Original Article

Effect of pregabalin on postoperative pain and instrumentation-induced dysuria in patients undergoing percutaneous nephrolithotomy: A prospective randomized, double-blinded placebo-controlled study

Shivakrishna Choppa, Indira Gurajala, Prachi Kar, Kavitha Jayaram, Padmaja Durga, Rahul Devraj[1], Ramreddy Chilumula[1]

Departments of Anesthesia and Critical Care, [1]Urology, Nizam's Institute of Medical Sciences, Telangana, India

Abstract

Background and Aims: The manipulation of urinary tract, the mandatory requirement of ureteral stenting, and bladder catheterization in patients undergoing percutaneous nephrolithotomy (PCNL) produces significant pain and dysuria postoperatively. The present study compared the efficacy of pregabalin with placebo in attenuation of these symptoms in patients undergoing PCNL.

Material and Methods: This randomized controlled study was conducted in 110 patients of either sex, aged 18–65 years undergoing elective PCNL requiring nephrostomy tube under general anesthesia. Group G (n: 53) received pregabalin 150 mg and Group P received placebo (n: 49) orally 1 h before the anesthetic induction. All the patients received standard anesthetic protocol. Pain at the site of nephrostomy, instrumentation-induced dysuria (IID), anxiety, and sedation scores were recorded at 0 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h postoperatively. Hemodynamics, total requirement of rescue analgesia, and incidence of any adverse effects were also noted.

Results: Patients were demographically comparable between the two groups. There is no difference in nephrostomy site pain between the groups at different points of measurements. IID was less with pregabalin at 0 min, 15 min, 30 min, 1 h, and 2 h after extubation (P value < 0.05, 43% in Group G vs. 68% in group P). Severe urgency was seen in 4%, moderate in 31%, and mild in 33% of patients in placebo group. No patient in pregabalin had severe grade of instrumentation-induced dysuria score ($P < 0.05$). Patients in Group P required more rescue analgesic (P: 0.009). Anxiety scores, sedation scores, and hemodynamic parameters were comparable.

Conclusion: A single dose of 150 mg pregabalin as oral premedication given 1 h before surgery reduced the incidence and intensity of IID compared to placebo in patients undergoing PCNL without significant adverse effects.

Keywords: Instrumentation-induced dysuria, pregabalin, premedication

Introduction

Patients undergoing percutaneous nephrolithotomy (PCNL) have discomfort in the postoperative period for two reasons—the nephrostomy site pain and an intense urge to micturate. Recent changes in the practice of PCNL like the "mini-perc" technique, tubeless PCNL as well as use of smaller nephrostomy tubes

Address for correspondence: Dr. Kavitha Jayaram, Department of Anesthesiology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad - 500080, Telangana, India.
E-mail: drkarunya@gmail.com

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reduce pain. However, these methods may not be applicable in all the patients. Studies which investigated pain after PCNL focused on traditional measures such as the use of nonsteroidal anti-inflammatory drugs and opioids. These drugs have their own side effects and limitations particularly in patients with potential renal failure.[1-3]

Urological procedures cause an intense urge to urinate. The site of origin of dysuria is not clear. Most literatures suggest that the discomfort is primarily due to the presence of catheter in the urinary bladder. However, catheter-related bladder discomfort (CRBD) alone does not explain the higher incidence of dysuria accompanying urological procedures when compared to nonurological surgeries which require bladder catheterization.[4] We hypothesize that extensive manipulation of the urinary tract during the endoscopic procedures causes dysuria. Ureteral stent placed at the end of PCNL contributes additionally to the dysuria. The term instrumentation-induced dysuria (IID) was introduced by us to describe the symptoms associated with ureteric stenting and CRBD.

To date, there is a paucity of literature that addresses both nephrostomy tract pain and IID holistically. The early success in the treatment of trigeminal neuralgia with anticonvulsant drugs such as gabapentin and pregabalin has led to many studies that assessed their analgesic potency after a variety of surgical procedures.[5,6] The primary objective of the study was to assess the utility of pregabalin for the relief IID in a prospective double-blind, randomized, placebo-controlled trial. The secondary objectives were to assess the anxiolytic and analgesic efficacy (for nephrostomy site pain) of pregabalin with placebo in patients undergoing PCNL.

Material and Methods

The ethical approval has been obtained from NIMS Institutional Ethics committee on 17/05/2018 No. EC/NIMS/2085/2018. This randomized controlled study was conducted after the approval of the Institutional Research Ethics Committee and written informed consent during the period September 2017–July 2018. One hundred and ten patients of either sex, aged between 18 and 65 years, belonging to the American Society of Anesthesiology (ASA) grades 1 and 2 undergoing elective standard PCNL requiring nephrostomy tube under general anesthesia were enrolled. Patients were randomized into two groups by a computer-generated random number table and sealed opaque-envelope technique. The patient and the person administering the drug were blinded to the drug used. Patients who were ASA grade 3 or above, pregnant, with renal failure or seizure disorders, on treatment with sustained-release opioids, antidepressants or antipsychotics, allergic to pregabalin, and unwilling to give consent were excluded. Cases were excluded after inclusion if renal stones required more than one puncture, having staghorn calculus which might cause more bleeding, duration of surgery extended more than 3 h, patient required postoperative ventilation, data acquisition was incomplete, and if patient withdraws from the study. Group G (*n*: 55) received pregabalin 150 mg and group P (*n*: 55) received placebo capsule orally 1 h before the anesthetic induction. All patients were orally premedicated with 0.5 mg of alprazolam at night before surgery.

In the operation theater, all patients were premedicated with an intravenous (IV) injection of glycopyrolate (0.005 mg/kg) and fentanyl 2 mic/kg after establishing IV access. General anesthesia was induced with IV thiopentone sodium (4–5 mg/kg of 2.5% solution) titrated to the loss of eyelash reflex. Endotracheal intubation was done by using IV atracurium as muscle relaxant in the dose of 0.5 mg/kg and anesthesia was maintained with isoflurane (0.4–0.8% vaporizer dial settings) with N_2O: O_2 (66:33). Standard monitoring included electrocardiogram, noninvasive blood pressure, end-tidal concentration of carbon dioxide, and pulse oximetry (Datex-Ohmeda S5 monitor [GE Healthcare Europe GmbH, Freiburg, Germany]). IV fluid, Ringer's lactate, was administered at the rate of 60–80 mL/h. In all patients, antiemetic ondansetron 4 mg IV was given before extubation. Half an hour before extubation, IV inj. paracetamol 1 g was given for postoperative analgesia. At the end of surgery, under fluoroscopy guidance, the local anesthetic bupivacaine 0.5% was infiltrated with a 23-g spinal needle (10 cm length) along the nephrostomy tube at 6 o'clock and 12 o'clock positions (10 mL in each tract) including renal capsule, muscles, subcutaneous tissue, and skin. Patients were extubated after the reversal of residual neuromuscular blockade with IV neostigmine (0.05 mg/kg) and glycopyrolate (0.01 mg/kg).

Parameters studied were hemodynamics during intraoperative period at different time intervals. In the postoperative period, sedation was measured at 0 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h in the postoperative period with Ramsay sedation scale (RSS). The anxiety levels in the patient were measured by anxiety score (AS) at same time intervals. The anxiety score was measured as 5-point score from 0 to 4, 0 being calm and comfortable to 4 being frightened and terrified. Pain at the nephrostomy site was assessed by visual analog score (VAS score) at same time intervals after extubation.

The urge to pass urine due to the presence of ureteric stent and urinary catheterization was assessed using "instrumentation

induced dysuria score" measured in the postoperative period. IID was graded as described in Table 1.

Inj. tramadol 1 mg/kg was given as rescue analgesic for *VAS score of ≥4 and IIDS ≥3*. The amount of rescue analgesia and the number of doses were also recorded. Nausea, vomiting, constipation, drowsiness, respiratory depression (defined as RR <8/min or SpO_2 <88%), and any other complications were recorded preoperatively, at extubation as well as at 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h after extubation.

Statistical analysis

Sample size calculation was performed with power/sample size calculator from the site www.stat.ubc.ca from the results of a pilot study of 15 patients in each group. A mean IIDS of 1.7 in the placebo group and 1.3 in the pregabalin group with standard deviation (SD) of 0.7 yielded a sample size of 49 in each group. Fifty-five patients were included in each group to account for any dropouts. Statistical analysis was performed using IBM SPSS (version 20, IBM, IL). The descriptive analysis of normally distributed continuous variables, like hemodynamics and VAS, was expressed as mean with SD. The categorical variables like IIDS and anxiety scores were expressed as frequencies with percentages. The statistical analysis for comparison of continuous variables between the groups was performed using *t*-test and a two-tailed significance of $P < 0.05$ was considered as significant difference. The comparison of categorical variables between the groups was performed using Chi-square test or Fisher's exact test.

Results

A total of 110 patients scheduled for elective PCNL were enrolled in the study. Six patients in Group P and two patients in group G were excluded. In the final analysis, 49 patients in Group P and 53 patients in Group G were included as explained in consort diagram [Figure 1]. Patients were statistically comparable demographically as given in Table 2.

There was no difference in VAS between the groups at different points of measurements [Table 3]. There was a significant difference in the IIDS between placebo and pregabalin groups at 0 min, 15 min, 30 min, 1 h, and 2 h after extubation (P value < 0.05). After 4 h following extubation, there was no difference between the groups in the IIDS [Figure 2].

Table 1: Instrumentation-induced dysuria score (IID score)

Score	Grade	Explanation
1	None	No urgency
2	Mild	Pt c/o urgency only on questioning
3	Moderate	Pt c/o urgency voluntarily but does not request rescue medication
4	Severe	Pt c/o severe urgency, is restless, pulling on urinary catheter which decreases with rescue medication

At extubation, 57% of patients in the pregabalin group did not have urgency at extubation, whereas 68% of patients in the placebo group complained of urgency. Severe urgency was seen in 4%, moderate in 31%, and mild in 33% of patients in placebo group. No patient in pregabalin had severe grade of IIDS ($P < 0.05$) [Figure 3]. There was a significant difference in the requirement of tramadol between the groups with patients in Group P requiring more rescue analgesic (P: 0.009) [Figure 4].

There was no difference in the AS and RSS between the groups at different time points of measurements.

The hemodynamic parameters in both the groups were comparable [Table 4]. The commonest side effects were shivering and postoperative nausea and vomiting. Three patients in group G and seven in group P had postoperative nausea and vomiting.q Shivering was seen in two patients in group G and six in group P.

Discussion

The present study tested the hypothesis that a single dose of 150 mg pregabalin administered 1 h preoperatively would have beneficial effect on postoperative nephrostomy pain, IID, anxiety and sedation scores, and tramadol consumption in patients undergoing PCNL. Several techniques have been

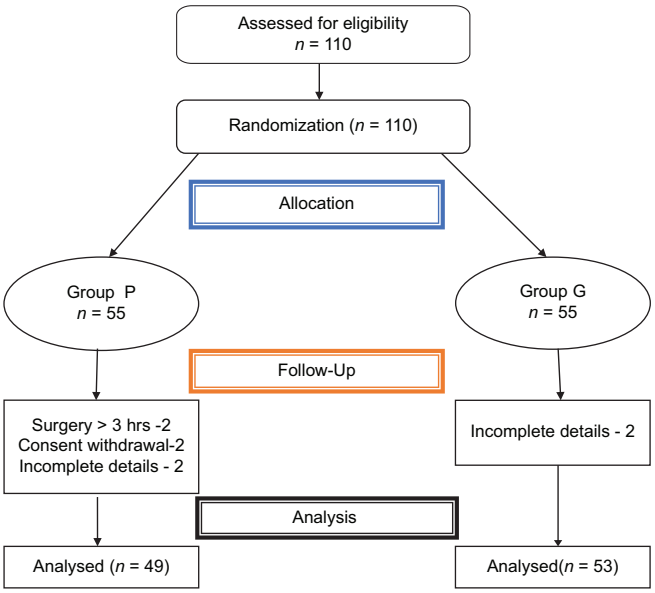

Figure 1: Consort diagram

Table 2: Demographic data

Demographic data	Group P (*n*: 49)	Group G (*n*: 53)	*P*
Age (years)	44.39±12.07	42.96±11.83	0.549
Gender (male: female) given as numbers	29:20	36:17	0.359
ASA grade: 1/2 given as numbers	34/15	34/19	0.575
BMI (kg/m^2)	24.13±2.03	24.37±1.76	0.511
Duration of surgery (hours)	2.25+0.8	2.3+0.4	0.93

Group P: placebo, group G: pregabalin

Table 3: Comparison of visual analog score between the groups P and G

VAS	Group P (mean±SD)	Group G (mean±SD)	*P*
0 min	2.94±2.68	2.45±2.39	0.547
15 min	2.53±2.02	1.93±2.05	0.356
30 min	2.42±1.73	1.78±1.87	0.194
1 h	2.27±1.48	1.55±1.50	0.061
2 h	2.10±1.69	1.47±1.40	0.327
4 h	1.94±1.39	1.36±1.24	0.333
8 h	1.73±1.05	1.47±1.26	0.473
12 h	1.47±0.93	1.13±1.09	0.154
24 h	1.43±0.97	1.08±0.99	0.324

Group P: placebo, group G: pregabalin, SD: standard deviation

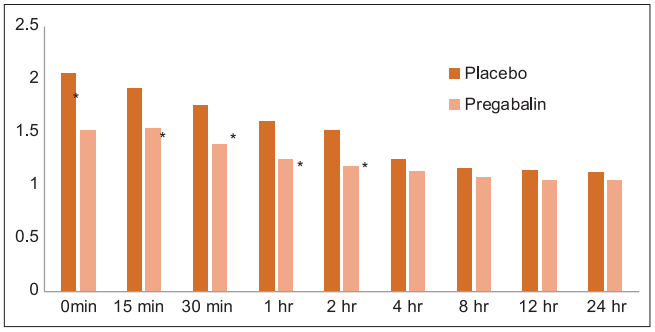

Figure 2: Comparison of instrumentation-induced dysuria score between the groups following extubation. **P* value < 0.05

reported to provide postoperative analgesia for nephrostomy site pain including paravertebral,[7] intercostal block,[8] local analgesic infiltration,[9] and systemic analgesics such as nonsteroidal analgesic drugs[10] and opioids.[11] Pregabalin, an analog of the inhibitory neurotransmitter GABA, was proven to be valuable in different postoperative pain situations including dental[12] and spinal surgery,[13,14] laparoscopic hysterectomy,[15] and cholecystectomy[16] with different dosage regimens. To the best of our knowledge, this is the first study designed to evaluate the effect of pregabalin on both postoperative nephrostomy pain and IID score in patients undergoing PCNL.

In this study, pain at the nephrostomy port site as assessed by VAS score postoperatively was similar between pregabalin and placebo groups ($P > 0.05$). At no time in the postoperative period, the mean VAS was more than 3 in both groups. This is in contradiction to earlier studies which found that pregabalin provides effective postoperative analgesia. Harun Aydoğan *et al.*[17] found that adding 75-mg pregabalin to analgesic regimen reduced VAS scores during the first 2 h and opioid consumption in adult patients who underwent PCNL procedure. Agarwal *et al.*[16] found that a single preoperative dose of pregabalin attenuated postoperative pain and opioid consumption in patients for laparoscopic cholecystectomy. Similar findings were observed by Pradeep Kumar *et al.*[14] in their study on 75 patients undergoing lumbar laminectomy. There was a significant decrease in the pain scores of the patients who received tramadol and pregabalin in comparison to the placebo group up to 6 h postoperatively ($P < 0.05$).

In a systematic review, it was concluded that gabapentanoids such as pregabalin and gabapentin provided better pain relief and effectively reduced opioid consumption. The difference in the results of our study could possibly be because (1) effective analgesia was already achieved by the combination of IV paracetamol and peritubal infiltration with bupivacaine in both the groups and pregabalin probably did not provide additional analgesia, and (2) PCNL per se causes less postoperative pain. Our study is different from previous studies in regards to dosage. A recent meta-analysis found that administration of pregabalin during a short perioperative period provides additional analgesia but at the cost of additional adverse effects. To reduce the associated adverse effects, we limited the dose of pregabalin to 150 mg.

Bladder irritation during urological surgery leads to muscarinic receptor (M2 and M3)-mediated involuntary contractions of the detrusor.[18] Inflammatory mediators and calcitonin gene-related peptide are also postulated to be responsible for pain and detrusor contraction leading to urgency to micturate.[4] The treatment modalities are many with mechanism of action ranging from antimuscarinic effects, peripheral and central pain modulation, and decreased synthesis of prostaglandins. Pregabalin's capacity to suppress the release of excitatory neurotransmitters is probably responsible for its analgesic properties. This may also decrease urgency. In this study, 150 mg of pregabalin attenuated IID when compared to placebo in the early postoperative period (i.e., up to 2 h after PCNL) without an increase in side effects. It also decreased tramadol consumption in the first 24 h postoperatively. There have been few studies focusing on pregabalin administration

Table 4: Comparison of heart rate and mean arterial pressure between the two groups

Time intervals	Heart rate			Mean arterial pressure		
	Group P (mean+SD)	Group G (mean+SD)	*P*	Group P (mean+SD)	Group G (mean+SD)	*P*
Baseline	80.29±15.57	81.15±14.16	0.769	104.18±13.48	104.85±11.58	0.791
1 min after intubation	86.49±18.71	86.77±15.56	0.934	106.96±21.07	108.04±21.87	0.801
5 min	83.16±16.60	84.70±16.25	0.638	95.02±18.47	97.00±15.59	0.561
10 min	81.55±17.04	78.47±14.99	0.334	95.92±18.46	95.63±16.28	0.935
15 min	77.31±14.88	76.17±16.28	0.715	93.47±18.67	91.54±14.34	0.560
30 min	75.71±13.21	74.98±15.25	0.798	96.57±15.35	94.38±14.82	0.472
45 min	75.33±13.37	76.41±14.88	0.713	97.65±14.03	98.04±16.86	0.904
60 min	78.44±18.03	76.33±15.71	0.589	100.93±14.61	103.54±18.88	0.501
75 min	75.76±12.58	78.45±17.23	0.540	104.00±14.52	102.85±14.23	0.785
90 min	71.76±9.84	67.92±16.99	0.447	107.12±18.10	105.50±18.67	0.817
2 h	72.71±9.72	72.13±15.61	0.933	97.86±16.44	101.88±16.50	0.645

Group P: placebo, group G: pregabalin, SD: standard deviation

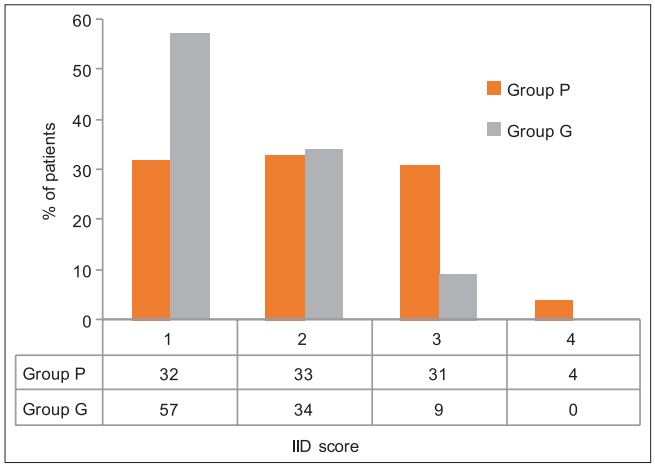

Figure 3: Instrumentation-induced dysuria score at extubation in groups P and G. Group P: group placebo (control), group G: group pregabalin

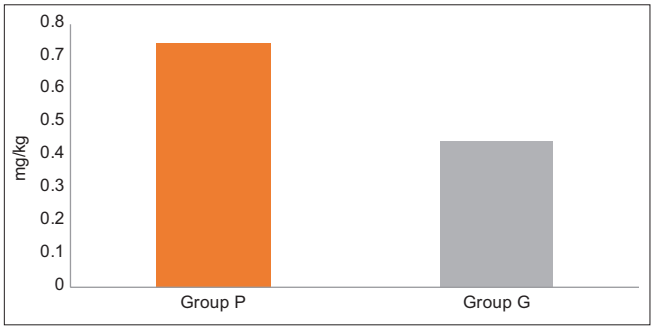

Figure 4: Comparison of requirement of tramadol between the groups P and G. Group P: placebo, group G: pregabalin, mg: milligram, kg: kilogram

for catheter-related bladder discomfort. Srivastava *et al.*[19] in their study on 60 patients undergoing elective spine surgery found that preoperative 150 mg pregabalin significantly decreased incidence of CRBD at 0 h, 1 h, 2 h, and 6 h. Samia Kohli[20] *et al.* found that preoperative use of 75 mg pregabalin decreased the incidence and severity of CRBD in patients undergoing PCNL at 0 h, 1 h, 2 h, and 6 h. However, they did not include assessment of pregabalin on port-site pain.[20]

There was no significant difference in the sedation score in pregabalin group compared to placebo groups at any point of measurement. White *et al.*[21] in his study found that preoperative pregabalin administration (oral 75–300 mg) increased perioperative sedation in a dose-related fashion. The severity of sedation was seen more when the dose used was 300 mg. Nutt *et al.*[12] evaluated acute onset of anxiolytic activity using a dental anxiety model in 89 patients using 150 mg pregabalin, alprazolam 0.5 mg, and a placebo 4 h before dental procedure and found significant improvement in anxiety and sedation with pregabalin and alprazolam compared with placebo.

Ozgencil *et al.*[13] in their study on 90 patients undergoing lumbar laminectomy showed that both pregabalin 300 mg/day and gabapentin 1200 mg/day have more analgesic, anxiolytic, and opioid-sparing effect and higher patient satisfaction than placebo. Gonano *et al.*[22] and Spreng *et al.*[23] similarly reported anxiolytic effect of pregabalin. However in our study, there was no anxiolysis with pregabalin compared to control group at any point of measurement. The low anxiety values in our study could be due to the relatively benign nature of the surgery. This is contrary to most of the studies, but in accordance with a study by White *et al.*[21] who studied 75 mg, 150 mg, 300 mg of pregabalin and found no difference in anxiety among all the groups.

Preemptive pregabalin was also shown to significantly alter hemodynamic data during operations in different clinical settings.[24,25] In this study, the mean arterial pressure and heart rate were similar between groups at any time. Similar results were seen in study by Gupta *et al.*[26] who evaluated pregabalin 150 mg premedication for hemodynamic stability during general anesthesia.

The common adverse effects of pregabalin are dose-dependent drowsiness and dizziness and the possible advantages of pregabalin may be mitigated by these troublesome side effects;

at the dose used, there were no significant side effects during the first 24 h after surgery in the present study in patients who received pregabalin.

The limitation of the study was that it was done only in single-puncture PCNL. The efficacy of pregabalin in cases with multiple punctures where the pain maybe more has not been studied.

To conclude a single dose of 150 mg pregabalin as oral premedication given 1 h before surgery reduced the incidence and intensity of IID compared to placebo in patients undergoing PCNL and also the requirement of postoperative analgesia without significant adverse effects.

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Conflicts of interest
There are no conflicts of interest.

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