Ketamine for treatment of catheter related bladder discomfort: a prospective, randomized, placebo controlled and double blind study

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Background. Intraoperative urinary catheterization might cause postoperative catheter related bladder discomfort (CRBD). We evaluated the efficacy of ketamine as a treatment modality for CRBD.

Methods. Fifty-four, ASA physical status I and II, male and female adult patients, having CRBD after elective percutaneous nephrolithotomy were randomized into two equal groups of 27 each. In the postoperative period, patients who complained of CRBD received medication depending upon group allocation. Group I (Control) received placebo, Group II (Ketamine) received i.v. ketamine 250 μg kg⁻¹. After induction of anaesthesia patients were catheterized with a 16 Fr Foley’s catheter and the balloon was inflated with 10 ml distilled water. Grading of CRBD was done as none, mild, moderate and severe by a blinded observer at 0, 1, 2 and 6 h after operation.

Results. Ketamine reduced the incidence of CRBD (P<0.001) at 2 and 6 h along with reduction in severity (P<0.05) at 1 h compared with control. Higher incidence of mild sedation was observed in the ketamine group (P<0.05) which was not associated with any untoward effects. Operative time and intraoperative fentanyl requirement were similar in both the groups.

Conclusion. I.V. ketamine (250 μg kg⁻¹) is an effective treatment for reducing the incidence and severity of postoperative CRBD.

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Catheter related bladder discomfort (CRBD) is common in patients awakening from anaesthesia who have had urinary catheterization during operation. The muscarinic receptor antagonist tolterodine has been reported to be effective in preventing CRBD.1 Ketamine in sub-hypnotic dose has been used for treatment of postoperative shivering.2 Incidentally, ketamine was observed to be effective in the treatment of CRBD while it was administered for treatment of postoperative shivering.3 The present study was therefore designed to evaluate the efficacy of ketamine as a treatment modality for CRBD during the postoperative period.

Methods

After approval from the Institute’s ethics committee and patients’ written informed consent, we conducted a prospective, randomized, double blind, placebo controlled study. Patients were consecutively included during the period of August 2004 until September 2005.

Assuming that the therapy would reduce the incidence of bladder discomfort secondary to intraoperative catheterization of the urinary bladder by 30%, power analysis with α=0.05, β=0.8 showed that we would need to study 24 patients in each group. To make provision for any dropouts, we therefore enrolled 27 patients in each group. The study therefore consisted of 54 consecutive adults (18–60 yr) of ASA physical status I and II patients of either sex, undergoing elective percutaneous nephrolithotomy for renal and upper ureteric stone and who spontaneously complained of CRBD, after operation. Exclusion criteria were bladder outflow obstruction, overactive bladder (frequency >3 times in the night or >8 times in 24 h), end stage renal disease (urine output <500 ml per 24 h), morbid obesity, disturbance of the central nervous system, chemical substance abuse, chronic pain, and cardiovascular, hepatic or any psychiatric disease.

All patients were premedicated with oral lorazepam 0.04 mg kg⁻¹ the night before and 2 h before surgery.
Induction of anaesthesia was with fentanyl 2 μg kg⁻¹ and propofol 2 mg kg⁻¹. Tracheal intubation was facilitated by vecuronium bromide 0.1 mg kg⁻¹. Urinary catheterization was done with a 16 Fr Foley’s catheter and its balloon inflated with 10 ml distilled water after induction of anaesthesia. K-Y jelly (a water base lubricating gel) was used to lubricate the catheter which was later fixed in the suprapubic area with an adhesive tape without any traction and was always left to free drainage.

Anaesthesia was maintained using 70% nitrous oxide in oxygen and a propofol infusion at 50–150 μg kg⁻¹min⁻¹ and intermittent bolus of fentanyl and vecuronium if required. Intraoperative monitoring consisted of five lead ECG, non-invasive blood pressure, ventilatory frequency, pulse oximetry and end tidal carbondioxide. At the end of surgery, the neuromuscular blocking agent was antagonized with a combination of neostigmine 0.05 mg kg⁻¹ and glycopyrrolate 0.01 mg kg⁻¹ and patients were transferred to the post-anaesthesia care unit (PACU). In PACU, all the patients received fentanyl i.v. for their postoperative pain management using patient controlled analgesia.

After operation, patients who complained of CRBD were randomized with the help of a computer generated table of random numbers into two groups. Group I (Control) patients received placebo; whereas Group II (Ketamine) patients received ketamine 250 μg kg⁻¹. Both drugs were made up to 2 ml in normal saline. A postoperative nurse, blinded to the treatment and not involved in subsequent care, administered these medications i.v. Severity of CRBD, level of sedation, postoperative nausea and vomiting (PONV), respiratory depression, hallucinations, unpleasant dreams and diplopia were assessed by an anaesthesia registrar (M.K.), blinded to the treatment, at the commencement of the study that is 0 h and thereafter at 1, 2 and 6 h. Severity of CRBD was recorded as—none: patients did not complain of any CRBD even on asking, mild: reported by the patient only on questioning, moderate: reported by patient on their own (without questioning and not accompanied by any behavioural responses) and severe: reported by the patient on their own along with behavioural responses. Behavioural responses observed were flailing limbs, strong vocal response and attempts to pull out the catheter.\(^1\) Patient’s sedation was recorded on a four point scale (none: patient fully awake, mild: patient somnolent and responsive to verbal command, moderate: patient somnolent and responsive to tactile stimulation, severe: patient asleep and responsive to painful stimulation.

Patients who complained of CRBD on their own on arrival in the PACU were included in this study that is moderate and severe CRBD. Duration of surgery and total consumption of fentanyl were also noted. Patients unable to cooperate were excluded from the study. Incidence of CRBD between the groups was analysed by Z-test; whereas, severity of CRBD (none, mild, moderate and severe) was analysed by Fisher’s Exact test. SPSS 9.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. \(P<0.05\) was considered as significant.

### Results

Four patients (two from each group) were unable to cooperate and were therefore excluded from the study. The two groups did not differ significantly regarding patient characteristics (Table 1). Duration of surgery and intraoperative fentanyl requirement were similar in both the groups (\(P>0.05\)) (Table 1). At the commencement of the study (i.e. at the arrival of patients in PACU), severity of CRBD was similar in both the groups (\(P>0.05\)) (Table 2). Ketamine reduced the incidence of CRBD at 2 and 6 h in the postoperative period compared with the control group (\(P<0.001\)) (Table 2). Ketamine reduced the severity of CRBD compared with the control group at 1 h in the postoperative period (\(P<0.05\)) (Table 2).

A higher incidence of mild sedation was observed in the ketamine group at 1 and 2 h after operation (\(P<0.05\)). There was no difference in sedation (moderate, severe) and PONV between groups. None of the patients in either group had respiratory depression, hallucination or unpleasant dreams. One patient in the ketamine group reported diplopia at 1 h after ketamine administration which resolved within the next hour (Table 3). Absolute risk reduction, relative risk reduction and number needed to treat with 95% confidence boundary in the ketamine group were 20 (00–39), 80% (–26 to 97%) and 5 (3–100), respectively.

### Discussion

We observed a significant reduction in the incidence and severity of CRBD in patients treated with i.v. ketamine (\(P<0.05\)). A higher incidence of mild sedation was observed.
in the ketamine group. There were no differences in other side-effects between the groups.

Patients awakening from anaesthesia, who have undergone intraoperative catheterization of urinary bladder, often complain of CRBD (an urge to void or discomfort in the suprapubic region) in the postoperative period. These symptoms are similar to symptoms related to an overactive bladder (urinary frequency and urgency, with or without urge incontinence) and are attributed to involuntary contractions of bladder mediated by muscarinic receptors.1

The urinary bladder receives cholinergic innervation by the pelvic nerves and adrenergic innervations by the hypogastric nerve. Similar to other smooth muscle structures, the urinary bladder exhibits heterogeneous populations of muscarinic receptors with a predominance of M2 muscarinic receptor subtype and a minor population of M3 receptor. The M2 receptor activation causes the contraction of the detrusor smooth muscles, whereas, selective M3 receptor inactivation leads to M2 mediated contraction of the detrusor muscle.4

Ketamine (a phencyclidine derivative) is known to interact with multiple binding sites, including NMDA and non-NMDA glutamine receptors, mono-aminogenic and opioid receptors, nicotinic and muscarinic cholinergic receptors.5 Theoretically, ketamine can reduce the contractile response of the smooth muscles by an effect on the central nervous system, the preganglionic fibres, the nicotinic receptors in the postsynaptic membrane of the intramural ganglion, the postsynaptic fibres, the muscarinic receptors, the chemical signal transmission between the receptors and the contractile elements, the contractile element or any combination above.6 Durieux7 demonstrated that clinically relevant concentration of ketamine profoundly inhibit muscarinic receptor signalling.

The muscarinic receptor antagonist tolterodine (a pure muscarinic receptor antagonist) has been used successfully as a prophylaxis for the management of CRBD in the postoperative period.7 Ketamine administered i.v. as a treatment modality for CRBD has an advantage over tolterodine as it has an immediate onset of action (within 30 s and the maximum effect occurs in about 1 min) whereas tolterodine has to be administered orally which is an inconvenient route of administration in the postoperative setting and has a delayed response (peak plasma concentration 1–2 h). Ketamine (250 μg kg⁻¹) improves SpO₂ when administered with opiate after operation because of good analgesia. This enables the patients to breathe more deeply and cough better. Additionally, it has a direct broncho-dilatation effect.8

Ketamine in a sub-anaesthetic dose has been reported to have an analgesic effect. This analgesic action might be additive or synergistic with its anti-muscarinic effect leading to the observed decrease in the incidence of CRBD. Similarly increased level of sedation in the ketamine group might have led to a decrease in the incidence of CRBD. However, this possibility is unlikely as the level of sedation was mild and patients were communicable.

In this study, we enrolled patients who complained spontaneously of CRBD on arrival in the PACU (i.e. moderate and severe CRBD). This was done with the aim to evaluate the efficacy of ketamine as treatment modality for CRBD of moderate and severe nature. We intentionally did not evaluate the effect of ketamine therapy on mild CRBD (reported by the patient only on questioning) because we believe that this might introduce a bias in the study and may further lead to undesirable over-treatment. We did not evaluate the dose–response or the effect of therapy in patients who were catheterized for other medical procedure not requiring any surgical intervention. Further studies are suggested in these areas.

In conclusion, i.v. ketamine (250 μg kg⁻¹) reduces both its incidence and severity of CRBD. A higher incidence of mild sedation was observed in the ketamine group but this was not associated with any untoward effects. The side-effect profile was similar between the groups. We suggest that a sub-hypnotic dose of ketamine is an effective and safe modality for the treatment of CRBD in the postoperative setting.

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<th>Table 3 Incidence of side-effects, data presented as numbers. *P&lt;0.05 during inter group comparison</th>
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<td><strong>Time (h)</strong></td>
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<td>Diplopia</td>
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<td>Sedation (mild)</td>
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