.* (2007) reported no significant alteration in the serum level of sodium post administration of 2.5 mg kg⁻¹ ketamine hydrochloride while Kim *et al.* (2005) and Venkatesan *et al.* (2006) reported significant reduction in the serum sodium levels of the species studied after injection of 10 and 15 mg kg⁻¹ ketamine hydrochloride respectively. The observed increase in serum sodium level in the three experimental groups in this study may be the consequence of decreased renal perfusion after use of 30 mg kg⁻¹ ketamine hydrochloride. It has been shown that level of renal hormone, rennin increases during extracellular fluid depletion leading to angiotensin release and consequently increased aldosterone secretion from the adrenal cortex. These processes lead to increased sodium re-absorption within the distal tubules of the kidney (Lobo *et al.*, 2013).

CONCLUSION

This study showed that quality of anesthesia produced by ketamine hydrochloride was unsatisfactory in rabbits with experimentally induced unilateral ureteral obstruction. Also cardiopulmonary depression observed in rabbits anaesthetized with ketamine hydrochloride post UUO may further compromise renal function as well as tissue oxygenation in these patients during anaesthesia. We therefore conclude that ketamine hydrochloride is not a choice anaesthetic for use in patients with UUO.

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