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CATHETER RELATED BLADDER DISCOMFORT

COMPARISON OF KETAMINE AND TOLTERODINE;FOR REDUCTION OF CATHETER RELATED BLADDER DISCOMFORT.

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ABSTRACT: Introduction: Bladder discomfort is a common side effect after surgical procedures that involve either extensive bladder dissection or prolonged postoperative catheter drainage. Various treatments have been tried with varying degrees of success for managing this adverse effect. In this study we compared the efficacy of ketamine and tolterodine in prevention of catheter induced bladder discomfort. **Patients and Methods:** Three hundred patients who were scheduled for open prostatectomy or transurethral resection of prostate (TURP) were randomized into three groups. The first group received placebo, the second one received tolterodine before operation, and the third group received ketamine250ig/kg IV, just before the anesthesia induction. Bladder discomfort was assessed by anesthesiologist who was unaware of the type of medication. The assessment was done on arrival in the post anesthesia care unit (PACU) and then at 0, 1, 2 and 6 hours after patient's consciousness. Severity of discomfort was recorded as none, mild, moderate, or severe. The absence or presence of adverse effects were recorded. The data were analyzed using SPSS and Pearson chi-squared and ANOVA tests were applied for further statistical evaluations. **Results:** Both the incidence rate of bladder discomfort and its severity in the control group was significantly higher compared with ketamine and tolterodine groups (P< 0.001). Comparing the ketamine and tolterodine groups, tolterodine had lead to lesser degree of bladder discomfort at 0, 1, 2 hours, while ketamine was more effective at 6 hours. **Conclusions:** Pretreatment with either ketamine or tolterodine is effective in decreasing the incidence and severity of catheter related bladder discomfort in patients under going open prostatectomy or TURP.

Key words: Tolterodine, ketamine, bladder discomfort.

INTRODUCTION

Bladder discomfort is a common and troublesome side effect of surgical procedures in which either extensive bladder dissection or prolonged postoperative catheter drainage are applied[1-3].

Various treatments have been tried with varying degrees of success for management of this adverse effect.

Current used treatment modalities for this side effect are opioids, anticholinergics, musculotropic bladder smooth muscle relaxants, and local anesthetics[4-5]. Although the overall severity of bladder spasm is reduced when patients are treated with the mentioned methods, spasms can still persist. Furthermore, excessive use of opioids and anticholinergic medications can lead to other complications including; illeus, respiratory depression, sedation, emesis, and urinary retention[6-7]. Two widely

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used drugs in this case are ketamine and tolterodine[4, 8-9].

Ketamine, which is widely used agent in anesthesiology, has been shown to be effective in the treatment of catheter related bladder discomfort (CRBD) when it was applied for the relief of postoperative shivering[10-11]. Furthermore, ketamine in low dose can play role in alleviation of postoperative pain[12-13]. Meanwhile, tolterodine, a competitive muscarinic receptor antagonist, has been used successfully to treat overactive bladder and mixed urinary incontinence[14-17]. Since there is no ideal treatment or prevention strategy for this complication, in this study we aimed to compare the efficacy of ketamine and Tolterodine with each other and with placebo in reduction of CRBD.

MATERIALS AND METHODS

Study design and participants: In a double-blinded randomized clinical trial 300 patients were allocated in three groups (placebo, ketamine and tolterodine). Exclusion criteria are illustrated in the table-I.

After approval from the institute's ethics committee and written informed consent from the patients, patients were randomized with the help of a computer-generated table of random numbers into three groups. Group C received placebo "normal saline and placebo tablet", group T received tolterodine tablet 2 mg PO one hour before operation in addition to normal saline, and group K received ketamine 250 microgram/kg IV and a tablet of placebo, just before the induction.

The patients received oral Diazepam 5mg the night before the operation and 2 h before the induction of anesthesia. Induction of anesthesia was done with fentanyl 3 microgram/kg, midazolm 1-1.5 mg and propofol 2 mg/kg. Atracurium 0.5 mg/kg administered as muscle relaxant. Patients were catheterized intraurethral (for TURP) or suprapubic (for open prostatectomy) using a 20 Foley catheter and its balloon was inflated with 40 ml of normal saline. Anesthesia was maintained using 60% nitrous oxide in 40% oxygen and propofol infusion of 50-150 microgram/kg/min and intermittent fentanyl and atracurium as required. At the end of the surgery, the muscle relaxant was reversed using neostigmine 0.05 mg/kg and atropine 0.025mg/kg then patients were transferred to the PACU. In the PACU, all patients were observed and given pethedine on demand.

MEASUREMENTS

Bladder discomfort (urge to pass urine or discomfort in suprapubic region) was assessed by an anesthesiologist who was unaware of the type of medication received by the patient, on arrival in the PACU and after patient's consciousness at 0 h and again at 1,2and 6 h later.

Severity of discomfort was recorded as mild (reported by the patient only on questioning), moderate (reported by the patient without questioning; not accompanied by any behavioral responses), or severe (reported by the patient and accompanied by behavioral responses such as flailing limbs, strong vocal response and attempts to remove the catheter). The absence or presence of adverse effects was recorded. For ethical aspect patient with severe pain was treated by 25 mg intravenous pethedine as required.

STATISTICAL ANALYSIS

The data were analyzed by using SPSS via Pearson chi-squared and ANOVA tests. The statistical significance was considered as p value less than 0.05.

RESULT

The information of three hundred eligible patients was considered for final analysis. The mean age of patients in ketamine, tolterodine and control group was 64.18, 64.59 and 67.93 respectively and there was no significant difference in the demographic characteristics of patients including; age, gender and duration of operation.

Table II shows the overall incidence of bladder discomfort that was significantly lesser in ketamine and tolterodine groups compared with the control group (P< 0.001).

As it is showed in table-III; comparing the ketamine and tolterodine group, in reducing CRBD, revealed that tolterodine had better effect at 0, 1, 2 hour than ketamine which was more effective at 6 hours (P-value <0.001).

None of patients in three groups had diplopia, unpleasant dreams, respiratory distress or blurred vision. But still side effects such as nausea, dry mouth, vomiting, facial flushing, hallucination, and abdominal discomfort were present. The difference in occurrence of adverse effects in three groups demonstrated in figure 1. Three groups did not differ significantly regarding these side effects. The only significant difference was in abdominal discomfort that was obviously higher in ketamine group ($P<0.05$). Administration of narcotics reduced significantly in ketamine and tolterodine groups compared with control group ($p<0.001$).

Table-I. Exclusion criteria

- Patients who were not cooperative due to sedation
- Patients who had problems like those caused by ketamine and tolterodine such as nausea, vomiting, dry mouth, blurred vision, facial flushing, unpleasant dreams, hallucination, diplopia or respiratory distress.
- 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
- Functional or anatomical impairments in central nervous system
- Cardiovascular, hepatic or any psychiatric disease

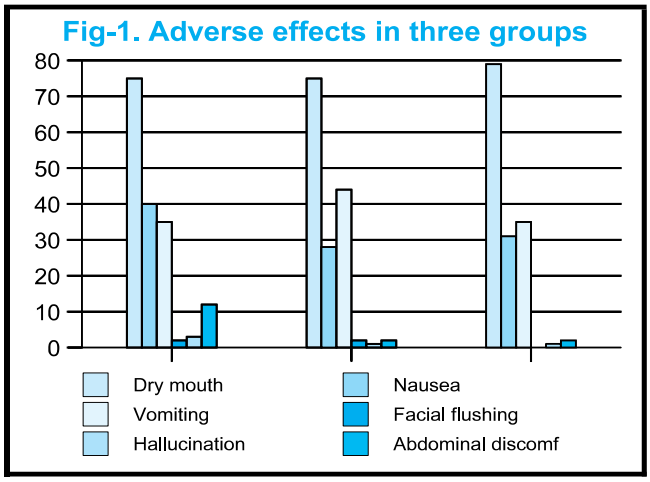
Table-II. Incidence rate of CRBD in three groups

Time (h)	0 (After attaing consciousness)			1 (After one hour)			2 (After two hours)			6 (After six hours)		
Groups	**C**	**K**	**T**	**C**	**K**	**T**	**C**	**K**	**T**	**C**	**K**	**T**
No pain	10%	29%	50%	1%	3%	21%	1%	0%	8%	1%	15%	2%
Mild pain	55%	45%	42%	21%	44%	56%	9%	48%	60%	4%	50%	24%
Moderate pain	26%	12%	5%	63%	53%	18%	64%	52%	30%	59%	35%	54%
Severe pain	9%	16%	3%	15%	0%	5%	26%	0	2%	36%	0%	20%
P-value	p<0.001			p<0.001			p<0.001			p<0.001		

Table-III. Comparing the efficacy of ketamine versus tolterodine

	0 (After attaing consciousness)		1 (After one hour)		2 (After two hours)		6 (After six hours)	
Groups	**K**	**T**	**K**	**T**	**K**	**T**	**K**	**T**
No pain	29%	50%	3%	21%	0%	8%	15%	2%
Mild pain	43%	42%	44%	56%	48%	60%	50%	24%
Moderate pain	12%	5%	53%	18%	52%	30%	35%	54%
Severe pain	16%	3%	0%	5%	0	2%	0%	20%
P-value	p<0.001†		p<0.001†		p<0.001†		p<0.001*	

† Efficacy in reduction of CRBD in tolterodine group was significantly higher
** Efficacy in reduction of CRBD in ketamine group was significantly higher*



DISCUSSION

Patients suffering from CRBD cannot always be successfully managed, since there is no ideal treatment for this complication[7,18]. This study is perhaps first survey that compares the efficacy of ketamine and tolterodine in reducing CRBD. Our study demonstrates a significant reduction in the incidence and severity of catheter related bladder discomfort in postoperative period in patients who had received either ketamine or tolterodine.

The increase of incidence of bladder discomfort at 2 and 1 hour compared with 0 hour could have been attributed to the fact that, on arrival in the PACU, patients might not have been able to comprehend and report their discomfort properly because they were still drowsy due to residual effect of anesthetic medications.

The maximum incidence of bladder discomfort occurs at 2 hours after arrival in the PACU. We observed that tolterodine had better effect in reducing CRBD at 0, 1, 2 hour after the arrival in PACU than ketamine which was more effective at 6 hour while Agarwal and colleagues observed that ketamine administrated intravenously as a treatment modality for CRBD has an advantage over tolterodine as it has an immediate onset of action , within 30 seconds 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[8,19]. Indeed, there are several differences between the two studies such as; we used ketamine before operation while the other study used it after surgery, additionally our study was conducted among TURP and open prostatectomy patients, whereas Agarwal selected patients who had elective percutaneous nephrolithotomy. We, in the line of previous study by Bell RF et al, gave ketamine preoperatively. Bell RF stated that administration of ketamine before surgical incision (0.5mg/kg bolus followed by continuous infusion with rate of 10ìg/kg/min) can provide better pain relief in comparison with administration of ketamine post-operation[12]. Agrawal et al, similar to our findings, observed that application of tolterodine and oxybutiline can play an efficient role in reduction of CRBD when applied after operation[1,8,19].

We also witnessed high incidence of dry mouth within the three groups (79% in control group and 75% in both the tolterodine and the ketamine group) which might be attributed more to the inappropriate hydration through surgery rather than drug side effects.

There were no significant differences in most of the side effects caused by these two drugs such as nausea, vomiting, facial flushing, hallucination, respiratory distress, diplopia, blurred vision, and unpleasant dreams. The only significant difference was higher frequency of abdominal discomfort in ketamine group compared to both tolterodine and control group. It is worth noting that this problem was seen more in the subject undergone open prostatectomy than in those who had TURP. Accordingly it can be postulated that abdominal incision was accused for this side effect.

The administration of narcotics was reduced significantly in those who placed in tolterodine group; the reason behind this might be a delay in analgesic effect of ketamine, which is 6 hours after administration.

Our study has certain shortcomings. For instance, in this study we investigated the response of a single dose of ketamine and tolterodine rather than the dose response titration in postoperative period.

In conclusion we introduce tolterodine as a more

convenient agent in reduction of CRBD, since it can be tolerated better due to lesser degree of side effects and is more effective in initial hours after surgery.

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