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SCIENTIFIC ARTICLE

Adding 75 mg pregabalin to analgesic regimen reduces pain scores and opioid consumption in adults following percutaneous nephrolithotomy

Harun Aydoğan[a,*], Ahmet Kucuk[a], Hasan Husnu Yuce[a], Mahmut Alp Karahan[a], Halil Ciftci[b], Mehmet Gulum[b], Nurten Aksoy[c], Saban Yalcin[a]

[a] *Department of Anesthesiology and Reanimation, Harran University Medical Faculty, Sanliurfa, Turkey*
[b] *Department of Urology, Harran University Medical Faculty, Sanliurfa, Turkey*
[c] *Department of Clinical Biochemistry, Harran University Medical Faculty, Sanliurfa, Turkey*

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KEYWORDS
Pregabalin;
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Abstract
Background and objectives: Adding novel adjunctive drugs like gabapentinoids to multimodal analgesic regimen might be reasonable for lessening postoperative pain scores, total opioid consumption and side effects after percutaneous nephrolithotomy. We aimed to evaluate the effect of pregabalin on postoperative pain scores, analgesic consumption and renal functions expressed by creatinine clearance (CrCl) and blood neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C (Cys C) levels in patients undergoing percutaneous nephrolithotomy (PCNL).
Methods: 60 patients undergoing elective PCNL were enrolled in the study. Patients were randomized to oral single dose 75 mg pregabalin group and a control group. Visual Analog Scale pain scores (VAS), postoperative intravenous morphine consumption during the first 24 postoperative hours, serum NGAL, Cys C levels and creatinine clearance (CrCl) was measured preoperatively and post-operatively at 2nd and 24th hour.
Results: Postoperative VAS scores were significantly decreased in the pregabalin group at the postoperative 30th min, 1st, and 2nd hour ($p = 0.002$, $p = 0.001$ and $p = 0.027$, respectively). Postoperative mean morphine consumption was statistically significantly decreased for all time intervals in the pregabalin group ($p = 0.002$, $p = 0.001$, $p = 0.001$, $p = 0.001$, $p < 0.001$, respectively). No statistically significant differences were found between the two groups with regard to CrCl, or Cys C at preoperative and postoperative 2nd and 24th hour. Postoperative 24th hour NGAL levels were significantly decreased in the pregabalin group ($p = 0.027$).

* Corresponding author.
E-mail: drharunaydogan@yahoo.com (H. Aydoğan).

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Conclusions: Oral single-dose preemptive 75 mg pregabalin was effective in reducing early postoperative pain scores and total analgesic consumption in patients undergoing PCNL without leading to hemodynamic instability and side effects.
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PALAVRAS-CHAVE
Pregabalina;
Analgésicos opiáceos;
Nefrolitotomia percutânea

Adição de 75 mg de pregabalina ao regime analgésico reduz escores de dor e consumo de opiáceos em adultos após nefrolitotomia percutânea

Resumo
Justificativa e objetivos: A adição de novos medicamentos adjuvantes, como os gabapentinoides, ao regime analgésico multimodal pode ser razoável para diminuir os escores de dor no pós-operatório, o consumo total de opiáceos e os efeitos colaterais após nefrolitotomia percutânea. Nosso objetivo foi avaliar durante o período pós-operatório o efeito de pregabalina nos escores de dor, consumo de analgésicos e funções renais expressas por clearance de creatinina (ClCr) e níveis séricos de cistatina-C (Cis-C) e lipocalina associada à gelatinase de neutrófilos (LAGN) em pacientes submetidos à nefrolitotomia percutânea (NLPC).
Métodos: Sessenta pacientes submetidos à NLPC eletiva foram incluídos no estudo. Os pacientes foram randomizados para receber pregabalina oral em dose única de 75 mg – grupo pregabalina e grupo controle. Os escores de dor medidos pela Escala Visual Analógica (EVA), o consumo de morfina intravenosa nas primeiras 24 horas de pós-operatório, LAGN sérico, níveis de Cis-C e clearance de creatinina (ClCr) foram mensurados no pré-operátorio e na segunda e 24a horas de pós-operatório.
Resultados: Os escores EVA no pós-operatório foram significativamente menores no grupo pregabalina nos tempos de 30 min, 1 e 2 horas ($p = 0,002$, $p = 0,001$ e $p = 0,027$, respectivamente). A média do consumo de morfina no pós-operatório foi estatisticamente significante menor em todos os intervalos de tempo no grupo pregabalina ($p = 0,002$, $p = 0,001$, $p = 0,001$, $p = 0,001$, $p < 0,001$, respectivamente). Não houve diferença estatisticamente significante entre os dois grupos em relação ao ClCr ou Cis-C no pré-operatório e na segunda e 24a horas de pós-operatório. Os níveis de LAGN na 24a hora de pós-operatório foram significativamente menores no grupo pregabalina ($p = 0,027$).
Conclusões: A dose única de 75 mg de pregabalina oral administrada precocemente foi eficaz na redução dos escores de dor no pós-operatório imediato e o consumo total de analgésicos em pacientes submetidos à NLPC, sem causar instabilidade hemodinâmica e efeitos colaterais.
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Introduction

Percutaneous nephrolithotomy (PCNL) is a common surgical method used for the treatment of renal calculi.[1] Postoperative pain due to dilatation of the renal capsule, the parenchymal tract, and peritubal distressing of the nephrostomy tube[2,3] is one of the complex pain conditions in urology. Multimodal postoperative pain management may decrease the incidence of complications, the requirement for hospitalization, and decrease recovery times and health costs.[4]

Opioids have an important role in postoperative pain management despite important side-effects[5] that might have significant impact on patient recovery after surgery.[6] Thus, multimodal postoperative pain management might also be valuable in reducing opioid-related side-effects.[7] Adding novel adjunctive drugs like gabapentinoids to a multimodal analgesic regimen, which has been shown to be effective in postoperative analgesia in different procedures, might be reasonable for lessening postoperative pain scores, total opioid consumption and side effects after percutaneous nephrolithotomy.[8–11]

Pregabalin is a structural analog of the inhibitory neurotransmitter gaba-aminobutyric acid, with anticonvulsant, anti-hyperalgesic, and anxiolytic properties like gabapentin, but with a more favorable pharmacokinetic profile.[12,13] It was proven to be valuable in different postoperative pain situations, including dental and spinal surgery, laparoscopic hysterectomy, and cholecystectomy with different dosage regimens, besides the success in neuropathic pain management.[14–19]

We hypothesized that adding pregabalin to the analgesic regimen would have an effect on postoperative pain scores and renal functions and reduce opioid consumption. To the best of our knowledge this is the first study designed to evaluate the effect of single dose preoperative 75 mg pregabalin on postoperative pain scores, analgesic consumption and renal functions expressed by creatinine clearance (CrCl) and blood neutrophil gelatinase-associated lipocalin

(NGAL) and cystatin C (Cys C) levels in patients undergoing PCNL.

Materials and methods

Patient selection

This prospective, randomized, study was started after Institutional Ethics Committee approval (Harran University Medical Faculty Ethics committee no: 12-01-24) and after obtaining written informed consent from all patients. The study was conducted according to the most recent version of the Declaration of Helsinki. 60 patients between the ages of 18 and 60 years with ASA I-II physical status who underwent elective PCNL under general anesthesia were enrolled in the study. Patients were randomized to pregabalin 75 mg and a control group with a sealed envelope technique. Pregabalin was given orally, 1 h prior to surgery by a staff nurse who was not included in the study (Fig. 1). Anaesthesiologists, surgeons and biochemists were blinded to the groups. A physician, who was not a member of the anesthesia or surgical team, recorded the study data.

Exclusion criteria

Patients with a history of drug or alcohol abuse and patients with chronic pain or daily intake of analgesics, uncontrolled diabetes mellitus and/or hypertension, atherosclerotic heart disease, seizures, impaired kidney or liver functions, body mass index $\geq$35 kg/m^2, and whom could not control a patient-controlled analgesia (PCA) device were excluded from the study.

Anesthetic management and operation

Standard monitoring comprised of non-invasive arterial pressure, electrocardiography, and pulse oximetry was performed. A Bispectral Index (BIS) A 2000 monitor (Aspect Medical Systems, Natick, MA, USA) was also employed and baseline values for all variables were obtained. The values of MAP, HR and SpO_2 were recorded at baseline, 5, 10, 15, 20, 25, 30, 60 and 120 min during the operation. The anesthesia technique was uniform in all the groups. Patients were induced with remifentanil 1 μg kg^{-1} and propofol 2 mg kg^{-1}; orotracheal intubation was facilitated by rocuronium 0.6 mg kg^{-1}. Anesthesia was maintained with 2–3% sevoflurane, 50% nitrous oxide in oxygen and with 0.15 μg kg^{-1} min^{-1} remifentanil infusion. A target BIS range of 40–55 was used to guide sevoflurane administration.

Patient controlled analgesia and pain scores

At the end of surgery, residual neuromuscular paralysis was antagonized with neostigmine 0.04 mg kg^{-1} and atropine 0.02 mg kg^{-1}. The patients were connected to a morphine patient controlled analgesia (PCA) pump on arrival at the PACU. The PCA pump was set to deliver a loading dose of 2.5 mg and an incremental dose of 2.5 mg at a lockout interval of eight minutes and a four-hour limit of 50 mg. The incremental dose was increased to 3 mg, the lockout interval decreased to six minutes and the four-hour limit increased to 60 mg, whenever the analgesia was inadequate after one hour. Before the operation, the patients were trained on how to use the PCA pump.

They were also taught how to express the level of pain they experienced using an 11-point Visual Analog Scale (VAS), with 0 indicating no pain and 10 indicating the worst probable pain. Vital signs, pain scores, morphine consumption and adverse effects such as nausea, vomiting, pruritus, urinary retention, somnolence, dizziness, vision abnormalities (double or blurred) and headache were recorded. Intravenous tenoxicam 20 mg was used as a rescue analgesic.

Blood sampling

Preoperative and post-operative blood samples were collected for measurements of Cys C, NGAL, BUN, creatinine (Cr), sodium and potassium in the preoperative period in the operating room and in the postoperative 2nd and 24th hour. CrCl was calculated with the Cockroft–Gault Formula.[20]

Biochemical analysis

Serum Cys C [ALX-850-292-KI01 Cys C (human) Elisa Kit, BioVendor, Lorrrach, Germany] and NGAL (RD191102200R Human Lipocalin-2/NGAL Elisa Kit, BioVendor trademark, Heidelberg, Germany) levels were analyzed using ELISA kits.

Statistical analysis and study sample size calculation

Statistical analysis was performed using SPSS for Windows, version 11.5 (SPSS, Chicago, IL, USA). Distribution of continuous variables was analyzed with the one-sample Kolmogorov–Smirnov test, and all data were distributed normally. Comparisons among groups with respect to demographic data were evaluated using Chi-square; pain scores, morphine consumption and biochemical values were evaluated using independent *t*-tests. Repeated-measures ANOVA with Bonferroni post hoc test was used to compare baseline and follow-up HR and MAP measurements in each group and independent sample *t*-test was used to compare these hemodynamics between groups in different time intervals. The results were expressed as mean and SD or median and range where appropriate. A two tailed *p*-value less than 0.05 was considered to be statistically significant.

Power calculations based on a pilot study with the first 12 patients to detect a significant difference in morphine consumption revealed mean morphine consumption as 1.6 $\pm$ 0.61 mg vs. 1.2 $\pm$ 0.58 mg in control and pregabalin groups, respectively. From these differences and assuming a two tailed α value of 0.05 (sensitivity 95%) and a β value 0.20 (study power: 80%), we determined that at least 30 patients were required in each group.

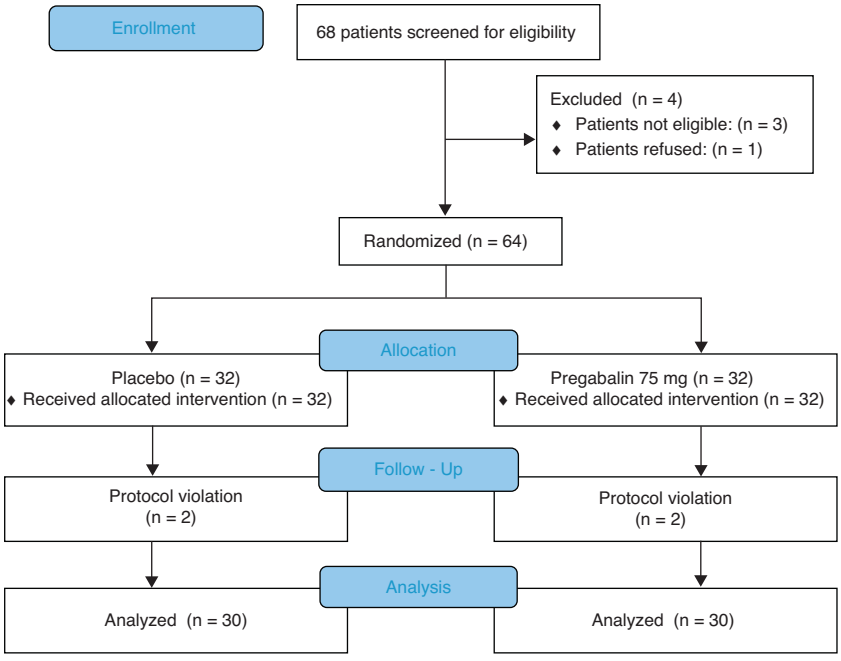

Figure 1 Flow diagram of the study.

Results

A total of 68 patients were assessed for eligibility and four cases were excluded. Of the 64 subjects receiving medication after randomization, 60 subjects completed the study (2 patients in each group were excluded due to protocol violation). Of the 60 patients who completed the study, 30 received pregabalin (Fig. 1).

There were no statistically significant differences between the groups regarding age, sex, body mass index, operation time, and intraoperative remifentanil consumption (Table 1).

Postoperative VAS scores of patients were significantly decreased in the pregabalin group at the postoperative 30th min, 1st, and 2nd hour when compared with the control group ($p = 0.002$, $p = 0.001$ and $p = 0.027$, respectively, Table 2). However, there were no statistically significant differences between postoperative VAS values at the 6th, 12th, and 24th hours, between groups ($p > 0.05$, for all comparisons, Table 2).

Postoperative mean morphine consumption was statistically significantly decreased for all time intervals in the pregabalin group compared to the control group ($p = 0.002$, $p = 0.001$, $p = 0.001$, $p = 0.001$, $p < 0.001$, respectively, Table 3). None of the patients need tenoxicam as rescue analgesic.

The hemodynamic data, including MAP, HR, and SpO_2, were not different between the groups at any time point ($p > 0.05$ in all time intervals).

The most frequent adverse effects were PONV, pruritus and urinary retention during the first 24 h after surgery. Incidence of PONV, pruritus and urinary retention, dizziness, vision abnormalities, and headache were similar among the groups ($p > 0.05$; for all comparisons, Table 4). No other adverse effects, such as respiratory depression and somnolence, were recorded in any patient from either group.

No statistically significant differences were found between the two groups with regard to renal function, CrCl, or Cys C at preoperative and postoperative 2nd and 24th hour. Postoperative NGAL levels in the pregabalin group were not significantly different in preoperative and postoperative 2nd hour whereas postoperative 24th hour NGAL levels were significantly decreased in the pregabalin group ($p = 0.027$, Table 5).

Table 1 Demographic and clinical data for each group and intraoperative dose of remifentanil.

Characteristics	Control ($n = 30$) Mean ± SD	Pregabalin 75 mg ($n = 30$) Mean ± SD
Age (years)	38.45 ± 13.51	39.2 ± 11.66
Height (cm)	164 ± 7.51	167.85 ± 8.82
Weight (kg)	68.55 ± 10.05	72 ± 10.37
Gender (M/F)	16/14	18/12
ASA (I/II)	10/20	12/18
BMI (kg/m^2)	25.39 ± 2.34	25.45 ± 2.08
Intraoperative remifentanil (μg)	1172 ± 332	1196 ± 334
Operation time (min)	115.25 ± 32.99	109.9 ± 22.27

$p > 0.05$ for all comparisons.

Discussion

With the present study, we have tested the hypothesis that single dose 75 mg pregabalin administered 1 h

Table 2 Mean Visual Analog Scale pain scores.

Pain intensity VAS	Control ($n = 30$)	Pregabalin 75 mg ($n = 30$)	p
30 min	5.65 ± 0.67	4.95 ± 0.6	0.002[a]
1 h	3.85 ± 1.18	2.95 ± 0.39	0.001[a]
2 h	2.4 ± 0.94	1.85 ± 0.81	0.027[a]
6 h	1.25 ± 0.71	1.25 ± 0.85	0.616
12 h	0.9 ± 0.3	1.05 ± 0.75	0.671
24 h	0.8 ± 0.41	1 ± 0.79	0.484

VAS, Visual Analog Scale.
Values are means ± SD.
[a] p 0.05 when comparing with the control group.

Table 3 Mean morphine consumption of groups (mg).

Hour	Control ($n = 30$)	Pregabalin 75 mg ($n = 30$)	p
1 h	1.8 ± 0.62	1.2 ± 0.57	0.002[a]
2 h	3.5 ± 0.90	2.5 ± 0.94	0.001[a]
6 h	7.02 ± 2.5	4.55 ± 1.42	0.001[a]
12 h	9.6 ± 4	6.02 ± 2.56	0.001[a]
24 h	12.1 ± 5.4	7.07 ± 2.7	<0.001[a]

Values are means ± SD.
[a] $p < 0.05$.

Table 4 Side effects among groups.

Side effect	Control ($n = 30$)	Pregabalin 75 mg ($n = 30$)	Chi-square p
Nausea and vomiting (n)	3 (10%)	1 (3%)	NS
Pruritus (n)	2 (6.6%)	0	NS
Urinary retention (n)	2 (6.6%)	0	NS
Respiratory depression (n)	0	0	NS
Somnolance (n)	0	0	NS
Dizziness (n)	0	1 (3%)	NS
Vision abnormalities (n)	0	1 (3%)	NS
Headache (n)	0	1 (3%)	NS

Side effects among groups were evaluated using the Chi-square test.
NS, not significant.

Table 5 Laboratory evaluation among groups of patients.

	Control ($n = 30$)	Pregabalin 75 mg ($n = 30$)	p
NGAL (ng/mL)			
Baseline	172.2 ± 51.1	188.8 ± 43.6	0.23
2 h	188.9 ± 47	142.4 ± 76.6	0.58
24 h	200.4 ± 48.7	171 ± 55.2	0.027[a]
Cystatin C (ng/mL)			
Baseline	1061.9 ± 48.5	1071.2 ± 59.7	0.89
2 h	1045.5 ± 292.3	1043.4 ± 184.1	0.76
24 h	1104.4 ± 79.7	1093 ± 97.4	0.6
CrCl (mL/min)			
Baseline	95.3 ± 4.1	95 ± 6.8	0.60
2 h	92.8 ± 3.4	93.4 ± 6.4	0.30
24 h	91.9 ± 4.3	92.75 ± 5.7	0.28

Values are means ± SD.
[a] $p < 0.05$ when comparing with the control group.

preoperatively would have effect(s) on postoperative pain scores, morphine consumption, renal function, and hemodynamic parameters in patients undergoing PCNL. We have shown that (1) VAS scores were statistically decreased in the first 2 postoperative hours in the pregabalin group, (2) morphine consumption was significantly decreased at postoperative 24 h in all time intervals in the pregabalin group, (3) postoperative 24th hour NGAL levels were also significantly decreased in the pregabalin group (4) and both groups have similar hemodynamic effects, with a similar side effect profile.

Several techniques have been reported to provide postoperative analgesia for percutaneous nephrolithotomy, including paravertebral, spinal and epidural block, local analgesic infiltration, and systemic analgesic therapy modalities, such as nonsteroidal analgesic drugs and opioids.[21–25] There has been no study focusing on preemptive single dose pregabalin administration in PCNL.

The use of pregabalin in acute postoperative pain has been assessed in recent studies. A meta-analysis focusing on perioperative pregabalin in the management of acute postoperative pain revealed decreased opioid consumption and opioid-related adverse effects after surgery; however, postoperative pain intensity was not found to be decreased by pregabalin.[26] In another meta-analysis, administration of pregabalin during a short perioperative period provides additional analgesia in the short term but at the cost of additional adverse effects, and they reported the lowest effective dose as 225–300 mg/d.[27]

Numerous studies on the efficacy of pregabalin for postoperative pain have revealed contradictory results, probably due to differences in dosage, dosing regimen, or the characteristics of the surgical procedures.[26,28–33] There were only three studies that emphasized preoperative single dose 75 mg oral pregabalin as being effective in decreasing postoperative pain scores in different clinical settings, such as septoplasty, laparoscopic cholecystectomy and mammoplasty, whereas 50 mg was shown not to be effective in pain control in laparoscopic cholecystectomy. In this study, we tried to administer the lowest dose that has been proven to be effective in a postoperative pain setting, so we used a preoperative single dose 75 mg pregabalin in PCNL. In this study, we were able to demonstrate superior analgesia with 75 mg of pregabalin over control in the early postoperative period (first two hours) without an increase in side-effects after PCNL. At the 6th, 12th, and 24th hour, no differences were observed in VAS levels.

Preemptive pregabalin administration has also been shown to decrease opioid consumption in several postoperative settings (mammoplasty, hysterectomy, lumbar spinal fusion surgery, gynecological laparoscopic surgery, laparoscopic sleeve gastrectomy, laparoscopic cholecystectomy).[17–19,31,32,34] We also found morphine consumption to be decreased for all time intervals during the postoperative 24 h. Increased morphine consumption in the control group might be the reason for similar VAS scores after the first two hours of the postoperative period.

In a clinical setting with PCNL patients, postoperative renal functions might also be in the consideration of clinicians. The surgery itself, underlying disease, and medications in the preoperative and postoperative period might all alter renal functions. In this study, our secondary outcomes were to compare CrCl and blood NGAL and Cys C levels in pre- and postoperative periods in the groups to assess renal functions. Cys C, which is a 13-kD cysteine proteinase inhibitor protein, was shown to predict acute kidney injury (AKI) earlier than other biomarkers[35] whereas N-GAL was shown to be one of the most promising biomarkers of kidney injury, which could predict AKI 24–72 h before a diagnostic creatinine increment.[36–40] Patients with increased serum NGAL and Cys C are at greater risk of adverse outcomes both in the presence or absence of an increase in serum creatinine.[41] In this study CrCl and serum Cys C levels were similar in the two groups in all measurements, as well as postoperative NGAL levels at preoperative and postoperative 2nd hour. However, NGAL was significantly decreased at the 24th hour in the study group compared to the control group. These results indicate that pregabalin did not have a considerable harmful effect on renal function, either clinically or biochemically, especially in this clinical setting. Preemptive pregabalin was also shown to significantly alter hemodynamic data during operations in different clinical settings.[42,43] In this study the MAP and HR were also similar between groups for any time interval.

The common adverse effects of pregabalin are dose-dependent drowsiness and dizziness[16,33] and the possible advantages of pregabalin may be mitigated by these troublesome side-effects; thus, it is crucial to determine the lowest optimal dose of pregabalin for analgesic use without the adverse outcomes. We did not observe any significant increase in side effects, including PONV, sedation, dizziness, headache, visual disturbance, pruritus, urinary retention, respiratory depression, somnolence, dizziness and vision abnormalities during the first 24 h after surgery in the pregabalin group compared to the control group. This might be attributed to the single low dose of pregabalin in this study.

Several limitations of the present study should be noted. The potential limitations are the absence of a placebo group and the absence of long-term clinical follow-up. Furthermore, the majority of our pregabalin and control group patients were in the middle age group. Different results might be obtained with children or a geriatric population due to possible altered pharmacodynamics and pharmacokinetics of pregabalin.

In conclusion, oral single-dose preemptive 75 mg pregabalin was effective in reducing postoperative pain scores and total analgesic consumption in patients undergoing PCNL without leading to hemodynamic instability and side effects.

Conflicts of interest

The authors declare no conflicts of interest.

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