

Intraoperative Administration of Diphenhydramine Attenuates Postoperative Catheter Related Bladder Discomfort in Patient Following Percutaneous Nephrolithotomy

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ABSTRACT

Background: We intend to evaluate the effect of intraoperative diphenhydramine administration on incidence and severity of catheter related bladder discomfort (CRBD) and pain after percutaneous nephrolithotomy.

Methods: In a double blind randomized clinical trial, adult male patients undergoing percutaneous nephrolithotomy were enrolled. They were randomized into two groups by a computerized digital random allocation method. Before anesthesia induction, group D (Diphenhydramine group) (n = 48) received 5 ml normal saline containing 0.5 mg/kg of diphenhydramine intravenously. In group C (Control group) (n = 48), 5 ml of normal saline was injected in the same manner. Induction and maintenance of anesthesia were identical in both groups. The incidence and severity of CRBD and postoperative pain were assessed at recovery room.

Results: The incidence of CRBD was significantly lower in group D than in group C (14% vs. 63%, P=0.001). The severity of CRBD was milder in group D in comparison to group C (P<0.05). Postoperative pain score was significantly lower in group D (P<0.05).

Conclusion: Intraoperative administration of diphenhydramine is an effective practice for the prevention of CRBD after percutaneous nephrolithotomy in male patients and can reduce postoperative pain as well.

Introduction

Percutaneous surgery although it seems easy, has many risks and problems. One of the problems is the confirmation of the stone inside the system so as not to be confused with other calcifications [1]. For this reason, ureteral catheter placement has become part of this technique. Placement of two catheters (ureter and urethra) exacerbates the symptoms of lower urinary irritation, which in patients with similar symptoms such as chronic prostatitis, neurogenic bladder, and enlarged prostate, significantly reduce quality of life [2].

At the end of the surgery, when the anesthetic is withheld and the patient is extubated, in addition to the surgical site pain, the annoying sensation that bothers the patients is the urinary catheter especially in males. The symptoms are similar to those of overactive bladder (urinary frequency and urgency, with or without urge incontinence), also burning sensation and pain in the suprapubic and penile areas, which result from involuntary contractions of the bladder mediated by muscarinic receptors [3]. Agitation and disorientation are also observed more frequently in the early recovery phase of general anesthesia in patients with catheter related bladder discomfort (CRBD) and causes traumatizing attempts to remove the urethral catheter, causing urethral

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injury and subsequent urethral stricture [4]. It can lead to dangerous events such as removal of intravenous lines and other catheters, and even severe injuries from falling down of agitated patient on the post anesthetic care unit (PACU) floor. For this reason, some clinicians have considered using ultrasound without retrograde pyelography for this surgery [5].

Several risk factors related to CRBD has been revealed such as male gender and Foley catheter [6]. Incidence of CRBD in male adults has been reported about 25 % to 50% [6]. After extubation in percutaneous nephrolithotomy (PCNL) patients admitted to the PACU have suffered from agitation more than other surgical patients, due to double urinary catheters (urethral and ureteral catheter) which is called CRBD. The mechanism of CRBD is mediated by muscarinic receptor activation, which increases acetylcholine release and then causes the detrusor muscles of the bladder to contract involuntarily [7]. Therefore, agents with anticholinergic or analgesics activities such as tramadol, hyoscine, N-butyl bromide, Gabapentin, Pregabalin and also anesthetics including ketamine have been successfully studied for the prevention and treatment of CRBD [8, 9]. Despite numerous researches on the prevention and treatment of CRBD in adult patients, many studies are still ongoing.

In addition to muscarinic receptors, histaminic receptors are another assumed mechanism of CRBD. Histamine released by mast cells in periphery plays important role in hypersensitivity development. Findings suggest that low concentrations of histamine acting on sensory neurons, produce pruritus with a high concentration leading to pain [10]. Diphenhydramine is a first generation H1 receptor antagonist that is used in perioperative period for the management of allergic reactions and prevention of postoperative nausea and vomiting [11-12]. It also has sedative effects and anti-muscarinic activity and can be used intravenously during the anesthesia [13].

In this study we hypothesized that intraoperative injection of diphenhydramine combination before induction of anesthesia would reduce the incidence of CRBD in male adult patients undergoing percutaneous nephrolithotomy and it may also diminish the postoperative pain and CRBD.

Methods

This, randomized double-blind study was conducted on 100 male patients undergoing Percutaneous nephrolithotomy surgery.

Inclusion criteria were male patient candidate for elective percutaneous nephrolithotomy (PCNL) surgery and had both urinary catheter and ureteral stent at the end of surgery. Exclusion criteria were drug addiction, glaucoma, history of diphenhydramine intolerance or hypersensitivity and patients who had DJ stent instead of ureteral stent. Male patients, whom were scheduled for

PCNL surgery, were divided into two groups (group D and group C) at the operating room entrance by a computer digital randomization program. After standard monitoring and before induction of anesthesia diphenhydramine 0.5 mg/kg diluted with normal saline to reach 5ml was injected intravenously and in the control group, the same volume of normal saline was injected by an anesthesiologist. General anesthesia regimen was identical for both groups. In both group after positioning of patients, morphine 0.1mg/kg intravenously administered and 15min before extubation 1gr intravenous acetaminophen was infused.

A lidocaine containing lubricating gel was used to lubricate urethra after placing the ureteral catheter. Then bladder catheterization was done with a 16 French Foley catheter and its balloon was inflated with 10 ml distilled water and ureteral catheter was fixed to it. The catheter was fixed in the medial side of the thigh with an adhesive tape without any traction and was always left for free drainage. Percutaneous access was obtained while the anesthetized patient was placed in prone position.

After extubation the incidence and severity of CRBD was recorded as follows: (1) feeling of urination, (2) feeling of urination and try to move, (3) agitation, strong vocal response, or attempt to pull out the catheter. The severity of postsurgical pain was assessed on arrival to recovery room and was checked 20 minutes after surgery by using Visual Analog System (VAS) score system with 0 standing for "no pain" and 10 for "the worst pain possible". The study lasted from extubation to 20 minutes after entering the recovery room (PACU).

The primary outcome was the incidence and severity of CRBD at PACU, and secondary outcome was the postoperative pain severity. As a rescue treatment for surgical site pain with VAS score ≥ 4 , Fentanyl (50 microgram) and for CRBD, Ketamine 0.5 mg/kg was given for CRBD greater than 2. With blind coding system, anesthesiologist, urologist and personnel in PACU were not aware of patients group.

To find the sample size, due to the high incidence of CRBD after surgery, near 60% in male patients [6] and assuming that, prophylactic administration of diphenhydramine reduces the incidence of CRBD by 25%, 45 patients in each group are required for statistically significant diagnosis with $\alpha = 0.05$ and $\beta = 0.10$.

After data collection, the statistical software SPSS v.17 was used for data analysis. P values of 0.05 or less were considered statistically significant.

The differences in the incidence and severity of CRBD and postoperative pain scores between two groups were analyzed by Chi square test. The severity of pain was measured on a VAS score and analgesic requirements were compared between groups by Student's t test.

This study was approved by the Ethical Board of affiliated university and was registered at <http://irct.ir> (registration number IRCT 20130304012695N7).

Results

In the study one hundred patients were assessed for eligibility and 96 subjects were enrolled and completed the study protocol (Figure 1). There were no significant differences between two groups in patients' characteristics and surgery durations (Table 1).

The incidence of CRBD postoperatively at PACU was significantly different between D and C groups (14% vs 63%, $P=0.001$). Therefore, the absolute risk reduction in

terms of CRBD with diphenhydramine treatment was near 50%. Diphenhydramine treatment also decreased the severity of CRBD in recovery period ($p < 0.05$) (Table 2). The severity of postoperative pain score was assessed by VAS, as D group showed significantly lower pain scores ($p < 0.05$) (Table 2).

Ketamine requirement for CRBD and Fentanyl for surgical site rescue treatments were significantly lower in diphenhydramine (Table 2). There were no postoperative nausea and vomiting, in both groups.

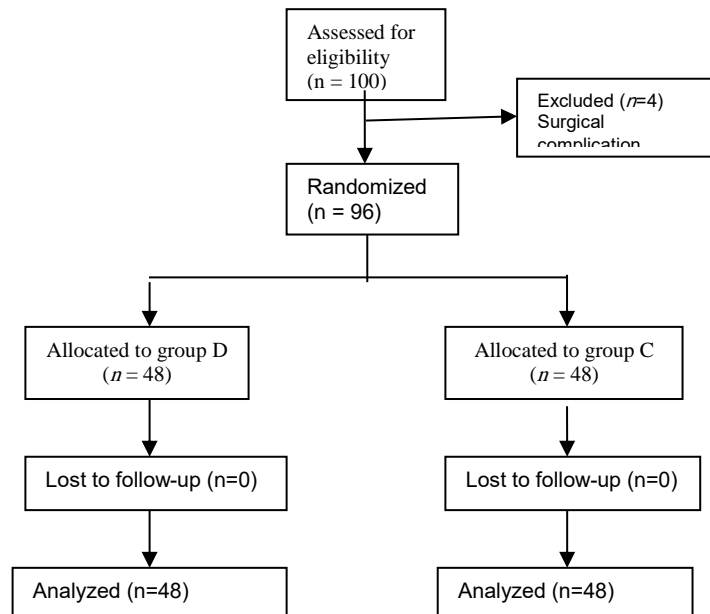


Figure 1- Study Flow Diagram: D, Diphenhydramine; C, Control

Table 1- Demographic data and duration of surgery

Variables	Diphenhydramine (N= 48)	Control (N= 48)	P value*
Age(yr)	40.33±7.27	41.37±9.44	0.1
Weight(kg)	76.9 ± 8.6	71.6 ± 9.9	0.7
Duration of surgery (min)	99.7 ± 34.0	94.2 ± 38.7	0.72

Data are presented as mean ± standard deviation (SD)

* Statistics: unpaired t test or Chi square test, as appropriate

Table 2- Incidence and severity of catheter-related bladder discomfort and pain score in recovery

Variables	Diphenhydramine group (N = 48)	Control group (N = 48)	P value *
CRBD n (%)	7(14.5)	30(62.5)	0.001
Severity, n (%)			
Mild	4(8.3)	12(25)	
Moderate	3(6.2)	11(23)	
Severe	0	7(14.5)	
Ketamine n (%)	6(12.5)	28(58)	0.001
VAS1 score (mean ± SD)	2.42±0.81	4.87±1.07	<.001
Fentanyl n (%)	14(29)	38(79)	
VAS20 score (mean ± SD)	1.25±0.43	2.24±0.85	<.001

Data presented as number (%) or mean ± standard deviation

* Statistics: Student's t test, Chi square or Fisher's exact test as appropriate

Discussion

The results of our clinical study show that intraoperative administration of 0.5 mg/kg diphenhydramine intravenously in the anesthetic induction effectively decreases the incidence and severity of postoperative catheter related bladder discomfort in percutaneous nephrolithotomy with two urethral catheters. In addition, this treatment reduced the severity of postoperative pain in recovery period.

Diphenhydramine, as an antihistamine, usually is used for treatment of allergic reactions and post-operative nausea and vomiting. It also has the analgesic and antinociceptive effects and can modulate pain sensations while added to an opioid drug (like morphine which has used in our study). Central anticholinergic and antihistaminic effects of diphenhydramine cause drowsiness and sedation [12]. In our study we administered lower doses of diphenhydramine in contrast with prior researches and also, we have added 0.1 mg/kg morphine and one-gram paracetamol to the drug regimen to gain better effects with lesser side effects. In the Ergenoglu study, the prophylactic effect of intravenous acetaminophen 30 minutes before the end of PCNL surgery on CRBD was investigated, and this drug alone reduced incidence of CRBD from 87% to 65% in the early recovery time [13,14]. We used morphine at the beginning of the operation and a low-potency analgesic, acetaminophen at the end of the surgery in both groups. Finally, the addition of diphenhydramine at the beginning of anesthesia appears to synergistically amplify the effects of other two drugs and helps to reduce the incidence of CRBD postoperatively. Diphenhydramine has an onset of effect within 3-4 minutes after intravenous administration and its duration of action takes 4-8 hours [15,16]. This prolonged duration of action, which may extend beyond the anesthesia period, and its sedative properties may help to reduce postoperative CRBD and surgical site pain intensity.

Diphenhydramine by anti-muscarinic activity diminishes both the incidence and severity of postoperative CRBD after gynecologic surgery. In terms of the prevalence of CRBD, diphenhydramine was able to reduce its incidence from 40% to 10% in recovery room [17]. These results seem different from the YYu Li study. They used just 30 mg diphenhydramine intravenously after induction of general anesthesia in patients undergoing gynecologic laparoscopic surgery. The incidence of CRBD at 1 hour postoperatively was not significantly different between diphenhydramine and control groups (41.3 vs. 51.2%) [18]. Our study is different from them in some aspects because it has covered the two major CRBD risk factors at the same time, on one hand all of the patients in our study were male subjects and on the other hand, because of the type of PCNL surgery, all patients were catheterized with a 16

F Foley catheter and a ureteral stent. By considering these differences between our study and prior researches, it seems that our study is more focused on the CRBD risk factors and its results could be more reliable and practical.

Many drugs with anti-muscarinic properties such as oxybutynin, tolterodine, ketamine, gabapentin, and tramadol have been investigated for the prevention and treatment of CRBD [19-22]. However, the peripheral and central anti-muscarinic effects of these drugs are able to reduce these symptoms to some extent and each of these compounds alone could reduce the incidence of CRBD by about 20 to 25 percent postoperatively [23,24, 25].

Conclusion

Intravenous administration of 0.5mg/kg diphenhydramine before anesthesia induction in PCNL surgery reduced both the incidence and severity of postoperative CRBD and surgical site pain without significant side effects.

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