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ORIGINAL ARTICLE

Efficacy of Gabapentin for Prevention of Postoperative Catheter-related Bladder Discomfort after Open Prostatectomy

Davoud Goodarzi[1], Ali Cyrus[1*], Javad Aghamohammadi[2], Bahman Sadeghi[3]

[1] Department of Urology, School of Medicine, Arak University of Medical Sciences, Arak, Iran
[2] School of Medicine, Arak University of Medical Sciences, Arak, Iran
[3] Department of Social Medicine, School of Medicine, Arak University of Medical Sciences, Arak, Iran

ABSTRACT

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

Materials and Methods: In this clinical trial, forty-two patients undergoing open prostatectomy were randomly allocated to intervention and placebo groups. The first group received stat dose of 300 and 100 mg q8h of gabapentin and the other group received placebo. After the operation, the patients were observed for the incidence and severity of CRBD and pain severity using visual analogue scale (VAS index). The doses of morphine that patient might need were recorded. This trial was registered at irct.ir (IRCT No.: IRCT2014063017811N4).

Results: The intervention group showed a significant reduction in the incidence and severity of CRBD at 6 and 24 h after surgery compared to the placebo group. Furthermore, a significant reduction in pain severity, measured as VAS mean score, was observed in patients receiving gabapentin in comparison with the placebo group (P≤0.05).

Conclusion: Gabapentin probably controls detrusor muscle overactivity by modulating the afferent input from the bladder and the excitability of the sacral reflex center. Gabapentin decreased severity of postoperative pain, morphine requirement, and incidence and severity of CRBD at 6 and 24 h after open prostatectomy.

Key Words: Catheter-related bladder discomfort, Gabapentin, Open prostatectomy

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INTRODUCTION

Catheter-related bladder discomfort (CRBD) secondary to an indwelling urinary catheter is common in patients undergoing open prostatectomy [1]. In cases of bladder manipulation, the incision is adjacent to the source of CRBD. In these patients Foley and suprapubic catheters thicker than 18F, along with male gender are recognized as CRBD risk factors [2].

"Symptoms of CRBD mimic those of an overactive bladder (OAB), that is, urinary frequency, urgency, as well a surge incontinence" [3]. There is a variety of mechanisms that underlie overactive bladder. A wide range of studies suggest the possible role of bladder receptors, afferent pathways, and spinal cord interneurons [4]. Therefore, their modulation was proposed as a possible approach to control CRBD symptoms, which are attributed to involuntary detrusor contractions [5].

Although, today, antimuscarinic drugs are the main treatment for CRBD, they show variable success because of poor selectivity for the bladder. Additionally, these drugs cause some adverse side effects, such as ileus, xerostomia, and blurred vision, which somewhat limit their applicability [6, 7].

Interventions with ketamin at subhypnotic dose [8], tramadol [3], and butylscopolamine [9] are also effective for prevention of postoperative CRBD. However, the effectiveness of these medications was limited to the first postoperative hours and they showed a wide spectrum of adverse effects.

Gabapentin is a structural analogue of amino

* *Corresponding author:* Ali Cyrus, Department of Urology, Valiasr Hospital, Medicine Faculty, Arak University of Medical Sciences, Arak, Iran. Email: cyrus @arakmu.ac.ir

butyric acid, but it does not interact with GABA [10]. It is approved as an anticonvulsant and has significant analgesic properties widely used for the treatment of peripheral neuropathic pain through inhibition of nerve activity of afferent C-fibers [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 per day [10]. Gabapentin was safe in children with neurogenic bladder [12]. Long-term treatment with 300 to 2100 mg of gabapentin was useful for the treatment of refractory genitourinary tract pain [13].

Gabapentin is effective in treating resistant cases of OAB, which are very similar to CRBD in symptoms [11, 14]. This medication has been used in doses up to 3000 mg for cases of refractory OAB, in which the conventional antimuscarinic therapy failed [10]. Pretreatment with 600 mg oral gabapentin was found to reduce the incidence and severity of postoperative CRBD in patients undergoing percutaneous nephrolithotomy (PCNL) under general anesthesia with no manipulation in the bladder. Only 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 reduction in OAB symptoms in patients with bladder pain syndrome [15]. In addition, gabapentin significantly improved urodynamic indices and stimulatory symptoms in neurogenic overactive bladder [4, 12].

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

This study aimed to determine the effect of gabapentin on CRBD and pain severity in patients undergoing open prostatectomy and to introduce gabapentin as an alternative for the conventional treatments, such as antimuscarian treatment, in patients with OAB.

MATERIALS AND METHODS

Study settings

This double-blind, placebo-controlled clinical trial was performed during 2013-14 at Valiasr Hospital of Arak University of Medical Sciences, Arak, Iran, during June 2013-March 2014.

Subjects

The inclusion criteria were the patients of American Society of Anesthesiologists (ASA) with physical status I-II undergoing elective open prostatectomy under spinal anesthesia, need for catheterization of the urinary bladder during the study period, weight 50–80 kg, and history of any of the following conditions: OAB (nocturnal urinary frequency >3 times and > 8 times at 24 hours), neurogenic bladder, diabetes mellitus, Parkinson's disease, and impaired renal function. The patients with chronic use of opiates or sedatives, antacid uptake in the past 48 h, or hypersensitivity to amide local anesthetics or gabapentin were excluded.

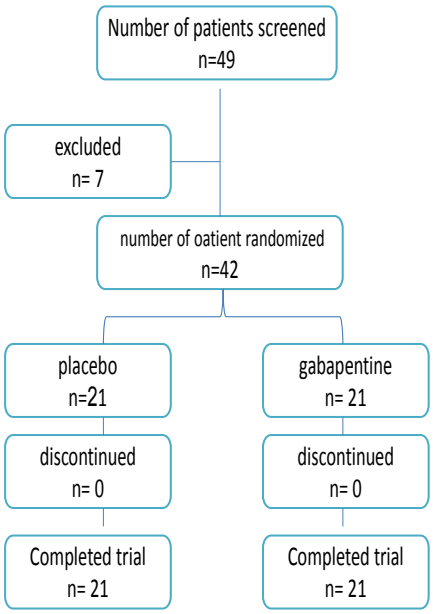

Figure 1. Consort diagram of the current clinical trial receiving gabapentin or placebo after open prostatectomy

Sampling

In this study, the purposive sampling method was applied. Subsequently, in this trial, 50 patients were screened, after which 45 were found eligible for inclusion. Forty-two patients were enrolled in the study. Figure 1 shows the Consort diagram of the patients.

Study design

The patients fasted for 8 h before surgery and randomly received 300 mg oral gabapentin or placebo in capsule form with a small sip of water 2 h prior to the administration of spinal anesthesia.

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

Patients received 0.9% normal saline at a dose of 8 ml/kg/h after transferring to the operating room. Routine monitoring by

electrocardiogram (ECG), noninvasive blood pressure (NIBP), and pulse oximeter was performed, and baseline heart rate, blood pressure, oxygen saturation, and respiratory rate were recorded. Patients were placed in the left lateral recumbent 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 dose 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 the 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 blunt needle in the midline every 2 min after injection until the level stabilized for four consecutive tests, and then at every 10-min interval until recovery to S2 dermatome.

Data collection

The highest dermatomal level of sensory blockade, the time to reach the highest sensory level, time to two-segment regression, and the time to S2 regression was 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 min until modified Bromage scale returned to zero. The anesthesiologist who administered the block and assessed the level of blockade was blinded to the administered drugs.

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

At the end of the surgery, urinary bladder catheterization was carried out using a 22-Fr Foley catheter with the aid of lubricating gel, and its balloon was inflated with 50 ml distilled water. Thereafter, the catheter was fixed in the suprapubic region with traction adhesive tape. Traction was removed after 24 h. In addition, an 18F suprapubic intravesical catheter and a16F Nelaton catheter drain were fixed. After the surgery, depending on the group, 100 mg gabapentin capsules or placebo were administered every 8 h as a maintenance therapy until 72 h.

The outcome measures

The primary outcome measure was bladder discomfort as assessed at 2, 6, 24, 48, and 72 h postoperatively by a physician registrar who was blinded to the type of medication received by the patients and was trained in pilot phase on 10 patients. Severity of bladder discomfort was recorded as severe (reported by the patients 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, the 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 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 suprapubic 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 illustrated worst imaginable pain. The number of patients requiring morphine sulfate and the total morphine consumption postoperatively up to 72 h were also recorded postoperatively. Furthermore, nausea and vomiting during the study period was assessed as a secondary outcome measure.

Statistical analysis

All the data was tested for normality. Independent t-test was performed to evaluate the difference between the groups in terms of age, pain at the operation site on a VAS scale, morphine requirement, and vomiting frequency. Presence and severity of discomfort (mild, moderate, and severe) were analyzed by Chi-squared test in SPSS version 16. P-value less than 0.05 was considered statistically significant.

Ethical considerations

The study was approved by Ethics Committee

of Arak University of Medical Sciences and registered under IRCT number 2014063017811N4. All the patients were informed of the study procedures and those who signed the written consent entered the study.

RESULTS

The patients' mean age was 65.86±5.50 years (range: 55-79 years). The mean ages of the placebo and gabapentin groups were 66.43±5.99 and 66.29±5.07 years, respectively. There was no significant difference between the two groups in this regard (P>0.05).

The total mean weight of the patients was 70.19±8.91 kg. The mean weights of the placebo and gabapentin groups were 70.61±9.16 kg and 69.75±8.89 kg, respectively; there was no significant difference between the groups regarding mean weight.

Presence and severity of CRBD significantly (P<0.05) reduced in the gabapentin group compared with the control group at 6 and 24 h postoperation (tables 1 and 2). There were no differences in CRBD presence and severity at 2, 24, 48, and 72h after surgery between the groups. In general, 6 (28%) and 7 (33%) patients did not show CRBD at 6 and 24 h after surgery, while only 1 (4.7%) patient in the placebo group did not present with CRBD.

Table 3 illustrates pain severity outcomes over the study period. The mean score of pain severity based on visual analogue scale was significantly lower in the gabapentin group in comparison with the placebo group at all follow-up times.

As presented in figure 2, the pain severity decreased overtime in both groups, but it was significantly less in the gabapentin group. Total morphine requirement significantly (P=0.007)

Table 1. The presence of catheter-related bladder discomfort in the gabapentin and control groups after open prostatectomy during the first 72 h

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	

*CRBD: catheter-related bladder discomfort, **P-value less than 0.05 was considered statistically significant

Table 2. The severity of catheter-related bladder discomfort in the gabapentin and control groups 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	

*CRBD: catheter-related bladder discomfort; **P-value less than 0.05 was considered statistically significant

Table 3. Pain severity in the gabapentin and control groups 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	

*P-value less than 0.05 was considered statistically significant

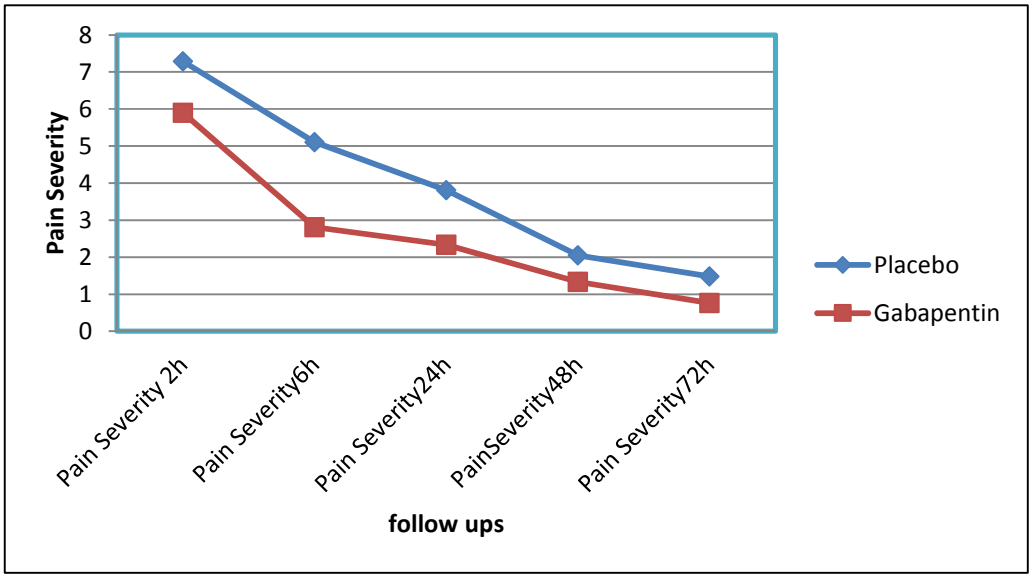

Figure 2. Comparison of pain severity based on visual analogue scale score in the groups

Table 4. Comparison of morphine requirement and the frequency of vomiting in the gabapentin and control groups 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	

*P-value less than 0.05 was considered statistically significant

Table 5. Postoperative sedation in the gabapentin and control groups 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	

*P-value less than 0.05 was considered statistically significant

decreased in the gabapentin group in comparison with the placebo group, but no significant difference was observed among the groups in terms of vomiting frequency (Table 4).

As shown in tables 5 and 6, no significant differences between the two groups in terms of postoperative sedation and nausea and vomiting was present.

DISCUSSION

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

Due to the literature review, there is a scarcity of studies evaluating the effect of

Table 6. Postoperative severity of nausea and the frequency of vomiting in the gabapentin and control groups 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	

*P-value less than 0.05 was considered statistically significant

gabapentin on CRBD in patients undergoing open prostatectomy. But, in contrast with our study, Agarwal et al. [14] 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, as well as 1,2, and 6 h after elective percutaneous nephrolithotomy. Although in those patients the bladder was not manipulated, the proximity of surgery incision and origin site of CRBD in our study made it difficult for the patients to distinguish CRBD from pain in the first few 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 that study, there was no incision in the bladder. In the present study, significant decrease in CRBD incidence and severity at 6 and 24 h after surgery support the results of the aforementioned studies. Gabapentin also diminished 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 et al. demonstrated that prophylactic gabapentin improved postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy [18].

Open prostatectomy is an extra peritoneal surgery; however, low incidence of nausea and vomiting is expected because of lack of manipulation in the abdominal organs. In our study, we tried to eliminate previous studies' limitations by following up patients for 72 h.

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

Peripheral tissue injuries, such as those caused by surgery, provoke two types of modifications in the responsiveness of the nervous system, that is, peripheral sensitization, which causes a reduction in the threshold of nociceptor afferent peripheral terminals, and central sensitization, which induces an activity-dependent increase in the excitability of spinal neurons [21]. Gabapentin appears to inhibit peripheral sensitization by inhibition of afferent C-fibers [14, 4] and may thus help with the treatment of OAB and CRBD. Gabapentin has also been effective in neurogenic detrusor overactivity [4]. Gabapentin probably controls detrusor overactivity 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 postoperative surgery [22]. We presume that the 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 concentration is attained at 2–3 h. The bioavailability of a single 300 mg oral dose of gabapentin is 60% [23]. Therefore, considering the one-hour duration of open prostatectomy, its administration at 2 h before operation seems to be the optimal time. This drug 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 at 6 h postoperation, then we continued its administration with

gabapentin capsules 100 mg per 8 h as a maintenance dose.

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

CONCLUSION

Our findings represent the probable effectiveness of pretreatment with gabapentin in reduction of the postoperative bladder discomfort in patients with an indwelling catheter after open prostatectomy.

The results of our trial are sufficiently encouraging to justify further studies with larger sample sizes and a multi-dosage approach.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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