

The Effect Of Preoperative Gabapentin on Pain Severity After Posterior Urethral Surgery: A Randomized, Double-Blind, Placebo-Controlled Study

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Purpose: Prevention and treatment of postoperative pain is a major challenge in posterior urethroplasty surgery. Gabapentin can control postoperative pain by preventing excessive sensitivity of the central nervous system. In this study, we aimed to evaluate the effect of gabapentin compared with placebo on reducing patients' pain following posterior urethroplasty.

Material and Methods: This prospective, randomized, double-blind study was performed in Shohada-e-Tajrish hospital. A total of 100 patients who were candidates of posterior urethral stricture were included. Patients were then randomly assigned into two groups (n=50 in each group) and received either single-dose Gabapentin or placebo, preoperatively. Then, all patients underwent posterior urethroplasty. Using the visual analog scale (VAS), the level of patients' postoperative pain was assessed at two hours, four hours, six hours, eight hours, 12 hours, and 24 hours after surgery.

Results: There was a significant difference in the VAS pain scores after two hours, four hours, six hours, eight hours, 12 hours, and 24 hours post-surgery ($P < 0.001$). This resulted in a significant decrease in morphine consumption in the gabapentin group compared with the placebo group ($P < 0.001$). Furthermore, post-surgery adverse events such as vomiting, nausea, drowsiness, and pruritus were significantly less frequent in the gabapentin group versus the placebo group.

Conclusion: The results of our study revealed that gabapentin can control postoperative pain after posterior urethroplasty, decrease the need for opioid consumption, and reduce the occurrence of post-surgery adverse events such as nausea, vomiting, drowsiness, and pruritus.

Keywords: gabapentin; pain; urethroplasty

INTRODUCTION

The management and treatment of urethral tract strictures remains a major challenge in the field of urology.^(1,2) On the other hand, the rate of posterior urethral damage is also increasing in developing countries.⁽³⁾ A traumatic urethral tract can occur due to blunt trauma to the perineum, penetrating trauma, iatrogenic trauma, or pelvic fracture. Factors such as urbanization and industrial life have increased the incidence of urethral tract injury and pelvic fracture urethral disruption defects (PFUDD) due to the increased occurrence of vehicle crash accidents^(4,5). Generally, urethroplasty is divided into anterior and posterior repair, based on the site of the urethral tract damage.⁽⁴⁾

Prevention and management of postoperative pain following urethroplasty is a main challenge in postoperative care. Although opioid drugs are potentially capable of decreasing postoperative pain, their use is restricted due to side effects such as nausea, vomiting, itching,

drowsiness, and urinary retention.⁽⁶⁻⁷⁾

Epidural analgesics are also used for pain control, although they are less effective and are associated with serious complications. Non-steroidal anti-inflammatory drugs (NSAIDs) are also prescribed for postoperative pain but they can increase the risk of injury to the digestive system, nephropathy, allergic reflex, and heart failure. NSAID selective cyclooxygenase-2 has prothrombotic effects and increases the possibility of brain stroke and heart ischemia. Therefore, a multi-therapy method for post-operative pain relief is suggested⁽⁸⁾.

Surgery leads to pain by stimulating the central and peripheral nervous systems. Anti-hyperalgesic drugs can manage post-surgical pain by preventing excessive sensitivity of the central nervous system⁽⁹⁾. Gabapentin and pregabalin are examples in this regard, having anticonvulsant, analgesic, and anti-anxiety properties. Gabapentin and pregabalin act by binding to the $\alpha 2$ - δ -1 subunit of voltage-dependent calcium channels

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Table 1. Demographic and clinical data of patients undergoing posterior urethroplasty.

Characteristic	Gabapentin (n = 46)	Placebo(n = 47)	P-value
Age (years)	43.4 ± 8.9	44.2 ± 8.2	0.6
BMI (kg/m ²)	25.7 ± 3.2	26.8 ± 3.1	0.1
Duration of surgery (minute)	242.5 ± 36.4	249.7 ± 25.6	0.2
Duration of anesthesia (minute)	266.5 ± 36.4	273.7 ± 25.6	0.2
SBP (mmHg)	138 ± 12.6	139.5 ± 12.9	0.5
DBP (mmHg)	76.9 ± 8.4	77.6 ± 6.7	0.6
HR (beats per minute)	76.7 ± 8.6	78.3 ± 7.5	0.3
Type of posterior urethroplasty			
Simple	37	40	0.3
Complex	9	7	0.3

Qualitative data was analyzed by chi-square test and quantitative data was analyzed by independent T-test and Mann-Whitney *U* test.

Abbreviations: BMI, Body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate

available in the central nervous system. In addition to calcium channel blockage, other proposed mechanisms of gabapentin include interaction with NMDA receptors or monoaminergic systems. It is well-established that the use of gabapentin reduces the irritability of the central nervous system and subsequently, neuropathic pain, and can result in the control of postoperative pain (10,11,12-14).

Shohada-e-Tajrish hospital in Tehran, Iran, is a referral center for reconstructive urology. Annually, many patients from across the nation and also neighboring countries are admitted to this center for this purpose. Here, we aimed to compare the effect of gabapentin with placebo on reducing the pain following posterior urethroplasty in patients admitted to this center. We hope that the results of this study will provide a better overview of the long-term outcome of the treatment of these patients and provide a more accurate decision about the best treatment option for controlling postoperative pain in these patients.

MATERIAL AND METHODS

Ethics Approval

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (ethics code: IR.SBMU.RETECH.REC.1398.231). Written informed consent was obtained from all patients prior to enrollment in the study.

Study Population

This prospective, randomized, double-blind study was conducted in Shohada-e-Tajrish hospital. In this study, 100 patients with posterior urethral stricture (age range= 30-60 years old) who were admitted to our hospital during 2018-2019 for urethroplastic surgery were included. Patients were randomly assigned to two groups (n=50 in each group) and received either single dose Gabapentin or placebo, preoperatively. The same

surgeon performed posterior end-to-end urethroplasty for all patients by using the same technique. Then, an 18F lubricated silicon urethral catheter was inserted for all patients and was fixed to the skin using adhesive tapes. Inclusion criteria were as follows: 1) age > 18 years old and 2) confirmed diagnosis of posterior urethral stricture by retrograde urethrogram (RUG) and flexible cystoscopy.

Cases with concurrent consumption of anti-epileptic or antidepressant drugs, presence of malfunction kidney disease, diabetes, history of chronic pain, history of substance abuse, any allergy to drugs, and an American Society of Anesthesia (ASA) physical status ≥ III were excluded from the study.

Procedures

Based on a random technique, patients were divided into two equal groups. Randomization was performed by a resident physician who was not participating in the survey by using sealed envelopes labeled as gabapentin (group A) or placebo (group B). All patients underwent general anesthesia using the same technique by the same surgeon. After blinding of patients, an hour prior to administration of general anesthesia for posterior urethroplasty, patients in group A received a single dose of gabapentin 600 mg (neuroleptin®, SOHA), whereas in group B, a single dose of placebo was given. In order to minimize bias during the completion of the visual analog scale (VAS) questionnaire, the researchers that filled in the questionnaire were made blind to patients' study group. Gathered information was then extracted by another colleague who was not involved in the study.

Evaluations

Before surgery, participants were educated regarding the VAS questionnaire. Then, the pain level was assessed and evaluated by the VAS at two hours, four hours, six hours, eight hours, twelve hours, and 24 hours post-surgery and based on the level of pain, a score

Table 2. Severity of postoperative pain (VAS score) and amount of opioid consumption (morphine) across the two groups (gabapentine vs placebo).

Characteristic	Gabapentin (N =46)	Placebo(N =47)	P-value
Pain score by VAS (Mean ±SD)			
2 hrs after intervention	4.7±0.7	7.4±0.6	< 0.001
4 hrs after intervention	3.8±0.7	6.9±0.6	< 0.001
6 hrs after intervention	3±0.5	5.3±0.7	< 0.001
8 hrs after intervention	3±0.5	4.4±0.7	< 0.001
12 hrs after intervention	1.9±0.6	2.9±0.5	< 0.001
24 hrs after intervention	0.6±0.4	1.6±0.6	< 0.001
Morphine consumption (mg)	14.2±4.3	30.9±6.1	< 0.001

Quantitative data was analyzed by independent *T*-test and Mann-Whitney *U* test

Table 3. Frequency of adverse effects across the two groups

Characteristic	Gabapentin (N =46)	Placebo(N =47)	P-value
Vomiting	6(13%)	18(38.2%)	0.008
Nausea	7(15.2%)	19(40.4%)	0.01
Headache	5(10.8%)	8(17%)	0.5
Dizziness	10(21.7%)	17(36.1%)	0.1
Shivering Sensation	11(23.9%)	15(31.9%)	0.4
Drowsiness	2(4.3%)	18(38.2%)	< 0.001
Pruritus	9(19.5%)	19(30.4%)	0.04

Qualitative data was analyzed by chi-square.

ranging from 1 to 10 was given. Any patient with a VAS score of more than three was given 5mg morphine infusion as needed. In this study, more than three points difference in the VAS score was considered as a clinically significant outcome.

Time since general anesthesia to the first dose of analgesic, total analgesic dose during hospital stay and usage of analgesics after discharge was recorded. Furthermore, posterior urethroplasty procedure was categorized into two subgroups of simple and complex urethroplasty. Patients who had undergone reoperation and those who had stenosis longer than 3 cm, accompanying perineal and GI fistulas, presence of diverticulitis adjacent to the duct, and non-competent bladder neck were defined as complex cases. Complex cases are more likely to need prolonged surgery, manipulation and partial pubectomy. This likely leads to more pain in these cases in comparison with simple urethroplasty.

Statistical Analysis

Data was analyzed using SPSS version 21 (IBM, Illinois, USA). Two sample paired t-test was used to compare VAS before and after administration of gabapentin or placebo. Data is reported as mean value \pm S.D. A *p*-value of < 0.05 was considered statistically significant.

For evaluation of pain, patients were categorized as fol-

lows based on pain intensity score at different assessment points: 1) mild pain: score < 4 or 2) moderate to severe pain: score \geq 4. Qualitative data was analyzed by Chi-square test and quantitative data was analyzed by independent t-test and Mann-Whitney-*U* test.

RESULTS

Patients' allocation flowchart is shown in Figure 1. One-hundred and thirty patients were initially enrolled of which 30 were excluded from the study: six because of ASA physical status \geq III, two due to diabetes, two due to malfunction kidney disease, nine due to analgesic drug abuse and 11 due to antiepileptics or antidepressant consumption.

Finally, a total of 100 cases were included and were equally divided into two groups of 50 patients. There was no significant difference regarding patients' demographic data, blood pressure, heart rate, number of complex posterior urethroplasty, duration of anesthesia and surgery between the study groups (Table 1). However, we observed a significant difference in the pain level as evaluated by the visual analog scale at two hours, four hours, six hours, eight hours, twelve hours, and 24 hours after surgery (*P* < 0.001). We also found a significant decrease in morphine consumption in the gabapentin group as compared with the placebo group

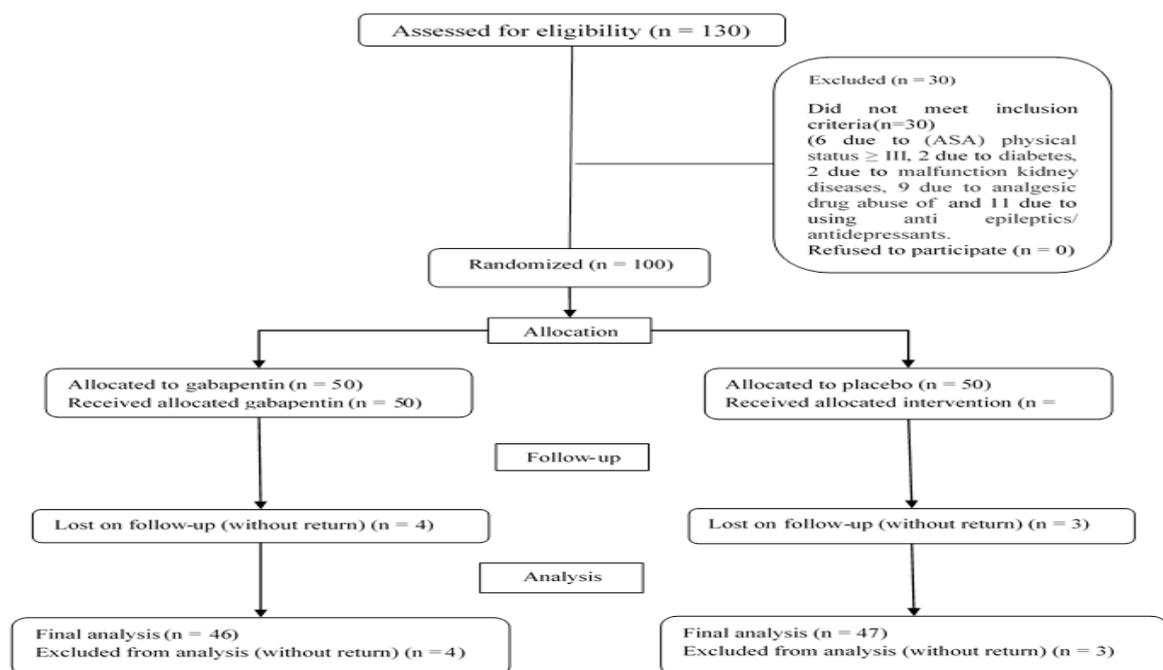


Figure 1. Patients' allocation flowchart.

($P < 0.001$) (Table 2). Furthermore, post-surgery assessments showed significantly lower adverse events such as vomiting, nausea, drowsiness, and pruritus in the gabapentin group than the placebo group (Table 3).

DISCUSSION

Treatment of postoperative pain following posterior urethroplasty is a major challenge in post-surgery care. Although opioid drugs are routinely prescribed to manage post surgical pain, their use is restricted due to occurrence of side effects such as nausea, vomiting, itching, drowsiness and urinary retention. Therefore, a multimodal analgesic approach has been attempted^(6,7). For instance, gabapentin has been introduced as an alternative option for the treatment of postoperative pain. Gabapentin is approved as an anti-epileptic medication but it is also used as an off-label analgesic drug^(15,16). The purpose of this study was to elobarote whether gabapentin could possibly have a role in the improvement of postoperative pain. Although no definite dosage of gabapentin has been recommended to be optimal, we decided to administer 600 mg single-dose gabapentin, preoperatively. The results of our study showed that prescribing preoperative gabapentin (600 mg) has a significant correlation with decreased postoperative pain and less need for opioid consumption after end-to-end urethroplasty.

The outcomes of this study support our hypothesis, demonstrating ameliorated VAS pain scores in patients who receive gabapentin preoperatively as compared with patients in the placebo group. These results are consistent with that of previous studies.^(17,18) Previous studies have also reported decreased postoperative pain and less need for opioid consumption after preoperative administration of gabapentin.^(3,19) In a meta-analysis study performed by Fabritius et al., it was demonstrated that, regardless of type of surgery, there is marked reduction in morphine consumption after pre or postoperative gabapentin administration⁽²⁰⁾. Moreover, Doleman et al. concluded that Gabapentin is the most successful treatment for reducing VAS postoperative pain scores at 1 hour, 2 hours, 6 hours, 12 hours, and 24 hours after surgery compared with other analgesics (p -value < 0.001)⁽²¹⁾.

Gabapentin has the ability to reduce the irritability of the central nervous system (from other regions of the brain) by binding to $\alpha 2$ - δ -1 subunit of voltage-dependent calcium channels in the posterior horn of the spinal cord and inhibiting its regulatory pathway.^(13,14) However, further research is warranted in order to estimate the efficacy of gabapentin on preventing and decreasing postoperative pain after posterior urethroplasty.

Nausea and vomiting are common postoperative side effect of prolonged anesthesia after urethroplasty surgery. In this study, post-operative nausea, vomiting, drowsiness, and pruritus occurred significantly less in the gabapentin group compared with the placebo group; no significant difference existed regarding other complications such as headache, dizziness, and shivering sensation between the two groups.⁽⁶⁾ A meta-analysis by Seib et al. showed that gabapentin reduces postoperative nausea and vomiting.⁽²²⁾ Irwin and Kong also reported that nausea, vomiting, and pruritus occur less in cases who receive gabapentin.⁽²³⁾

The mechanism of gabapentin on postoperative nausea and vomiting remains unidentified; however, it could

possibly be due to the indirect effect of decreased opioid consumption or possibly decreased neurotransmitter activity of tachykinin.⁽²⁴⁾

The results of this randomized placebo-controlled study showed that gabapentin is efficient in treating postoperative pain following posterior urethroplasty and can reduce the need for opioid consumption. Furthermore, adverse events such as nausea, vomiting, drowsiness, and pruritus seem to occur significantly less in patients who receive gabapentine, preoperatively.

CONCLUSIONS

Gabapentin is efficient in treating postoperative pain following posterior urethroplasty and can reduce the need for opioid consumption. Furthermore, adverse events such as nausea, vomiting, drowsiness, and pruritus seem to occur significantly less in patients who receive gabapentine, preoperatively.

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CONFLICT ON INTEREST

The authors declare that they have no conflict of interest.

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