

The Effect of Pregabalin on Preoperative Anxiety and Postoperative Pain in Patients Undergoing Percutaneous Nephrolithotomy: A Randomized Controlled Trial

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Abstract

Background: Percutaneous nephrolithotomy (PCNL) is the preferred surgical technique for treating kidney stones. Preoperative anxiety is a common psychiatric symptom experienced by many patients undergoing surgery. We aimed to evaluate the effects of pregabalin administration on preoperative anxiety and postoperative pain in patients undergoing PCNL.

Methods: This randomized controlled trial included 104 patients who were scheduled for PCNL surgery and were randomly assigned to 1 of the 4 groups: placebo, 75 mg of pregabalin, 150 mg of pregabalin, or 300 mg of pregabalin. The anxiety level was measured using the Hamilton Rating Scale for Anxiety (HRSA), and the postoperative pain was assessed using the visual analog scale (VAS). Methods such as the Wilcoxon Signed Ranks Test was used for the before-after test and the Kruskal Wallis Test was used for between-group time comparisons. The generalized estimation equation (GEE) and Poisson log-linear were used for the link function.

Results: After comparing the different doses of pregabalin to the placebo, no statistically significant relationships were detected ($P=0.931$ and $P=0.886$, respectively). In the group-time study of these patients, the pain level in all 4 groups decreased with time. This decrease in pain was statistically significant for most of the groups ($P<0.05$).

Conclusion: Administering pregabalin before PCNL surgery does not significantly reduce anxiety in patients before the procedure. However, preoperative administration of pregabalin has been found to be beneficial for alleviating postoperative pain in patients who have undergone PCNL surgery, with the optimal dosage of 75 mg pregabalin.

Keywords: Percutaneous Nephrolithotomy, Perioperative Anxiety, Postoperative Pain, Pregabalin

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Introduction

Percutaneous nephrolithotomy (PCNL) surgery is the preferred surgical technique for treating kidney stones. It can be performed using either fluoroscopy or ultrasound guidance. One of the major advantages of PCNL is that it

allows for the removal of Staghorn stones, which were previously difficult to treat without open surgery. The continued development and refinement of PCNL techniques have made it a highly effective and minimally invasive option

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↑What is “already known” in this topic:

The effects of pregabalin have been proven to reduce pain in various cases and after different surgeries. Additionally, conflicting results have been reported regarding the reduction of patients' anxiety after using this medication.

→What this article adds:

In this article, we specifically investigated the effects of pregabalin on pain and anxiety in patients who are candidates for percutaneous nephrolithotomy surgery, and we also determined the most effective dose of this medication with the fewest possible side effects.

for patients with kidney stones (1, 2). Although smaller nephroscopes and techniques such as miniperc and micropcni have become increasingly popular in PCNL surgery, pain after the procedure remains a common issue. Ongoing research and development in this area are aimed at identifying more effective and less invasive pain management strategies for PCNL patients. Postoperative pain after PCNL can result from various sources. Some of the most common causes of pain include the creation of a percutaneous access tract through the parenchyma, parenchymal shearing, accumulation of fluid around the kidney, renal pelvic pressure, low back pain due to the nephrostomy tube, and visceral pain (1, 3).

Although nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are commonly used for managing postoperative pain and inflammation, their use is not without limitations. NSAIDs can cause gastrointestinal bleeding, kidney damage, and an increased risk of cardiovascular events, especially in older patients or those with preexisting medical conditions. Opioids can lead to sedation, respiratory depression, and constipation, which can further complicate patient recovery. Therefore, healthcare providers need to carefully weigh the benefits and risks of these drugs for each patient and consider alternative approaches, such as regional anesthesia, nerve blocks, or acupuncture, to manage postoperative pain and inflammation. Additionally, nonpharmacological interventions—such as physical therapy, relaxation techniques, and cognitive-behavioral therapy—may also help manage postoperative symptoms (4).

Preemptive analgesia, also known as perioperative analgesia, was proposed by Ronald Melzack and Patrick Wall in 1988. The idea behind preemptive analgesia is to provide analgesia before pain develops rather than waiting for pain to develop. This approach has been shown to be effective at reducing the need for opioids and NSAIDs after surgery by preventing the development of central sensitization, a process that amplifies pain signals in the central nervous system. By reducing the need for opioids and NSAIDs, preemptive analgesia can help minimize the risk of adverse effects associated with these drugs and improve postoperative outcomes (5).

Preoperative anxiety is a common psychiatric symptom experienced by many surgical patients. According to a systematic review and meta-analysis published in 2018, the global pooled prevalence of preoperative anxiety among surgical patients was 48%. Factors that have been identified as contributing to preoperative anxiety include age, sex, type of surgery, and the use of anesthesia. While a certain level of stress and anxiety is normal and adaptive during surgery, a maladaptive response to surgical stress can result in negative outcomes and increase the risk of postoperative complications such as increased heart rate, blood pressure, and respiratory rate, as well as increased postoperative pain and longer hospital stays, infection, wound healing problems, cardiovascular complications, respiratory complications, and psychiatric complications. Healthcare providers use various strategies to minimize the risk of these complications—such as preoperative optimization of medical con-

ditions, perioperative pain management, and stress reduction. Therefore, identifying and managing preoperative anxiety is essential for improving patients' overall surgical experience (6, 7).

The success of anticonvulsant drugs—such as gabapentin and pregabalin—in managing neuropathic pain conditions (eg, trigeminal neuralgia) has led to their investigation as potential adjuncts in managing postoperative pain. Additionally, anticonvulsant drugs (eg, pregabalin and gabapentin) have anxiolytic and sedative effects. The mechanism of action of these drugs involves modulating the activity of neurotransmitters, such as gamma-aminobutyric acid (GABA) and calcium channels, which helps prevent pain transmission and reduces central and peripheral sensitization. Pregabalin, in particular, is an alkylated analog of GABA that is structurally related to gabapentin. Both drugs have been shown to be effective at reducing opioid requirements, improving pain control, and reducing adverse events associated with opioids, such as nausea and vomiting, in patients undergoing surgery. However, the optimal dosage, timing, and duration of administration of these drugs for managing postoperative pain are still being studied (3, 8, 9).

This study aimed to investigate whether preoperative pregabalin administration reduces preoperative anxiety and postoperative pain in patients undergoing PCNL surgery. The primary objectives are to evaluate the effectiveness of preoperative pregabalin administration in reducing preoperative anxiety and postoperative pain and to determine the optimal dosage and timing of pregabalin administration for minimizing side effects and maximizing its impact on pain and anxiety management.

Methods

Study Population

The patients who took part in this study were those who met the study criteria and were scheduled for PCNL surgery due to kidney stones. This study was conducted between April 2022 and June 2023 at Shohada-e Tajrish Hospital in Tehran, Iran.

The inclusion criteria included patients aged between 18 and 60 years and with an American Society of Anesthesiologists (ASA) class I or II. The exclusion criteria included patients who were currently taking medications that interacted with pregabalin, had diabetes mellitus, or neuropathy; had a history of alcohol consumption; had a history of psychiatric disorders; had a history of heart failure or renal failure; or were pregnant or lactating. The study included a total of 140 patients who met the inclusion criteria for PCNL surgery due to kidney stones. All of the patients were assessed through psychiatric interviews by a psychiatrist and none of them had a significant psychiatric diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. After the initial screening, 104 patients remained and were randomly assigned to 1 of the 4 groups for the study (Figure 1).

Study Design

This study was a prospective single-center, double-blind randomized controlled trial. Patients were blinded to their

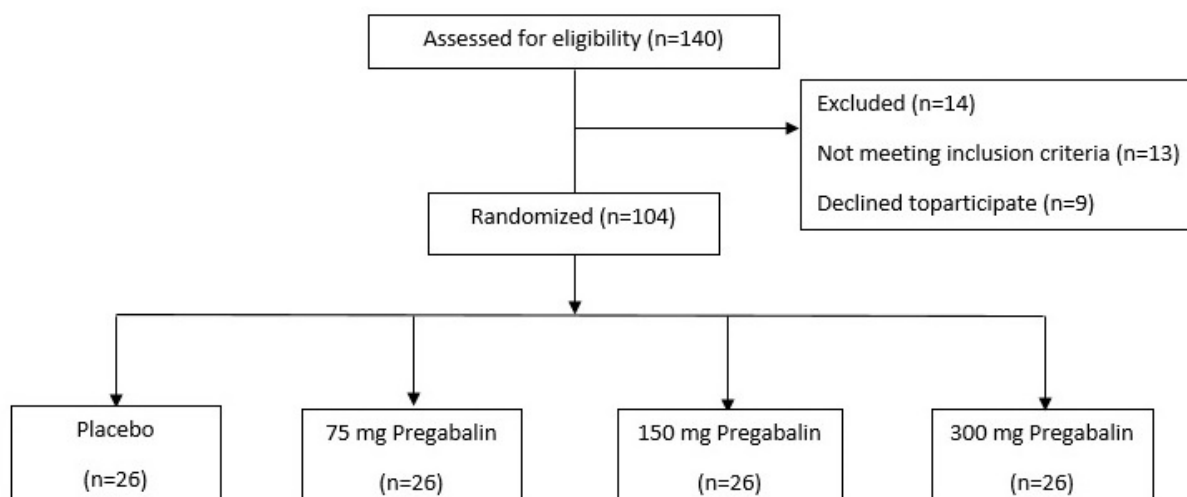


Figure 1. The CONSORT flow diagram of how to enter patients into the study and divide them into four groups

group assignment, as they received either pregabalin or a placebo. To maintain blinding, identical packaging was used for both pregabalin and placebo. The outcome assessors were also blinded to the treatment group assignments.

The sample size for each group was determined using repeated measures analysis of variance (ANOVA) with G-power software. The required sample size for each group was calculated to be 26 patients. ($\alpha = 0.05$, effect size = 0.36, power = 0.95).

Participants were randomly assigned to 1 of the 4 groups using a sealed opaque envelope method and pseudorandom number generator. The envelopes were prepared by an independent statistician and were numbered sequentially from 1 to 104. The randomization ratio was 1 to 1 to 1 to 1, with 26 patients allocated to each group. To ensure concealment, the envelopes were sealed in a way that prevented anyone from knowing what was inside. The statistician checked the sequence for any errors or anomalies and verified that it was truly random. We also took steps to ensure that the outcome assessors remained blinded to the treatment group assignments throughout the study.

One of the 4 patient groups received a placebo 2 hours before the PCNL surgery, while the other 3 groups received 75 mg, 150 mg, and 300 mg of pregabalin, respectively.

This study aimed to investigate whether preoperative pregabalin administration reduces preoperative anxiety and postoperative pain in patients undergoing PCNL surgery and to determine the optimal dosage.

The level of anxiety of the patients was measured and recorded in 2 stages. The first measurement was taken immediately before the patients received the medicine (about 2 hours before the surgery), either the placebo or one of the pregabalin doses. The second measurement was taken approximately before the start of PCNL surgery.

Anxiety level was assessed using the Hamilton Rating Scale for Anxiety (HRSA), which is a widely used and validated tool for measuring anxiety levels. The reliability and

validity of Hamilton's anxiety questionnaire were both considered satisfactory, with a reliability score of 0.85 and a validity score of 0.6. A value of 0.85 for Cronbach's alpha suggested that the items in Hamilton's anxiety questionnaire were strongly related to each other (10,11). The HRSA consists of 14 questions, each with a score ranging from 0 to 4. The total score of the questionnaire can range from 0 to 56. The scores are interpreted as follows: a score less than 7 indicates no anxiety, a score between 8 to 14 indicates mild anxiety, a score between 15 to 23 indicates moderate anxiety, and a score greater than 24 indicates severe anxiety. This scoring system is widely used in clinical practice and research to assess the severity of anxiety symptoms. By measuring anxiety at 2 time points, the study was able to assess the effectiveness of pregabalin on anxiety levels over time.

The pain level of patients after surgery was measured using the visual analog scale (VAS) at 4 different time points after surgery—2, 6, 12, and 24 hours. This scale ranges from 0 to 10, where 10 indicates the worst pain and 0 indicates no pain.

Surgical Procedure

During the premedication phase, all patients received an intravenous (IV) injection of 2 $\mu\text{g/kg}$ fentanyl and 0.02-0.03 mg/kg midazolam. To induce general anesthesia, IV thiopentone sodium 4 to 5 mg/kg was administered. Endotracheal intubation was performed using IV atracurium as a muscle relaxant at a dose of 0.5 mg/kg. Anesthesia was maintained using isoflurane and N₂O: O₂. Normal saline was administered intravenously at a rate of 60 to 80 mL/h as an IV fluid. Patients were extubated after the reversal of residual neuromuscular blockade with IV neostigmine 0.04-0.07 mg/kg and atropine 0.02 mg/kg.

All patients underwent PCNL surgery with a single access point using a size 30 Fr nephroscope, which was performed by a consistent surgical team, and anesthesia was

administered by a fixed anesthesia team throughout the procedure. A nephrostomy tube was inserted for all patients.

Outcome Assessment

The main aim of this study was to examine the impact of pregabalin on the anxiety levels of patients before PCNL surgery and to assess its effect on pain levels during the first day after surgery. Additionally, this study aimed to determine the optimal dosage of pregabalin for these patients. The secondary outcome of this study was to investigate any potential side effects associated with pregabalin administration at varying doses for those who were eligible for PCNL surgery.

Statistical Methods

Descriptive statistical methods, including means \pm standard errors of the mean, frequencies, and percentages, were used to analyze demographic variables by treatment group. Using nonparametric statistical techniques, the Hamilton score was compared twice: (1) before and after in each group using the Wilcoxon Signed Ranks Test, and (2) between the four groups each time using the Kruskal Wallis Test.

The repeated measure structure of categorical data for VAS scores was analyzed using the generalized estimation equation (GEE) model and the link function was analyzed using Poisson log-linear model. Various covariance structures were used and assessed with 2 goodness-of-fit indices criteria including (1) Quasi Likelihood under the Independence Model Criterion (QIC) and (2) Corrected Quasi Likelihood under the Independence Model Criterion (QICC). Finally, the best model was selected with unstructured covariance matrices and QIC = 119.211 and QICC = 143.096.

The Bonferroni test was used for post-hoc tests.

The side effects were analyzed using Pearson chi-square and Fisher exact tests. All statistical analyses were done with IBM SPSS Statistics 26 and R Version 4.3.1.

Results

A total of 140 patients were included in this study, and after several exclusions, 104 patients were evaluated. These patients were then divided into 4 groups, each containing 26 patients. The groups had similar characteristics—such as age, sex, body mass index (BMI), surgery duration, and anesthesia duration. No significant differences were observed between the groups with the Kruskal-Wallis test (Table 1). The patients in this study ranged in age from 19 to 59 years. Although the placebo group had greater use of morphine after surgery, this relationship was not statistically significant ($P=0.095$); moreover, it cannot be concluded that higher doses of pregabalin lead to a decrease in narcotic use after surgery.

First of all, the Shapiro-Wilk test results showed that the Hamilton score did not follow a normal distribution. Thus, for comparison between scores in the 4 groups, instead of ANCOVA, Rank ANCOVA was used.

The Hamilton questionnaire scores of all patient groups increased significantly after administering the medication before surgery ($P<0.05$) (Figure 2). This finding can be attributed to the stress of undergoing surgery and the presence of patients in the operating room at the outset. Upon comparing the different doses of pregabalin to the placebo (before drug administration and after drug administration), no statistically significant relationship was identified ($P=0.793$ and $P=0.741$, respectively), and pregabalin did

Table 1. Patient Demographic and Clinical Characteristics

Variable	Placebo	75 mg Pregabalin	150 mg Pregabalin	300 mg Pregabalin
Age	40.46 \pm 8.860	41.12 \pm 10.801	39.77 \pm 13.295	33.85 \pm 10.567
Sex (M/F)	16/10	15/11	17/9	15/11
Body mass index, kg/m ²	27.5546 \pm 4.10619	27.2700 \pm 4.01885	27.8869 \pm 4.22344	28.6177 \pm 4.67144
Surgery time, min	135.00 \pm 22.847	110.77 \pm 27.521	114.81 \pm 23.600	116.54 \pm 27.596
Anesthesia time, min	150.58 \pm 24.180	125.77 \pm 27.521	129.81 \pm 23.600	131.54 \pm 27.596
Morphine use after surgery	9 (47.4%)	4 (21.1%)	3 (15.8%)	3 (15.8%)

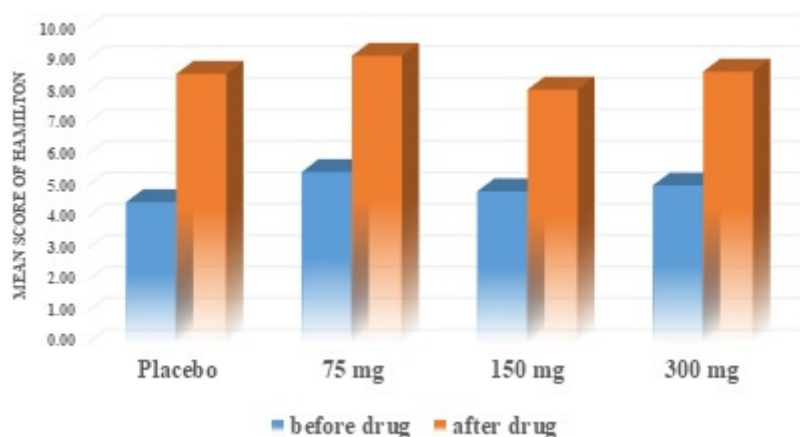


Figure 2. Hamilton score before and after drug in four groups

Table 2. Hamilton Anxiety Questionnaire Before Administration of Pregabalin and After Administration of Pregabalin

Hamilton Score	GROUPS					
	Placebo	75 mg	150 mg	300 mg	P Values**	
Pretest	4.46 ± 0.87	5.42 ± 0.85	4.81 ± 0.83	5.00 ± 0.88	0.793	
Posttest	8.54 ± 1.26	9.12 ± 1.22	8.04 ± 1.10	8.62 ± 0.96	0.741	
P Values*	0.000	0.000	0.000	0.000		
Shapiro-Wilk test statistic, P value	0.821(0.000)	0.909(0.024)	0.826(0.001)	0.909(0.025)		
ANCOVA-TEST						
SOURCE	SS	df	MS	F	P value	η ²
Hamilton pretest	53083.46	1	53083.46	133.931	0.00	0.575
GROUP	413.78	3	137.93	0.348	0.791	0.010

*Wilcoxon signed rank test for before-after test; ** for comparison between groups, Kruskal-Wallis test

Table 3. The Visual Analog Scale Score of Patients After Surgery Based on Group Time

Time, hours	Group			
	Placebo	75 mg	150 mg	300 mg
2	8.46 ± 0.177	7.5 ± 0.169	7.92 ± 0.146	7.77 ± 0.195
6	7.92 ± 0.183	5.69 ± 0.234	5.73 ± 0.245	5.27 ± 0.245
12	7.38 ± 0.167	4.23 ± 0.202	4.15 ± 0.213	3.31 ± 0.22
24	6.31 ± 0.24	2.85 ± 0.233	2.46 ± 0.209	2.31 ± 0.247

not demonstrate an effect on reducing presurgical anxiety in patients (Table 2). Also, ANCOVA results show that the P-value of the group was not significant ($P=0.791$), consequently by controlling pretest scores, no significant differences were observed between Hamilton scores in the 4 groups.

In the group-time study of these patients, the pain level in all 4 groups (placebo, pregabalin 75 mg, pregabalin 150 mg, and pregabalin 300 mg) decreased with time (Table 3). This decrease in pain over time was statistically significant for most of the 4 groups (ANOVA and Friedman Test $P<0.05$). Overall, the study suggested that pain levels decrease over time after surgery, regardless of whether patients receive a placebo or different doses of pregabalin (Figure 3).

An examination of these 4 groups of patients revealed no significant difference in pain scores between the placebo group and the pregabalin groups (75 mg, 150 mg, and 300 mg) at any time point ($P<0.05$), indicating that regardless

of the time passed since the end of the surgery, the patients who received pregabalin had lower pain scores than those who received a placebo. The post-hoc Bonferroni test did not find any significant difference in pain scores between the pregabalin groups at different doses (75 mg, 150 mg, and 300 mg). These findings suggested that all the 3 doses of pregabalin were equally effective at reducing pain, and it cannot be concluded that higher doses of pregabalin (150 mg and 300 mg) had a significantly greater effect on reducing postsurgical pain than did the lower dose of pregabalin (75 mg) (Table 4). Additionally, without considering the group effect, over time, the pain level of the patients decreased significantly according to VAS scores ($P<0.001$) (Table 4).

The generalized estimation equation or GEE method was used, and the Poisson log-linear model and the Bonferroni correction were also used. The matrix structure was considered unstructured.

When investigating the side effects of the drug, it was

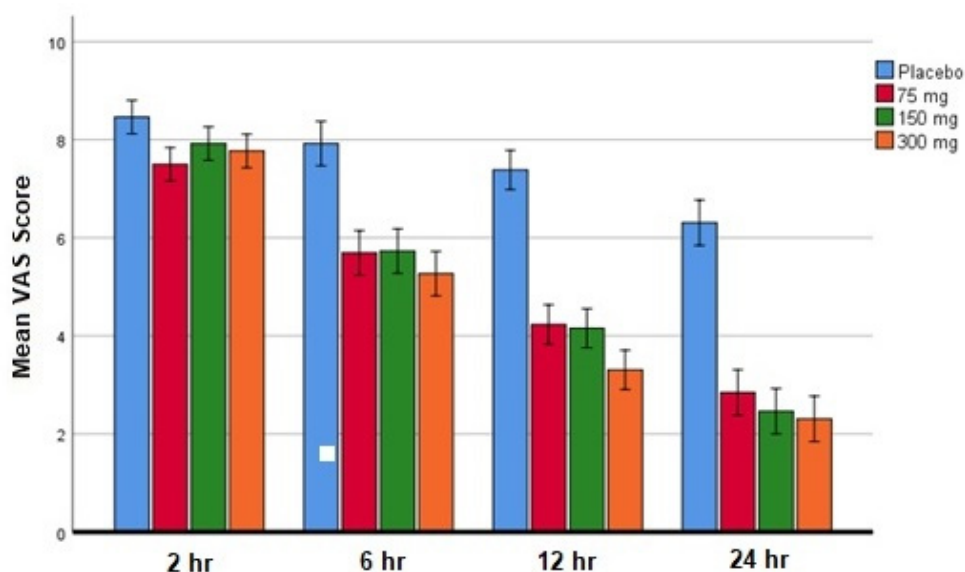
**Figure 3.** Postoperative pain in patients considering the group-time effect

Table 4. The Visual Analog Scale Score of Patients After Surgery Based on Treatment Group, Time, and group time

Source	Wald Chi-Square	df	P Value
Intercept	7550.45	1	<0.001
Group	266.41	3	<0.001
Time	776.80	3	<0.001
Group * Time	251.07	9	<0.001

Table 5. Pregabalin Side Effects

Side effect	Placebo	75 mg Pregabalin	150 mg Pregabalin	300 mg Pregabalin	P Value
Dizziness	2 (6.9%)	6 (20.7%)	9 (31.0%)	12 (41.4%)	0.015
Nausea	8 (16.3%)	11 (22.4%)	14 (28.6%)	16 (32.7%)	0.129
Headache	5 (11.4%)	10 (22.7%)	13 (29.5%)	16 (36.4%)	0.015
Dry Mouth	1 (5.6%)	4 (22.2%)	5 (27.8%)	8 (44.4%)	0.081
Shivering	2 (8.7%)	6 (26.1%)	7 (30.4%)	8 (34.8%)	0.201
Diplopia or Blurred Vision	0 (0.0%)	4 (26.7%)	5 (33.3%)	6 (40.0%)	0.091
Angioedema	0 (0.0%)	0 (0.0%)	1 (33.3%)	2 (66.7%)	0.287

observed that the frequency of side effects—including dizziness, nausea, headache, dry mouth, shivering, diplopia or blurred vision, and angioedema—were greater in the pregabalin user groups and increased with increasing pregabalin dose. However, this relationship was significant only for headache ($P=0.0129$) and dizziness ($P=0.015$); for other complications, there was no statistically significant correlation (Table 5).

Discussion

Postoperative pain refers to discomfort experienced after invasive diagnostic or therapeutic procedures. Failure to manage pain effectively after surgery can result in serious complications such as delayed healing and pulmonary embolism (5, 12). To prevent these issues and ensure proper pain control, pain management should be considered after, during, and before surgery (preemptive analgesia). Studies have shown that preemptive analgesia is more effective at managing pain than similar interventions administered after surgery (13, 14). The effectiveness of anticonvulsant medications (eg, gabapentin and pregabalin) for managing neuropathic pains has led researchers to investigate their impact on postoperative pain (15, 16).

In a recent meta-analysis published in 2022, Xuan et al compared and evaluated 19 different preemptive analgesia regimens—including acetaminophen, lornoxicam, gabapentin, ibuprofen, and pregabalin—using data from 188 published studies. One study revealed that preemptive analgesia regimens containing gabapentin were effective at reducing postoperative pain, narcotic use, and the incidence of postoperative nausea (14). Similarly, in a meta-analysis published in 2017, Wang et al reviewed 10 clinical studies and reported that preoperative administration of pregabalin was effective for managing pain, nausea, and vomiting after hysterectomy surgery (17). In a more recent study from 2022, Choppa et al investigated the effects of pregabalin on pain and dysuria after PCNL. The authors found that administering 150 mg of pregabalin 1 hour before the procedure significantly reduced instrumentation-induced dysuria but did not significantly reduce postoperative pain (3). In the present study, we found that administering 75 mg of pregabalin before PCNL surgery significantly decreased

postoperative pain. Our results suggest that preemptively administering pregabalin for analgesia is a safe measure, as no significant complications have been reported. However, increasing the dose of the drug did not result in any further reduction in pain but rather led to an increase in side effects associated with the medication.

It is noteworthy that while in our study population, there was no significant difference in the results based on varying doses of pregabalin, some previous studies have reported an increase in the effectiveness of this drug with higher doses. For instance, in a study published in 2011 by Przesmycki et al, 74 hysterectomy candidates were randomized to receive 75, 150, or 300 mg of pregabalin or a placebo 1 hour before surgery. The results showed that pain scores were significantly lower in only the group receiving 300 mg of pregabalin than in the other groups (18). These findings suggest that higher doses of pregabalin may be more effective for pain management during certain types of surgeries.

In the surgical setting, patients may experience psychological distress leading up to their procedure, which can result in preoperative anxiety. This type of anxiety is triggered by hospitalization and impending surgery (19, 20). Preoperative anxiety can impact the need for anesthesia and analgesia, as well as the severity of postoperative pain. In some cases, surgery may even increase postoperative morbidity and mortality (21). In a recent review, Wang et al discussed and reported on various nonpharmacologic approaches to alleviate preoperative anxiety (22). However, due to the time-consuming nature and limited results of these methods, there is a growing preference for pharmacological interventions. In many medical centers, benzodiazepines are commonly used for this purpose, but their adverse effects have led to the need for alternative drugs to manage preoperative anxiety (8, 23).

In the last few years, several studies have explored the impact of gabapentinoids, such as pregabalin, on patients' anxiety levels before surgery. A review by Torres-González et al in 2020 revealed that administering 150 mg of pregabalin before surgery can reduce anxiety in patients based on the results of 12 clinical trials (8). However, other studies have produced conflicting results. For instance, in a

randomized clinical trial published in 2023 by Nimmaanrat et al, neither pregabalin nor diazepam had significant anti-anxiety effects compared with placebo (24). Our analysis also suggested that preemptive administration of pregabalin does not significantly reduce patients' anxiety levels.

The findings of this study support the usefulness of preemptive administration of pregabalin before PCNL surgery, in line with previous research on the benefits of preemptive analgesia.

Limitations of the study

Study limitations include a small sample size, a limited follow-up period, a single-center design, and a lack of intention-to-treat analysis.

Potential biases that may have affected this study include detection bias, measurement bias, and the Hawthorne effect.

To improve the generalizability of our findings and minimize these limitations, we propose the following strategies: increasing the sample size to capture a more representative range of population variability, recruiting patients from multiple centers to enhance representation and diversity, collecting more detailed patient characteristic data to facilitate subgroup analysis, conducting a longer follow-up period to capture long-term outcomes, and performing sensitivity analyses to explore potential sources of heterogeneity.

Conclusion

The findings of the study suggest that administering pregabalin before PCNL surgery does not significantly reduce anxiety in patients before the procedure. However, preoperative administration of pregabalin has been found to be beneficial for alleviating postoperative pain in patients who have undergone PCNL surgery. According to the results of the present study, the optimal dosage of pregabalin was found to be 75 mg, as increasing the dose does not result in further pain reduction but rather leads to an increase in drug-related side effects.

Authors' Contributions

Anahita Ansari Djafari: conception and design, writing, reviewing & editing; Amir Alinejad Khorram: conception and design, writing the original draft, Data curation; Seyyed Ali Hojjati: analysis and interpretation of data, writing the original draft; Mohammad Fayaz: analysis and interpretation of data, writing, reviewing & editing; Amir Hossein Eslami: conception and design, writing the original draft, data curation; Maryam Garousi: analysis and interpretation of data, writing the original draft; Saba Faraji: analysis and interpretation of data, writing the original draft; Elnaz Aghabeiki: writing, reviewing & editing.

All authors contributed equally to the manuscript and read and approved the final version of the manuscript. All authors are accountable for all aspects of the work.

Ethical Considerations

The research conducted in this study adhered to the prin-

ciples outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethical Code No. IR.SBMU.RETECH.REC.1400.762) and also approved by the Iranian Registry of Clinical Trials (IRCT20200402046915N2).

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Conflict of Interests

The authors declare that they have no competing interests.

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