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ORIGINAL ARTICLE

Efficacy of Gabapentin for Prevention of Postoperative Catheter-related Bladder Discomfort in Patients Undergoingopens prostatectomy

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Key words:*Gabapentin, Catheter-related Bladder Discomfort (CRBD), Open prostatectomy*

ABSTRACT

Introduction: Catheter-related bladder discomfort (CRBD) secondary to catheterization of urinary bladder is distressing. The aim of our study was, to evaluate gabapentin for preventing CRBD and pain severity in patients undergoing open prostatectomy.

Methods: Forty-two patients undergoing open prostatectomy were randomly allocated to 2 intervention and placebo groups. First group received stat dose of 300 mg and 100 mg q8 h of gabapentin and the other one received placebo. The patients were observed for the incidence and severity of CRBD in the postoperative period and pain severity (VAS index). Amount of morphine that patient might need, were recorded. This trial is registered at irct.ir at number IRCT2014063017811 N4.

Despite expected, intervention cases showed significantly decrease in incidence and severity of CRBD at hour 6 and 24 after surgery compared with placebo subjects. Although significant correlation was observed with pain severity and patient who received gabapentin showed lower mean of VAS score in comparison with placebo group ($P \leq 0.05$).

Conclusions: Gabapentin probably controls detrusor muscle over activity by modulating the afferent input from the bladder and the excitability of the sacral reflex center. Gabapentin decreased the postoperative pain severity as well as morphine requirement and reduced incidence and severity of CRBD at 6 and 24 hours after the open prostatectomy. *JOURNAL OF IRANIAN CLINICAL RESEARCH* 2015;1(2):*72-79*

INTRODUCTION

Catheter-related bladder discomfort (CRBD) secondary to an indwelling urinary catheter is common in patients undergoingopen prostatectomy [1]. Since there is more manipulation, the incision is nearby source of CRBD and for all patient improvise two foley and supra pubic catheter thicker than 18 F which recognized as a CRBD risk factor as well as male gender [2].

"Symptoms of CRBD mimic those of an overactive bladder (OAB) i.e., urinary frequency, urgency, with or without urge incontinence" [3]. There is variety of mechanisms that underlay overactive bladder. Many studies suggest the possible role of bladder receptors, afferent pathways and spinal cord interneurons [4]. Therefore, modulation of them has been proposed as a possible approach to control CRBD symptoms, which are attributed to involuntary detrusor smooth muscle of bladder contractions [5].

The antimuscarinicdrugs are today the main treatment of CRBD instead their variable success because of poor selectivity for the bladder. These drugs cause troublesome adverse effects, such as ileus, dry mouse and blurred vision that somewhat limit their usefulness [6,7].

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Intervention with ketamin in subhypnotic dose [8], tramadol [3], butyl scopolamine [9] have also been effective for prevention of postoperative CRBD. However, the effectiveness of these drugs was limited to first hours after operation and they showed many annoying adverse effects.

Gabapentin is a structural analogue of amino butyric acid but it does not interact with GABA [10]. It is approved as an anticonvulsant but has significant pain control properties widely used for the treatment of peripheral neuropathic pain through inhibitory activity on afferent C-fibers nerve activity [5], which may play a role in certain cases of urge incontinence, OAB, and sensory urgency [11]. Gabapentin was well tolerated even in high dose of 3000 mg in a day [10]. Gabapentin also was safe in children with neurogenic bladder [12]. Long-term treatment with 300 to 2100 mg of gabapentin was useful for treatment of refractory genitourinary tract pain [13].

Gabapentin has been effective in treating resistant cases of OAB, which are very similar to CRBD in symptoms [11, 14]. It has been used in doses up to 3000 mg for cases of refractory OAB where the conventional antimuscarinic therapy failed [10]. Pretreatment with 600 mg oral gabapentin was found to decrease the incidence and severity of postoperative CRBD in patients undergoing percutaneous nephrolithotomy (PCNL) under general anesthesia surgery, which no manipulation in bladder was done, and just an indwelling urinary catheter was fixed in each patient [14]. Low-dose triple therapy using gabapentin, amitriptyline, and a nonsteroidal anti-inflammatory drug results in a clear decrease in OAB symptoms in patients with bladder pain syndrome [15]. In addition, gabapentin significantly improved urodynamic indexes and stimulatory symptoms in neurogenic over active bladder [4,12].

An interesting aspect of considering gabapentin as a proper candidate drug for treatment of patients undergoingopen prostatectomy is its additional mechanisms of action that might be relevant for reducing pain and narcotics requirement [16, 17]. Gabapentin reduces postoperative nausea and vomiting [18].

The aim of present study was, to determine effect of gabapentin for preventing CRBD, pain severity in patients undergoing open prostatectomy, and introduce gabapentin as notable alternative of conventional modalities such as antimuscarian treatment in patients with OAB.

MATERIALS AND METHODS

Subjects

The local medical Ethics Committee approved the protocol. It was registered under IRCT number 2014063017811N4.

Patients of American Society of Anesthesiologists (ASA) physical status I-II undergoing elective open prostatectomy surgery underspinalanesthesiarequiring catheterization of the urinary bladder were included. All patients were informed of the procedures and those who signed the written consent entered the study.

Eligible patients were weighted 50–80 kg and patients with history of OAB (urinary frequency >3 times at night and > 8 times in 24 hours), neurogenic bladder, diabetes mellitus, Parkinson's disease and impaired renal function; chronic use of opiates or sedatives, antacid uptake in the past 48 hours; or hypersensitivity to amide local anesthetics or gabapentin were excluded.

Study design

In this double-blind, placebo-controlled clinical trial from 2013 to 2014 at Valiasr Hospital of Arak University of Medical Sciences, patients fasted for 8 hours before surgery and randomly received 300 mg gabapentin or matching placebo in capsule form orally, with a small sip of water, 2 hours prior to the administration of spinal anesthesia.

All medications were administered as identical capsules made of starch. The study drugs were prepared by the Department of Pharmacy and kept in opaque envelopes according to the code assigned. Executors were unaware of containers.

Patients received 0.9% normal saline at the rate of 8 ml/kg/h after shifting to the operating room. Routine monitoring by electrocardiogram (ECG), noninvasive blood pressure (NIBP), and pulse oximeter was done, and baseline heart rate, blood pressure, oxygen saturation, and respiratory rate were recorded. Patients were made to lie in left lateral position. Under all aseptic precautions, lumber puncture was performed using 26-G Quincke's needle at L2-L3 or L3-L4 intervertebral disk space. After identification of subarachnoid space by free flow of cerebrospinal fluid, 2.5 mL of 0.5% hyperbaric bupivacaine was administered at the rate of 1 ml/10 sec with no barbotage.

Immediately after administration of the drug, the patients were turned to supine position and remained in that position until the sensory block

reached its highest level. All patients received oxygen via venti-mask throughout the surgical procedure. The level of sensory block was determined by pinprick sensation tested with a 22-G blunted needle in the midline every 2 minutes after injection until the level stabilized for 4 consecutive tests, and then at every 10-minute interval until recovery to S2 dermatome. The highest dermatomal level of sensory blockade, the time to reach the highest sensory level, time to 2 segments regression, and the time to S2 segment regression were noted. The time at which the intrathecal injection finished was considered as time zero. Motor blockade was assessed by using the modified Bromage scale when maximum sensory level was achieved (considered as maximum motor block) and then at every 10 minutes until modified Bromage scale returned to zero. The anesthesiologist who administered the block and assessed the level of block was blinded to the contents of the study drug given.

Patients' heart rate and blood pressure were recorded every 3 minutes during the first 15 minutes after spinal anesthesia and then every 5 minutes until the end of surgery. Hypotension was defined as a decrease in systolic blood pressure to <90 mm Hg or a 30% decrease from the baseline. It was treated with intravenous fluid and boluses of 3 mg mephentermine. Bradycardia was defined as a decrease in the heart rate to <40 beats/min and was treated with 0.5 mg of intravenous atropine.

At the end of surgery, urinary bladder catheterization was done using a 22-Fr Foley catheter with the aid of lubricating jelly, and its balloon was inflated with 50 ml distilled water. Thereafter, the catheter was fixed in the supra pubic region with adhesive tape with traction. Traction was removed after 24 hours. In addition, an 18F supra-pubic catheter and an extra bladder 16F nelaton catheter drain were fixed. After the surgery intervention continued and patient depends on which group they belong were received gabapentin capsules 100 mg or placebo per 8 hours as a maintenance therapy until 72 hours.

The primary outcome measure was bladder discomfort which assessed at 2 ,6,24,48 and 72 h postoperatively by a physician registrar who was unaware of the type of medication received by the patient and was trained in pilot phase on 10 patients. Severity of bladder discomfort was recorded as severe (reported by the patient themselves and accompanied by behavioral responses such as flailing limbs, strong vocal response, or attempts to pull the catheter out) or moderate (reported by the patient without questioning; not accompanied by any behavioral responses). If the patient did not complain of any bladder discomfort, then the same registrar engaged the patient in a casual conversation and asked their name, occupation, and residence. Thereafter, patients were asked whether they were comfortable after surgery and if the response was yes, it was presumed that they did not suffer from any bladder discomfort. However, if patients reported that they were not comfortable after surgery, they were then asked the site/location of discomfort to distinguish between surgical pain and bladder discomfort. If patients were having bladder discomfort (urge to pass urine or discomfort in the supra-pubic region), they were labeled as having mild bladder discomfort (reported by the patients only on questioning).

Postoperative pain was assessed at the same time using a visual analog scale (VAS) score of 0–10, where 0 represented no pain and 10 represented worst imaginable pain. The number of patients requiring morphine sulfate and the total morphine consumption postoperatively up to 72 h, were also recorded postoperative nausea, vomiting during the study period also assessed as a secondary outcome measure

Statistical analysis

All data were tested for normality. Independent t-test was performed to evaluate deference between groups for age, pain at the operative site on a VAS scale, morphine requirement and vomiting frequency. Presence and severity of discomfort (mild, moderate, and severe) was analyzed by chi2 test. The package SPSS 16 (Chicago, IL, USA) was used for statistical analysis. P< 0.05 was considered as significant.

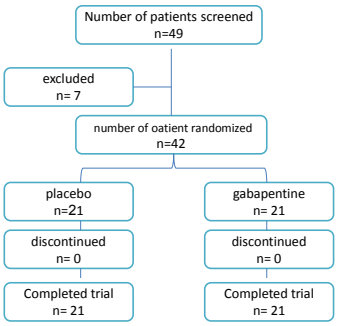

Figure 1. Consort table of our studied patients receiving gabapentin or placebo after open prostatectomy

RESULTS

Between June 2013 and March 2014, 50 patients were screened,after which 45 were found eligible for inclusion. Forty-two patientscompleted the study and enrolled into the study. Figure 1 showsthe flow of the patients.

The patients' mean age was 65.86 ± 5.50 years with a minimum of 55 and a maximum of 79 years. In the placebo group, the mean age was 66.43 ± 5.99 yr and for the gabapentin group was 66.29 ± 5.07 years. There was no significant difference between the two groups' age.

The mean patients weight was 70.19 ± 8.91 kg. In the placebo group the mean weight was 70.61 ± 9.16 kg and in the gabapentin group was 69.75 ± 8.89 and no statistically significant difference was observed.

Presence and severity of CRBD was significantly (P<0.05) reduced in the gabapentin group compared with the control group at 6 and 24 h after operation (Table 1& 2).

There were 6 (28%) patients who did not show CRBD at 6 hour and 7 (33%) patients at 24 h after surgery in comparison with 1 (4.7%) patient in placebo group at these times of following-up.

Table 1. The presence of CRBD in the gabapentin group and the control group after open prostatectomy during the first 72 hours

Variable	Groups	Present	Not present	P value
CRBD 2h	placebo	4	17	0.378
	Gabapentin	2	19	
CRBD 6h	placebo	20	1	0.038
	Gabapentin	15	6	
CRBD 24h	placebo	20	1	0.018
	Gabapentin	14	7	
CRBD 48h	placebo	16	5	0.495
	Gabapentin	14	7	
CRBD 72h	placebo	12	9	0.217
	Gabapentin	8	13	

There were no differences in CRBD presence and severity at 2, 24, 48 and 72h after surgery between the groups.

Table 2. The severity of CRBD in the gabapentin group and the control group after open prostatectomy during the first 72 hours

Variable	Groups	No symptoms	Mild	Moderate	Severe	p value
CRBD severity 2h	placebo	17	1	2	1	0.328
	Gabapentin	19	2	0	0	
CRBD severity 6h	placebo	1	13	5	2	0.004
	Gabapentin	6	12	3	0	
CRBD severity 24h	placebo	1	7	8	5	0.005
	Gabapentin	7	11	3	0	
CRBD severity 48h	placebo	5	11	5	0	0.09
	Gabapentin	7	13	0	1	
CRBD severity 72h	Placebo	9	9	3	0	0.372
	Gabapentin	13	7	1	0	

Table 3 shows pain severity outcomes over study period. The mean score of pain severity based on VAS significantly was lower in the gabapentin group in comparison with the placebo group at all following up times.

Table 3. Pain severity in the gabapentin group and the control group after open prostatectomy during the first 72 hours

Variable	Groups	Mean	SD	*P* value
Pain severity 2h	placebo	7.29	2.14	0.02
	Gabapentin	5.90	1.44	
Pain severity 6h	placebo	5.10	2.52	0.001
	Gabapentin	2.81	1.16	
Pain severity 24h	placebo	3.81	1.72	0.001
	Gabapentin	2.32	0.73	
Pain severity 48h	placebo	2.05	1.16	0.03
	Gabapentin	1.33	0.91	
Pain severity 72h	placebo	1.48	0.51	0.001
	Gabapentin	0.76	0.70	

Figure 2 shows that the pain severity tended to show decrease overtime in both groups but it was also significantly less in gabapentin group

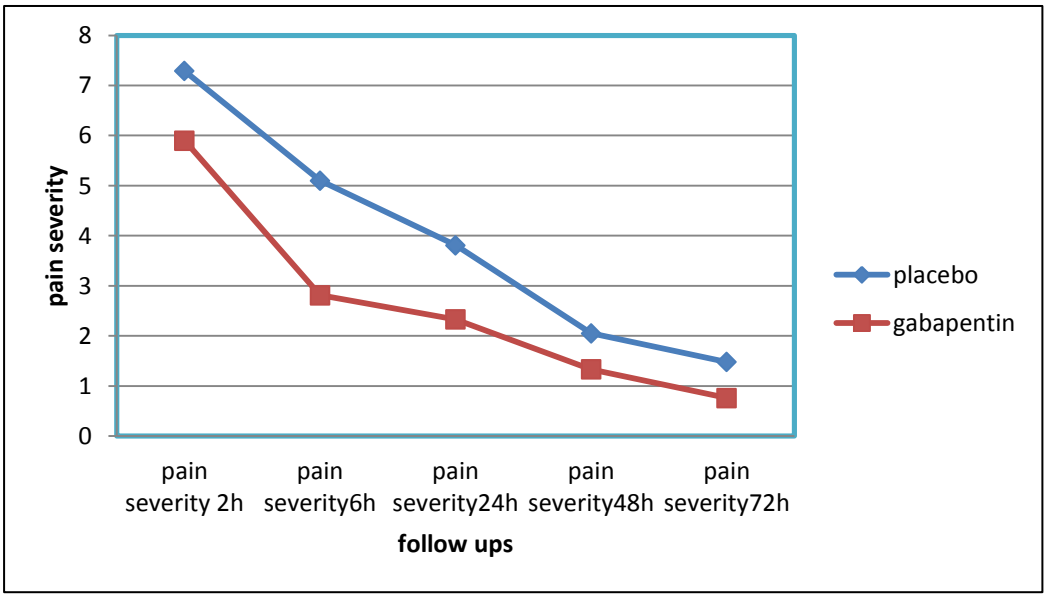

Figure 2. Comparison of pain severity based on VAS score in groups

Total morphine requirement significantly (*P*=0.007) decreased in gabapentin group in comparison with placebo group but no significant different were observed among group in vomiting numbers (Table 4).

Table 4: Comparison of morphine requirement and the number of vomiting in the gabapentin group and the control group after open prostatectomy during the first 72 hours

Variable	Groups	Mean	SD	p value
Morphine requirement	placebo	10.48	4.13	**0.007**
	Gabapentin	7.05	3.65	
Vomiting	placebo	0.14	0.65	0.842
	Gabapentin	0.19	0.87	

Table 5 and 6 show there were no significant differences between the two groups in postoperative sedation and nausea-vomiting.

Table 5. Postoperative sedation in the gabapentin group and the control group after open prostatectomy during the first 72 hours

Variable	Groups	No sedation	Mild	Moderate	p value
Postoperative sedation 2h	placebo	19	1	1	0.272
	Gabapentin	15	2	4	
Postoperative sedation 6h	placebo	19	2	0	0.208
	Gabapentin	15	4	2	
Postoperative sedation 24h	placebo	21	0	0	0.147
	Gabapentin	19	2	0	
Postoperative sedation 48h	placebo	21	0	0	0.311
	Gabapentin	20	1	0	
Postoperative sedation 72h	Placebo	21	0	0	1
	Gabapentin	21	0	0	

Table 6. Postoperative severity of nausea and the number of vomitings in the gabapentin group and the control group after open prostatectomy during the first 72 hours

Variable	Groups	No problem	Vomiting	Nausea	*P* value
N/V2h	placebo	17	1	3	0.519
	Gabapentin	19	0	2	
N/V6h	placebo	17	1	3	0.574
	Gabapentin	19	1	1	
N/V24h	placebo	15	0	6	0.08
	Gabapentin	19	1	1	
N/V48h	placebo	21	0	0	0.311
	Gabapentin	20	0	1	
N/V72h	placebo	21	0	0	1
	Gabapentin	21	0	0	

DISCUSSION

Catheter-related bladder discomfort, defined as an urge to void or discomfort in the suprapubic region, is extremely distressing to patients with an indwelling urinary catheter in the postoperative period and because of high incidence it is a subject of concern among many researchers.

This proof-of-concept study demonstrates that gabapentin reduced the incidence and severity of CRBD during 6 to 24 hours after the open prostatectomy along with reduction in the postoperative pain since. We observed that patients who received gabapentin had a significant lower pain severity compared with the placebo group. In addition, morphine requirement in gabapentin group was significantly lower than placebo group. However, there were no significant differences

between the two groups in postoperative sedation and nausea vomiting.

We found no research, which evaluates the effect of gabapentin on CRBD in patient undergoing open prostatectomy.

Despite our study, Agarwal et al. [14] study showed that gabapentin (600 mg) administered orally 1 h before surgery reduced the incidence and severity of CRBD, postoperative pain, number of patients requiring fentanyl and postoperative total fentanyl requirement at baseline and 1,2 and 6 hours after elective percutaneous nephrolithotomy. However, they had not any manipulation in bladder since the approximation of surgery incision and origin site of CRBD in our study make for patient difficult to separate CRBD and pain from each other in primary hours. Inda et al. [5] showed that gabapentin 1200 mg administered before surgery was more effective than gabapentin 600 mg decreasing the incidence of postoperative CRBD in adult patients undergoing elective transurethral resection of bladder tumor (TURBT). In this study, there was no incision on bladder. In present study, significant decrease in CRBD incidence and severity at 6 and 24 hours after surgery support the result of aforementioned studies. Gabapentin also reduced pain severity and opiate requirement in patients in our study as well as previous studies [5, 8,14, 18-20].

Contrary to our findings, Pandey CK *et al.* demonstrated that prophylactic gabapentin improved postoperative nausea and vomiting in patients undergoing laparascopic cholecystectomy [18].

Open prostatectomy is an extra peritoneal surgery, whereas we expect lower nausea and vomiting because of lack of manipulation in abdominal organism. In our study, we tried to eliminate previous studies' limitations by following up patients for 72 hours.

Gabapentin has been widely used for the treatment of peripheral neuropathic pain through inhibitory activity on afferent C-fibers nerve activity [5], which may play a role in certain cases of urge incontinence, OAB, and sensory urgency [11].

Peripheral tissue injury, such as caused by surgery, provokes two types of modification in the responsiveness of the nervous system: peripheral sensitization, which causes a reduction in the threshold of nociceptor afferent peripheral terminals, and central sensitization, which causes an activity-dependent increase in the excitability of spinal neurons [21]. Gabapentin appears to inhibit peripheral sensitization by inhibitory activity on afferent C-fibers [14, 4] and may thus help in the treatment of OAB and CRBD. Gabapentin has also been effective in neurogenic detrusor over-activity [4]. Gabapentin probably controls detrusor over-activity by modulating the afferent input from the bladder and the excitability of the sacral reflex center [4]. The central action of gabapentin within the spinal cord or brain reduces the sensitization of dorsal horn neurons, thereby reducing the hypersensitivity associated with nerve injury, inflammation, and pain after surgery [22]. We presume that this combined peripheral and central action of gabapentin might be responsible for the observed reduction in the incidence and severity of CRBD along with the observed reduction in postoperative pain.

After a single 300 mg oral dose, the mean maximum plasma gabapentin concentrations are attained in 2–3 h. The bioavailability of a single 300 mg oral dose of gabapentin is 60% [23]. Therefore, considering the one-hour length of open prostatectomy, its administration at two hours before the surgery seems to be the optimal time. It is not metabolized in humans and is eliminated from the body by renal clearance. However, no patient in our study had renal dysfunction. The elimination half-life of gabapentin is 5–7 h after a single oral dose [23]. We observed its effect for 6 h postoperatively then we continued it with gabapentin capsules100 per 8 hours as a maintenance dose.

A limitation of our study was that gabapentin is not Food and Drug Administration approved for urologic dysfunction; although over the past decade, gabapentin appears to have attractive properties for treatment of refractory lower urinary tract symptoms also the sample size for surveying seems not big enough for postoperative nausea vomiting because of found limitation.

Coclusion:The results of our trial are sufficiently encouraging to justify further studies with larger sample size and multidosage approach.

Pretreatment with gabapentin reduces the postoperative bladder discomfort in patients with an indwelling catheter after open prostatectomy.

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