CLINICAL RESEARCH REGARDING PREEMPTIVE ANALGESIC EFFECT OF PREOPERATIVE KETAMINE AFTER TRANSURETHRAL RESECTION OF PROSTATE

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Objective: To investigate whether a single intravenous dose of ketamine before transurethral resection of prostate (TURP) led to reduced postoperative pain and tramadol consumption.

Methodology: Sixty patients undergoing elective TURP were randomized into one of two groups: the ketamine group (Group K, n=30) received intravenous 0.5 mg/kg ketamine 10 min before surgery, and the control group (Group C, n=30) received an equivalent volume of normal saline 30 min before surgery. A standardized general anesthesia method was used with a laryngeal mask airway device in all patients. Data on pain intensity, incidence of lower urinary tract discomfort, time to the first analgesic requirement, tramadol analgesia and consumption, overall patient satisfaction and side effects were recorded for 24 h after extubation of the patients.

Results: Group K had significantly decreased postoperative pain scores at 1, 2, 6, and 12 h. The number of patients who required postoperative analgesia was fewer and postoperative tramadol consumption was significantly less in Group K as compared with Group C. There was no significant difference in the incidence of lower urinary tract discomfort or any of side effects. The patients in Group K were more satisfied.

Conclusion: Preemptive 0.5 mg/kg ketamine has a definitive role of preemptive analgesia for TURP without influence of LUT discomfort or an increase of adverse effects.

Keywords: Ketamine, Transurethral resection of prostate, Preemptive analgesia.

Introduction

Preemptive analgesia is a pretreatment that prevents the establishment of central sensitization, which amplifies upcoming pain. Various drugs have been used for this analgesic method, but treatments that can prevent the development of central sensitization may have the greatest benefit. It has been shown that central sensitization could be attenuated by 4, 9 N-methyl d-aspartate receptor antagonists[1]. Ketamine, a NMDA receptor antagonist, is an interesting choice for preemptive analgesia. Previous studies indicated that a single small dose of preoperative ketamine can decrease postoperative pain and analgesic requirement in minor surgeries such as outpatient

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surgery, knee arthroscopy, gynecological laparoscopic surgery and laparoscopic cholecystectomy, which cause less tissue trauma[2-6]. Conceivably, small dose ketamine can't lead to obvious hemodynamic variation and additional psychotomimetic effects[6]. Transurethral resection of prostate (TURP) is associated with less pain and disability; nonetheless several components contribute to pain after TURP such as tissue trauma at the surgical site, pelvic organ nociception, stimulation due to irrigation and low urinary tract (LUT) discomfort. Most patients scheduled for TURP are elderly, frequently presented with cardiopulmanory comorbidities, increased pain threshold and decreased pain tolerance[7]; as such the improvement in pain control is necessary.

The aim of this study is to evaluate preemptive analgesic efficacy of preoperative intravenous 0.5 mg/kg ketamine after TURP under general anesthesia.

Materials and Methods

After obtaining the approval from the local Ethics Committee and written informed consent from the patients, the present study was conducted in a randomized and double-blinded manner on a total of 60 patients with American society of anesthesiologists (ASA) physical status Ⅰ-Ⅱ, scheduled for elective TURP using a standardized general anesthesia technique with a laryngeal mask airway (LMA) device.

Patients who were allergic to tramadol or ketamine, with a history of drug abuse, with psychiatric illness and communication difficulties and morbidly obese patients were excluded from the trial.

Randomization was performed with a computer-generated sequence of numbers and sealed envelopes were used to allocate patients into two groups. Group K patients received 0.5 mg/kg ketamine (Jiangsu Hengrui Medicine CO., LTD, Lianyungang, China) 10 min before the surgery, and Group C received an equivalent volume of normal saline. The study drugs were drawn and diluted to a fixed volume of 10 ml by an anesthesiologist who was not involved in the management of anesthesia. The other researchers and patients were blinded to the grouping allocation. All the patients were instructed on the visual analog scale (VAS) preoperatively and instructed of its use as a tool for measuring postoperative pain.

After shifting the patients to the operating theatre, electrocardiogram (ECG), heart rate (HR), blood pressure (BP), Narcotrend index (NI), end-tidal CO_2 ($ETCO_2$) and oxygen saturation (SpO_2) were monitored throughout the surgical procedure. All patients received 5 ml/kg normal saline over 20 min before anesthetic induction. The intravenous infusion was minimally maintained during the surgical procedure to avoid fluid overload. Anesthesia was induced with 0.3 mg/kg etomidate, 3 μg/kg fentanyl and 0.15 mg/kg cisatracurium. After preoxygenation for 3 min, intubation using a proper-sized LMA was performed.

Anesthesia was maintained with 6 to 8 mg/kg/h propofol and 0.008 mg/kg/h remifentanil, and intermittent administration of cisatracurium as needed. Intravenous 1 μg/kg fentanyl was given to all patients about 10 min before the completion of the surgery.

After extubation, the patients were shifted to the recovery room where the continuing observations were made and recorded by an independent anesthesia registrar who was unaware of the group situation. The pain intensity was evaluated and recorded at 0.5, 1, 2, 6, 12 and 24 h after extubation of the patients at rest. The time 0 h was taken as the time of extubation of the patient. Postoperative analgesia consisted of 1.5 mg/kg intravenous tramadol, which was administered intravenously when the patient complained of pain and the VAS score was more than 3. The time to the first analgesic request, the number of tramadol doses given and patients who required tramadol analgesia were recorded.

The pain intensity was assessed by a linear 10 cm VAS (0- no pain; 1, 2, 3- mild pain; 4, 5, 6- moderate pain; 7, 8, 9- severe pain; 10- worst imaginable pain) and the sedation score was evaluated with Ramsay sedation scale (RSS: 1- anxious and agitated; 2- cooperative and tranquil; 3- drowsy but responds to command; 4- asleep but responds to tactile stimulation; and 5- asleep and no response). The incidence of lower urinary tract (LUT) discomfort was recorded. The overall satisfaction degree for postoperative analgesia was also measured at the end of the study. The overall satisfaction degree was divided as follow: poor, moderate, good, excellent.

Adverse effects associated with ketamine, such as nausea, vomiting, and hallucinations were evaluated with a "yes" or "no" survey. Hallucination was defined as a false sensory experience in which the patients reported they saw, heard, smelled, tasted, or felt something that was non-existent. The study ended at the 24th hour after extubation of the patient.

The time to the first analgesic request was the primary endpoint of this study. According to clinical experiences and previous studies, we assumed that preoperative intravenous ketamine would prolong time to the first analgesic request by 30 min, 23 subjects were required in each group with two-sided α of 5% and β of 10%. We decided to enroll 30 patients per group for possible dropouts.

Data were analyzed with the SPSS 17.0 (SPSS Inc, Chicago, IL, USA). Data of the two groups were compared by unpaired Student›s t-test for normally distributed data, Mann–Whitney U-test for nonnormally distributed data (the number of tramadol doses, VAS and RSS scores), and Chi-square or Fisher's exact test for qualitative data. A value of $P<0.05$ was considered as a statistically significant.

Results

The demographic data and surgical characteristics were comparable with no significant differences between the two groups (Table 1).

Table 1
Demographic data and surgical characteristics

	Group K (n=30)	Group C (n=30)	*P-value*
Age (years)	67.2±9.5	64.9±10.3	0.372
Weight (kg)	63.2±11.1	66.3±9.6	0.252
Height (cm)	168.4±9.4	165.3±12.2	0.274
ASA Ⅰ/Ⅱ(n)	15/15	18/12	0.604
Duration of operation (min)	45.9±13.7	51.7±16.1	0.138
Prostate volume (g)	55.6±12.1	58.4±15.6	0.440

ASA: American Society of Anesthesiologists. Values are presented as mean±standard deviation and number of patients.

The VAS scores at 1, 2, 6 and 12 h were significantly higher in Group C as compared with the VAS scores at the same time point in Group K. At 0.5 and 24 h the VAS scores were comparable between the two groups (Fig. 1).

Table 2 summarizes the use of postoperative

Table 2
Postoperative tramadol use

	Group K (n=30)	Group C (n=30)	*P-value*
Time to the first tramadol request (min)	114.6±32.2	66.4±22.7	0.0001
Number of doses of tramadol (n)	1.8±0.7	1.4±0.6	0.031
Number of patients requiring tramadol analgesia: n (%)	18(60%)	27(90%)	0.015

Values are presented as mean±standard deviation and number of patients (%).

Table 3
Patient satisfaction

	Group K (n=30)	Group C (n=30)
Poor	1(3.3%)	5(16.7%)
Moderate	6(20.0%)	10(33.3%)
Good	10(33.3%)	11(36.7%)
Excellent	13(43.3%)	4(13.3%)
P-value	0.037	

Values are presented as number of patients (%).

Table 4
The incidence of lower urinary tract (LUT) discomfort and adverse effects

	Group K (n=30)	Group C (n=30)	*P-value*
LUT discomfort	8 (26.7%)	14 (36.7%)	0.179
Nausea	5 (16.7%)	3 (10.0%)	0.706
Vomiting	2 (6.7%)	0(0.0%)	0.491
Hallucination	0 (0.0%)	0(0.0%)	1.000

Values are presented as number of patients (%).

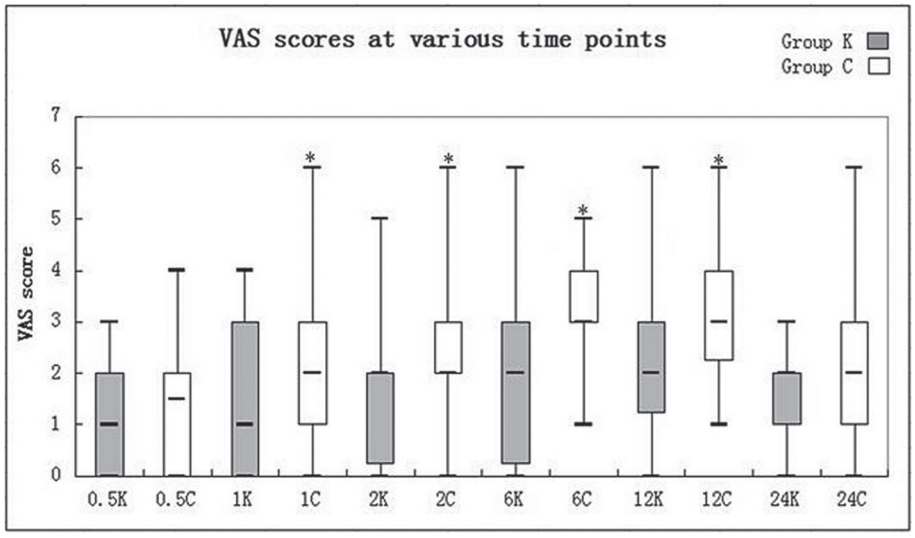

Fig. 1
*Visual analog scale (VAS) scores at various time points postoperatively. Box plots of postoperative VAS scores. Results are expressed in median. The top and bottom of each box indicate 75th and 25th percentiles and the error bars minimum and maximum. *p<0.05 compared with Group C.*

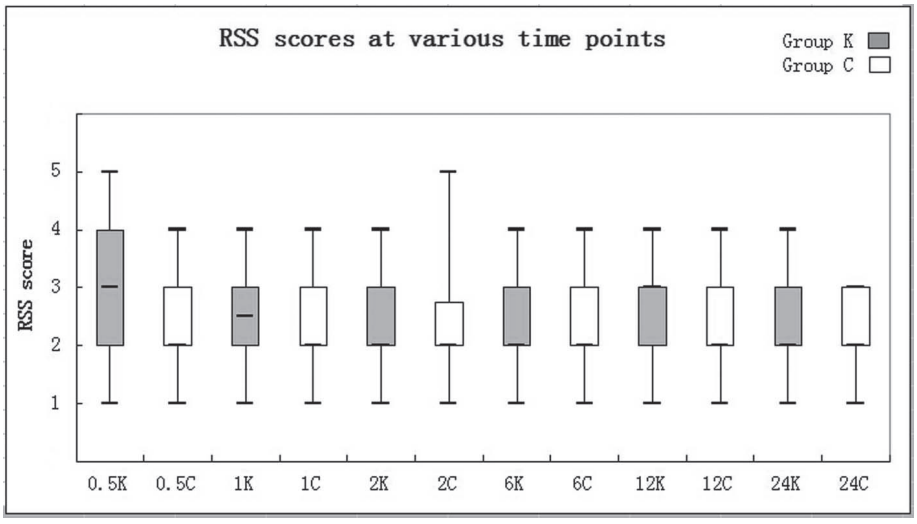

Fig. 2
Ramsay sedation scale (RSS) scores at various time points postoperatively. Box plots of postoperative RSS scores. Results are expressed in median. The top and bottom of each box indicate 75th and 25th percentiles and the error bars minimum and maximum.

tramadol analgesia. In Group K, the time to the first tramadol request was significantly longer, and the patients who required tramadol analgesia and the number of tramadol doses given were significantly fewer.

The overall patients' satisfaction degree is shown in Table 3. Patients in Group K were more satisfied compared to patients in Group C.

No statistically significant difference was noted on RSS scores between the two groups at all time points during the study (Fig. 2).

There were no significant differences between the two groups for the incidence of LUT discomfort or any of the adverse events (Table 4). All data of SpO_2 and respiration rate were within the normal range during the study period (93-100% for SpO_2 and 12-16 breath/min for respiration rate) in both groups.

Discussion

Surgical stimulation leads to release of glutamate which can activate postsynaptic NMDA receptors in the central nervous system. Activation of NMDA receptor is involved in development and exacerbation of hyperalgesia. Analgesic intervention before surgical stimuli, for example, preoperative administration of ketamine which is an NMDA receptor antagonist may attenuate or block sensitization and hence reduce acute pain[8].

The role of preoperative intravenous ketamine has been previously reported in outpatient surgeries,

gynecological laparoscopic surgery and laparoscopic cholecystectomy which are all minor surgeries with less tissue damage compared with other types of surgeries[4,5,6]. Singh et al have reported that VAS scores in the three groups receiving different doses of ketamine were comparable and 0.5 mg/kg ketamine had similar effect to 1.00 mg/kg. According to their study, 1.00 mg/kg ketamine was associated with higher incidence of side effects[6]. Therefore, the lowest dose of 0.5 mg/kg ketamine was chosen as the study dose in our study.

Our study demonstrated that the patients in Group K had significantly less postoperative pain. The result was consistent with the published researches mentioned above. Whereas some studies have demonstrated no beneficial effect of preoperative ketamine[9,10,11]. These negative findings could be ascribed to major surgeries in those studies. Major surgeries were usually associated with severe postoperative pain and maybe preoperative ketamine was not potent enough to block central sensitization in this kind of surgeries.

In the present study, intravenous administration of fentanyl 10 min before completion of the surgery might contribute to the comparable VAS scores at the time point of 0.5 h between the two groups. No significant difference was found on the incidence of LUT discomfort between the two groups. It might be associated with the result that ketamine had no function on muscarinic receptor.

The RSS scores were assessed as an indirect reflection of the adverse effect of ketamine. Patients in the two groups had comparable RSS scores at various time points. It implied that preoperative ketamine did not affect sedation status which should be attached attention to in the elder patients after general anesthesia.

In our study, no patients experienced hallucination in Group K. It corresponded to the incidence reported in the literature with the same dosage of ketamine[6]. The incidence of nausea and vomiting was comparable between the two groups and similar to the previous research[6]. It was not noted in this clinical trial that a small dose of ketamine could decrease postoperative nausea and vomiting[12].

There are limitations about this study. Ketamine is known to alter the neuroplasticity and reduce the development of chronic pain[13]. We didn't follow up the patients or evaluate whether chronic pain was reduced with 0.5 mg/kg ketamine. Further studies in this area are suggested.

We conclude that preoperative 0.5 mg/kg ketamine can reduce postoperative pain in patients undergoing TURP without an increase of side effects.

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