Original Article

Comparison between ketamine and hyoscine for the management of postoperative catheter-related bladder discomfort: A randomized controlled double-blind study

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Abstract

Background and Aim: Postoperative catheter-related bladder discomfort (CRBD) can be a distressing complication for patients in whom a urinary catheter was inserted intraoperatively and is accompanied with patients' dissatisfaction. This trial investigated the efficacy of hyoscine and ketamine on treatment of postoperative CRBD in patients undergoing various surgeries.
Material and Methods: This was a prospective randomized, double-blind study, which included 60 American Society of Anesthesiologists Class I-II male patients undergoing elective nonurological operations requiring intraoperative urinary catheterization under general anesthesia after ethical approval and written informed consent. Patients were allocated randomly into two groups: The hyoscine group (H group) (n = 30) received 20 mg of hyoscine intravenously and ketamine group (K group) (n = 30) received 0.25 mg/kg of ketamine intravenously immediately after the occurrence of CRBD. The severity of CRBD was assessed at 0, 1, 2, and 4 h postoperatively. Adverse effects of hyoscine and ketamine were also examined. Data were summarized using mean ± standard deviation, and comparisons between groups were done by unpaired t-test. For comparison of serial measurements within each group, ANOVA was used.
Results: There was a significant difference between the two groups in the severity of CRBD measured by visual analog scale score only 30 min after drug administration where it was higher in ketamine group (44.50 ± 7.70) compared to hyoscine group (36.00 ± 8.55) ($P < 0.001$), otherwise there was no significant difference at other time points between the two groups, also there was a significant rise in heart rate in hyoscine group but no significant difference in mean arterial pressure.
Conclusion: Intravenous hyoscine 20 mg is more effective in control of CRBD than ketamine (0.25 mg/kg) in the first 30 min; later on they have the same effect.

Key words: Catheter-related bladder discomfort, general anesthesia, hyoscine, ketamine, postoperative, urinary catheterization

Introduction

Urinary catheterization in a patient undergoing a surgical procedure may lead to postoperative catheter-related bladder discomfort (CRBD) with variable degrees of severity. CRBD symptoms are similar to those of overactive bladder (OAB) such as pain and discomfort in the suprapubic region, frequency, urge to void, and a burning sensation with or without urge incontinence.[1,2] These symptoms are usually very distressing to the patient, patients' relatives, and staff in the postoperative care unit (PACU). The clinical manifestations of CRBD and OAB are both associated with involuntary detrusor smooth muscle contractions, in which the release of prostaglandins has been reported to be responsible for micturition reflex by triggering bladder contraction.[3] Muscarinic receptors are closely related to CRBD. Muscarinic receptor antagonists,

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such as oxybutynin, have been successfully used for the treatment of OAB[4] and of CRBD.[5]

Many drugs, including tramadol,[2] tolterodine,[4] hyoscine[6] and ketamine,[7] which commonly block the muscarinic receptor, have been investigated as approaches in the prevention or treatment of CRBD.

Ketamine (a phencyclidine derivative) has been found to interact with a number of receptors such as opioids, muscarinic, and *N*-methyl-D-aspartate (NMDA) receptors.[8]

Hyoscine, an anticholinergic drug, has a high affinity for muscarinic receptors located in the smooth muscle cells of the gastrointestinal (GI) tract,[9] and it has been used to treat abdominal cramps and has incidentally been effective against CRBD. In addition, hyoscine does not cross the blood–brain barrier because of the attachment of butyl bromide, so no central side effects as blurred vision and flushing of the face with the use of this medication.[9]

Material and Methods

This prospective, randomized, double-blind, controlled, parallel-group trial was performed after ethical approval from the Institutional Review Board in the Anesthesiology Department during the period from August to September 2015. The protocol of this clinical trial was registered in the Pan African Clinical Trial Registry (www.pctr.org) with identification number PACTR201510001279149. Informed written consents were obtained from all patients and patients were educated about the CRBD (characterized as a burning sensation with an urge to void or discomfort in the supra-pubic area) and visual analog scale (VAS). The American Society of Anesthesiologists physical status classification I and II male patients aged 18-60 years old, who underwent elective nonurologic surgery under general anesthesia, were included in this study. Patients with a history of bladder outflow obstruction, prostate hyperplasia, OAB (defined as frequency more than 3 times during the night or more than 8 times in 24 h), neurogenic bladder, end-stage renal disease, morbid obesity, disturbances of the central nervous system, chronic analgesic abuse, cranium and cardiac surgeries, and hepatic or psychiatric disease were excluded from the study.

In the preparation room, intravenous (I.V.) cannula was inserted under local anesthesia. Midazolam 0.02 mg/kg and ranitidine 50 mg were given intravenously to all patients. Then, patients were transferred to the operating room, where standard monitors were applied (pulse oximetry, noninvasive blood pressure, and electrocardiogram).

General anesthesia was induced with propofol 1-2 mg/kg, fentanyl 2 μg/kg, and endotracheal intubation was facilitated with atracurium 0.5 mg/kg. Mechanical ventilator was adjusted to keep the end-tidal carbon dioxide between 30 and 35 mmHg. Anesthesia was maintained with 60% O_2 and isoflurane 1-1.5% with the top-up doses of atracurium 0.15 mg/kg every 20 min as appropriate. The urinary catheter was inserted using a 16 French Foley's catheter and the balloon was inflated with 10 ml of distilled water before incision. The catheter was fixed with an adhesive tape without any traction on the urethra and was drained into a urinary bag. After the surgery was completed, muscle relaxation was antagonized with neostigmine 0.05 mg/kg and atropine 0.01 mg/kg. All patients were prescribed to receive 0.01 mg/kg morphine intravenously every 8 h, ketorolac 30 mg/kg I.V. every 8 h, and ondansetron 4 mg I.V. for postoperative nausea and vomiting (PONV). Patients were followed by a blinded physician until the occurrence of CRBD. After the occurrence of CRBD, patients were randomized into two groups; randomization was done using computer-generated random numbers inserted into opaque envelopes; a number was inside these envelopes, which indicates the group to which the participant was assigned. Hyoscine group (H group; $n = 30$) received hyoscine 20 mg I.V. and ketamine group (K group; $n = 30$) received ketamine 0.25 mg/kg I.V.. Both medications were diluted with normal saline to make up 10 ml in identical syringes by an anesthetist blinded to the study and given slowly I.V. over 5 min. Follow-up of patients was done by another physician who was blinded to the study drugs. The primary outcome was defined as the reduction in the severity of CRBD. Secondary outcome measures were the requirement of rescue analgesic, heart rates (HRs), mean arterial pressure (MAP), and side effects including PONV, sedation, dry mouth, blurred vision, and hallucinations. All the outcomes except the hemodynamic variables (HR and MAP) were investigated at baseline (at occurrence of CRBD), intensity of CRBD were evaluated at 30 min, 1, 2, and 4 h after administration of the study drug and recorded as mild (reported by the patient only on asking), moderate (reported by the patient without asking), or severe (reported by the patient without asking and accompanied by behavioral responses). Behavioral responses were in the form of flailing limbs, strong vocal response, and trials to remove the catheter.[5] During each evaluation, the patient was asked to determine whether the pain was related to CRBD or to the wound of surgery. HR and MAP were recorded at 5, 10, and 20 min and 1 h after giving the study drugs. The severity of CRBD was recorded using VAS score ranging from 0 (no discomfort) to 100 (most severe discomfort). The rescue analgesic (fentanyl 50 μg) was administered when the postoperative pain on VAS crossed 30 despite the regimen of analgesia and the amount of rescue analgesics needed during

the study period was recorded. Sedation was evaluated using a modified Observer's Assessment of Alertness/Sedation score[10] at baseline, 30 min, and 1 h after administration of the study drug.

The sample size was estimated based on a previous study[7] and assuming that the treatment would decrease the severity of bladder discomfort by 30%. Power analysis with α error = 0.05, β = 0.8 showed that we would need to study 25 patients in each group. The sample size was increased by 20% for any dropouts. We therefore enrolled thirty patients in each arm; the software used was PS power and sample size calculation software program.

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22. Data were summarized using a mean ± standard deviation. Comparisons between groups were done by unpaired *t*-test. For comparison of serial measurements within each group, repeated measures ANOVA was used. $P < 0.05$ were considered statistically significant.

Results

One hundred and twenty-two male patients were recruited between August and September 2015 and 62 patients were excluded from after enrollment because they did not complain of CRBD during recovery [Figure 1]. Therefore, the data of the remaining sixty patients (30 in the ketamine group and 30 in the hyoscine group) were analyzed. Data on patients, surgeries, and anesthesia are presented in Table 1. There was a significant difference between the two groups in the severity of CRBD measured by VAS score only at 30 min after drug administration where it was higher in ketamine group compared to hyoscine group, there was no significant difference between the two groups at other time points [Table 2].

There was a statistically significant rise in HR in hyoscine group patients compared to ketamine group over time ($P < 0.001$), whereas no difference was observed in mean arterial pressure [Figures 2 and 3].

Moreover, there was a significant difference between the two groups regarding the level of sedation where it was lower in ketamine group compared to hyoscine group ($P < 0.001$), which was assessed by modified observer's assessment of alertness/sedation score [Figure 4].

Discussion

Postoperative CRBD is a common problem in the PACU or ward and the incidence of its occurrence at 1 h postoperatively is reported to be 55-63% in male patients.[5] Most patients complained of an urge to void and suffered from a discomfort in the suprapubic area. Therefore, it is recommended to prevent or treat CRBD in male patients who undergo intraoperative bladder catheterization.

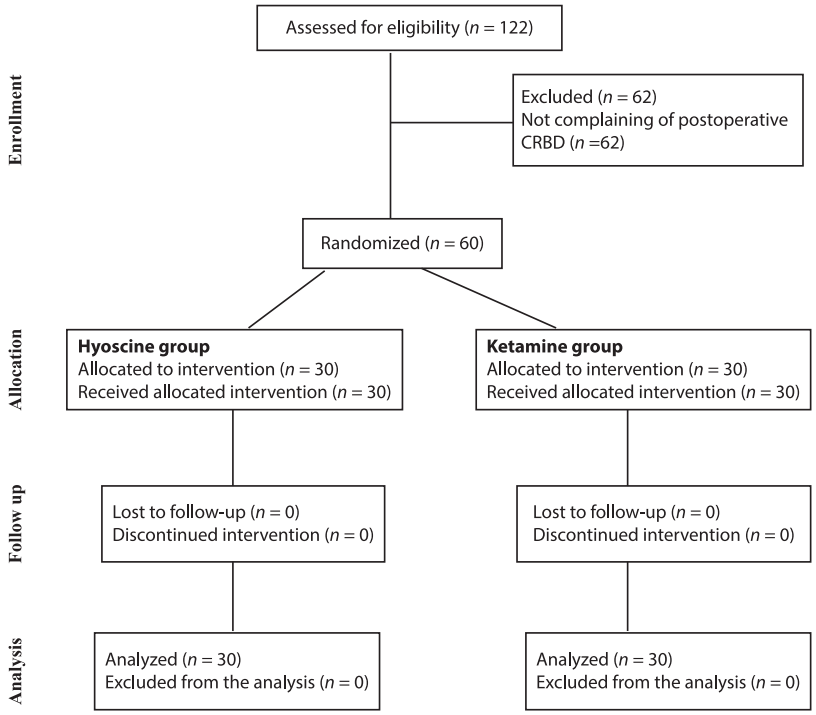

Figure 1: CONSORT flow participant diagram

Table 1: Data on patients, surgeries, and anesthesia

Parameter	Ketamine group (n = 30)	Hyoscine group (n = 30)	P
Age	44.5±10.2	42.2±10.1	0.390
ASA	1.3±0.5	1.4±0.5	0.599
Weight	75.3±3.7	75.6±3.5	0.724
Height	173.4±3.5	173.2±4.0	0.812
Duration of surgery	101.8±9.8	103.8±8.9	0.395
Duration of anesthesia	114.0±10.4	113.8±8.9	0.936
Total dose of fentanyl (μg)	172.3±21.7	173.3±20.7	0.982
Type of surgery (%)			
Abdominal	9 (30)	9 (30)	1
Orthopedics	8 (26.7)	8 (26.7)	1
Spine	7 (23.3)	8 (26.7)	0.91
Others	6 (20)	5 (16.6)	0.88

Data are presented as mean ± SD or numbers (%). ASA = American Society of Anesthesiologists, SD = Standard deviation

Table 2: Severity of catheter-related bladder discomfort (VAS), after administration of ketamine or hyoscine

Time	Ketamine group (n = 30)	Hyoscine group (n = 30)	P
Baseline	78.8±7.9	78.5±7.8	0.857
30 min after injection	44.5±7.7	36.0±8.6	<0.001
1 h after injection	28.9±4.9	31.3±8	0.172
2 h after injection	20.4±2.9	22.2±4.5	0.066
4 h after injection	19.2±2.6	17.7±3.6	0.071

Values are given as mean +/- SD, CRBD = Catheter-related bladder discomfort, VAS = Visual analog scale (0 = No pain, 100 = The worst possible discomfort), SD = Standard deviation

Ketamine (a phencyclidine derivative) is known to interact with multiple receptors, including *N*-methyl-D-aspartate (NMDA) and non-NMDA glutamine receptors and opioid receptors, nicotinic, and muscarinic cholinergic receptors.[8] Ketamine in a subanesthetic dose (0.25 mg/kg) has an analgesic effect. This effect might be synergistic with its antimuscarinic effect leading to decreased incidence and severity of CRBD.[8] Ketamine given I.V. as a treatment modality for CRBD has an advantage as it has an immediate onset of action (within 30 s and the maximum effect occurs in about 1 min).[8]

Hyoscine 20 mg I.V. has been used to treat abdominal cramps and GI spasm.[9] It has a high affinity for muscarinic receptors located on the smooth muscle cells of the GI tract and relaxes them. The mechanism by which hyoscine relieves CRBD may be explained by its antimuscarinic and spasmolytic properties and also a relaxant effect on the bladder. M2 and M3 muscarinic receptors subtypes are responsible for detrusor muscle contraction of the

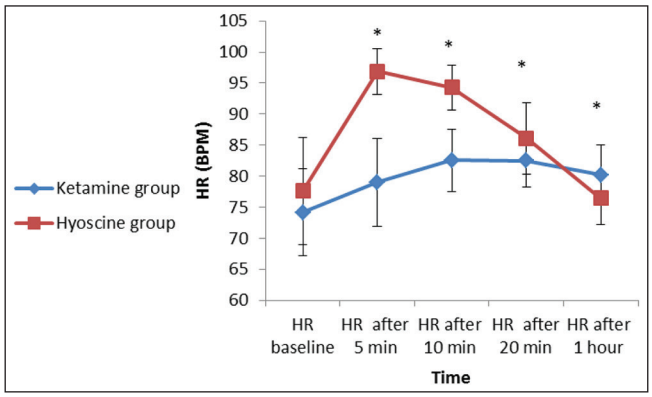

Figure 2: Heart rate (beat/min) over time data are expressed as mean and standard deviation, **P* value is significant

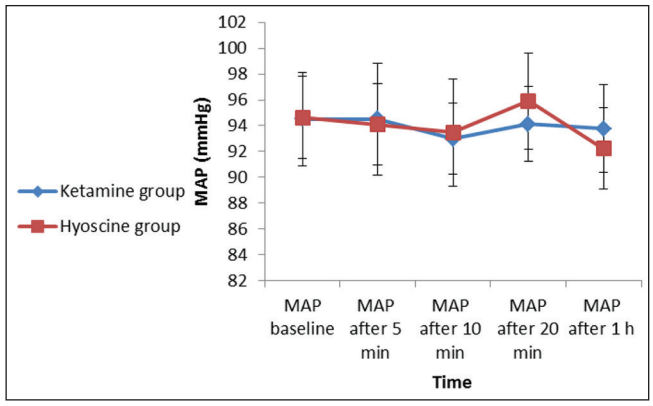

Figure 3: Mean arterial blood pressure over time, data are expressed as a mean and standard deviation

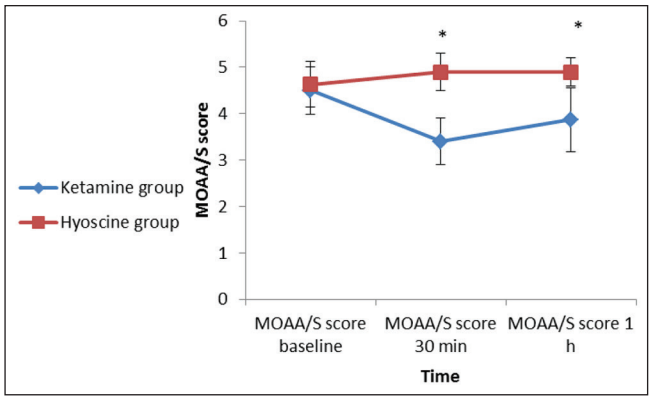

Figure 4: Modified observer's assessment of alertness/sedation score: 5, respond readily to name spoken in normal tone; 4, lethargic response to name spoken in normal tone; 3, responds only after mild prodding or shaking. Data are represented as mean and standard deviation, **P* value is significant

bladder,[11-13] and hyoscine is known to have a high affinity for human M2 and M3 muscarinic receptors subtypes. The onset of I.V. hyoscine is about 9 min with a peak action at 20-60 min and an elimination half-life ranging from 1 to 5 h.[9] The mechanism by which hyoscine relieves CRBD may be explained by its antimuscarinic and spasmolytic effects and also a relaxant effect on the bladder.[9]

In the present study, we randomized patients who complained spontaneously of CRBD on arrival to PACU (i.e., moderate and severe CRBD); the incidence of CRBD of all patients assessed for eligibility was 49.2% for moderate and severe CRBD. This was done with a view to evaluating the efficacy of ketamine or hyoscine as a treatment modality for CRBD of moderate and severe nature. We intentionally did not evaluate the effect of ketamine or hyoscine therapy on mild CRBD (reported by the patient only on questioning) to avoid bias.

The main results of the present study are both drugs ketamine and hyoscine are effective in treatment of postoperative CRBD with favorable effects of hyoscine in the first 30 min.

In a similar study, Agarwal *et al.*,[7] who used ketamine to treat postoperative CRBD in a prospective, randomized, placebo-controlled, and double-blind study, concluded that I.V. ketamine (250 μg/kg) reduces both its incidence and severity of CRBD, and suggested that a subhypnotic dose of ketamine is an effective and safe modality for the treatment of postoperative CRBD.

Also in a similar study, Ryu *et al.*[6] studied the efficacy of butylscopolamine for the treatment of CRBD in a prospective, randomized, placebo-controlled, double-blind study and concluded that butyl scopolamine 20 mg when administered I.V. after complaint of CRBD during recovery reduced both the severity of CRBD and the need for rescue analgesics without adverse effects in patients undergoing urological surgeries. But we compared the effects of ketamine and hyoscine in nonurologic procedures to avoid bias of pain originating from urological aspects.

Limitations of this study included that a single dose of either 20 mg hyoscine or 0.25 mg/kg ketamine was used in this study. The study did not evaluate the dose–response effects of both drugs for the treatment of CRBD. Other limitation I.V. hyoscine was effective for the treatment of CRBD as an antimuscarinic agent, but an inhibitory action of hyoscine on the activity of the detrusor muscle of the bladder has not been reported in animal or human studies. Moreover, opioid analgesics used for the management of postoperative pain can mask symptoms of CRBD, and there is no report that opioids are effective in the treatment of postoperative CRBD. Moreover, there was no control group but justification for this it was not appropriate to leave patients with CRBD without treatment.

Conclusion

The severity of CRBD was significantly decreased after administration of both hyoscine 20 mg I.V. and ketamine 0.25 mg/kg without serious adverse effects.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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