Preoperative pregabalin administration significantly reduces postoperative opioid consumption and mechanical hyperalgesia after transperitoneal nephrectomy

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Editor’s key points
- Antiepileptic agents, such as pregabalin, may have some activity in the acute perioperative setting.
- After nephrectomy, pregabalin was shown to reduce the area of hyperalgesia and opioid consumption.
- Further work is needed to assess how pregabalin may modulate central sensitization acutely.

Background. Preoperative administration of pregabalin is proposed as a promising way of enhancing postoperative pain control. Whereas a few studies have investigated the effect of pregabalin on postoperative opioid consumption, no study has focused on the influence on postoperative hyperalgesia. In this randomized, triple-blinded, placebo-controlled study, we aimed to demonstrate that a single, preoperative dose of pregabalin reduces postoperative opioid consumption, mechanical hyperalgesia, and pain sensitivity.

Methods. Patients undergoing elective transperitoneal nephrectomy received 300 mg pregabalin or placebo 1 h before anaesthesia. After operation, patients received piritramide via a patient-controlled analgesia device. Pain levels and side-effects were documented. The area of hyperalgesia for punctuate mechanical stimuli around the incision was measured 48 h after the operation with a hand-held von Frey filament. Mechanical pain threshold was tested before and 48 h after surgery with von Frey filaments with increasing diameters.

Results. In each group, 13 patients were recruited. Total piritramide consumption [77 (16) vs 52 (16) mg, \( P = 0.0004 \)] and the normalized area of hyperalgesia [143 (87) vs 84 (54) cm², \( P = 0.0497 \)] were significantly decreased in the pregabalin group. There were no significant differences in mechanical pain threshold levels [1.20 (0.56) log(g) vs 1.05 (0.58) log(g), \( P = 0.6738 \)]. No case of severe sedation was reported in both groups. No other side-effects were observed.

Conclusions. Our study has shown that preoperative administration of 300 mg pregabalin in patients undergoing transperitoneal nephrectomy reduces postoperative opioid consumption and decreases the area of mechanical hyperalgesia.

Keywords: analgesics, opioids; hyperalgesia; nephrectomy; pain, postoperative; pain threshold; preanaesthetic medication; pregabalin
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Within the last years, substantial progress in understanding the mechanisms of acute pain has led to new concepts of treatment. Sensitization of dorsal horn neurones after tissue damage has been demonstrated to lead to hyperalgesia or allodynia.\(^1\)\(^2\) Thus, this process is considered to play a key role in chronicization of pain after a noxious stimulus.\(^3\)\(^4\)

Reducing hyperexcitability of dorsal horn neurones by initiating analgesic treatment before tissue damage is pivotal in preventing central nervous up-regulation.\(^5\)

Preoperative administration of anticonvulsive agents, that is, gabapentin and its successor pregabalin, is proposed to be a promising way of enhancing postoperative pain control.\(^6\)\(^7\)\(^8\) Recent reviews of the preoperative administration of pregabalin showed a clear reduction in postoperative opioid consumption.\(^6\)\(^7\) By binding to calcium channels, anticonvulsants reduce the release of excitatory neurotransmitters, and therefore inhibit central sensitization.\(^9\) Results from animal experiments showed a significant effect of pregabalin in reducing hyperalgesia.\(^10\) A recent review of this topic concluded that there is substantial evidence from basic research that pregabalin has an impact on the prevention of postoperative hyperalgesia; however, clinical data are insufficient to allow any conclusion.\(^8\)

In this study, we aimed to demonstrate the effect of a single, preoperative dose of pregabalin on postoperative opioid consumption, hyperalgesia, and pain sensitivity.
Methods

After Ethics committee’s approval and registration of the study protocol (www.clinicaltrials.gov; identifier: NCT00957177; and EUDRA-CT: ref: 2008-002443-17), patients undergoing elective transperitoneal nephrectomy at the Medical University of Graz, Austria, were contacted, informed about the study, and included after obtaining written informed consent. Inclusion criteria for this randomized, controlled, triple-blinded trial were age above 18 yr, weight above 40 kg, and ASA classification grades I–III. Exclusion criteria were defined as anaphylaxis, contraindication to pregabalin, non-steroidal anti-inflammatory drugs or piritramide, creatinine levels >2.0 mg dl⁻¹, liver enzymes above the three-fold of normal values, history of peptic ulcer disease, haemorrhagic diathesis, coronary heart disease, bronchial asthma, seizure disorders, opioid abuse, pre-existing therapy with opioids, pregnancy, or any contraindication for the use of patient-controlled analgesia (PCA).

Study medication and placebo identical in shape, size, and colour were provided by the hospital pharmacy. For blinding and randomization, the medication was packed in sealed, non-transparent envelopes, marked only with the study name and a consecutive number according to a computer-generated random list. The patients received the envelopes in order of their inclusion in the study. The study was triple-blinded. Both the anaesthesiologists, who collected the pre- and postoperative data, and the anaesthesiologist in the operating theatre were blinded to the patients’ assignment. Likewise, the statistician was blinded to the verum and placebo group assignment.

Patients were instructed in using the PCA devices and the 11-point numerical rating scale (NRS). They received 300 mg pregabalin or placebo orally 1 h before anaesthesia. Additionally, 7.5 mg midazolam was administered orally at the same time for concealing a potential sedative effect of pregabalin.

Anaesthesia was induced with 100 µg fentanyl, 1.5–2.5 mg kg⁻¹ propofol, and 0.6 mg kg⁻¹ rocuronium and maintained by 0.8–1.3 MAC sevoflurane. Remifentanil 0.1–0.5 µg kg⁻¹ min⁻¹ was administered as an intraoperative analgesic. Transperitoneal nephrectomy was performed without infiltration of local anaesthetics according to the in-house standards by the same four surgeons via a subcostal incision extending from the xyphoid laterally and caudally to the level of the umbilicus. After reflection of the bowels, the renal vessels were ligated and radical nephrectomy was carried out including the adipose capsule and Gerota’s fascia. Retroperitoneal lymph node dissection was not routinely performed. The incision was closed in two layers; the inner layer via a running suture and the outer layer using interrupted sutures. Twenty minutes before the approximated end of surgery, patients received 0.2 mg kg⁻¹ piritramide. After operation, patients received piritramide via PCA. Bolus size was set to 0.02 mg kg⁻¹ of the ideal body weight, with a lock-out time of 10 min and a maximum of 5 boluses per hour. No additional analgesics were administered. The postoperative observation and data acquisition period was 48 h.

Pain levels were assessed at rest and during mobilization together with potential side-effects such as sedation, nausea, vomiting, or dizziness. According to our institutional standard operating procedure on pain management, mobilization was defined as the patient’s active movement and weight-bearing while avoiding any harm. For the first 4 postoperative hours, pain levels and side-effects were documented in a 1 h interval, then followed by 4 h intervals. Other side-effects, including postoperative headache, dry mouth, vertigo, and blurred vision, were documented on occurrence on the study’s case report form. PCA-usage was documented via the device’s internal memory. Sedation levels were documented by using an in-house score (0, awake; 1, sleeping, but easily rousable; 2, sleeping, hardly rousable; 3, not rousable). A free text field allowed additional documentation of other events.

In each patient, the area of hyperalgesia for punctuate mechanical stimuli around the incision was measured 48 h after the operation according to the method described in previous publications.11 12 With a hand-held von Frey filament (180 g, Semmes-Weinstein Monofilament, Touch-Test™ Sensory Evaluators, North Coast Medical Inc., Morgan Hill, CA, USA), the skin was stimulated in steps of 5 mm at intervals of 1 s starting outside of the hyperalgesic area in the direction of the incision. The distance from the incision to the first point where a ‘painful’, ‘sore’ or ‘sharper’ feeling occurred was measured and noted. This measurement was repeated at predefined radial lines around the incision. If no change in sensation occurred, the stimulation stopped at a distance of 5 mm to the incision. Since the area of hyperalgesia varies primarily on the length of incision, we propose a new approach for calculating a normalized area of hyperalgesia which is independent from the length of incision; as the area of hyperalgesia looks similar to an ellipsoid, we used the diameters of this ellipsoid for calculation. To eliminate the variable length of incision, this length was subtracted from the longer diameter leaving four radial distances from the end and from the middle of the incision (Fig. 1). The normalized area of hyperalgesia was calculated by summing up the areas of the remaining four triangles.

Mechanical pain threshold was tested by puncturing the expected area of surgical incision before surgery and at a distance of 50 mm from the incision 48 h after surgery with von Frey filaments with increasing diameters.12 Measurements were repeated in all four directions in 12 predefined positions. For further calculations, the results in grams were log-transformed and the mean of all 12 measurements was calculated.

At the time when this study was designed, no data were available to estimate the effect of pregabalin on the opioid consumption in patients undergoing nephrectomy and to calculate an a priori sample size; we therefore planned an interim power analysis after the first 20 patients. Based on these data [75.4 (17.5) vs 52.2 (18.2) mg, α=0.05], we
calculated a group size of 13 to reveal a statistically significant difference with 90% power.

As the data of the first 20 patients were used in the power analysis and later also in the final analysis, it has to be considered as multiple comparisons of the same data. To adjust for this, the Bonferroni correction was applied for the primary parameter and \( \alpha = 0.025 \) was considered significant.

Data are presented as mean (SD). Samples were tested for normality with Shapiro–Wilk’s \( W \)-test and were further analysed by Student’s \( t \)-test. Mechanical pain threshold was analysed by repeated-measurement one-way analysis of variance. Statistical analysis was performed using NCSS, version 07.1.5 (NCSS LLC, Keysville, UT, USA).

### Results

From April 2009 to October 2010, patients were recruited for this study. In each group, 13 patients were included. All patients completed the study as intended (Fig. 2). There were no significant differences in patient characteristics (Table 1). NRS score differed neither in rest nor during mobilization (Table 2). Total piritramide consumption and the normalized area of hyperalgesia were significantly lower in the pregabalin group (Table 2, Fig. 3). There was no significant difference in mechanical pain threshold (Table 2).

Two patients of the placebo group had long-term therapy with tricyclic antidepressants, compared with three in the pregabalin group. In all five cases, the medication was stopped on the day before surgery. No patient had a current therapy with \( \alpha \)-agonists or corticosteroids.

No case of severe sedation (>level 2) was reported in both groups (in the pregabalin group: sedation grade 0: 7 patients, grade 1: 5, grade 2: 1; in the placebo group: grade 0: 6 patients, grade 1: 7, grade 2: 0).

No other side-effects were observed. Postoperative nausea and vomiting occurred in four cases in the pregabalin and in six in the control group (\( P=0.225 \)).

### Discussion

This is the first study to demonstrate that a single dose of preoperative pregabalin significantly decreases the area of hyperalgesia. Nevertheless, it has to be stated that in our study, the assessment of hyperalgesia was only a secondary outcome and we therefore did not perform an \textit{a priori} sample size calculation for this parameter. Our \textit{post hoc} analysis revealed a power of 0.50.

Hyperalgesia is known to correlate with central sensitization and therefore with chronic persistent pain.\(^{13,14}\) Different authors recommended hyperalgesia as a primary parameter in incisional pain studies.\(^{15–17}\) However, the effect of preemptive pregabalin on the development of hyperalgesia or...
allodynia after incisional trauma has not been studied in humans, neither in the clinical setting nor in volunteers, whereas animal studies demonstrated a clear effect. Buvanendran and colleagues showed that the perioperative treatment with pregabalin for 14 days reduces S-LANSS scores, correlating to the incidence of neuropathic pain. Unfortunately, their study was limited by the lack of clinical assessment. Their findings by using a questionnaire are well supported by our clinical data related to reducing the area of hyperalgesia.

This study demonstrates that a single dose of 300 mg pregabalin reduced the postoperative opioid consumption after transperitoneal nephrectomy by 33% within the first 48 h. These findings are in accordance with recent meta-analyses which showed that perioperative treatment with pregabalin significantly reduces opioid consumption 24 h after operation. Interestingly, our data showed that piritramide consumption is significantly decreased beyond the time of action of pregabalin, which has an elimination half-life of 6.3 h. Even 40 h after administration, the consumption differs significantly between the groups. This could be attributed to a potential ‘preemptive’ effect of this drug. However, it should be clearly stated that applying this term for pregabalin lacks evidence. A preoperative verum vs placebo application is not suitable to detect a preemptive effect of a substance and to distinguish it from a pure analgesic effect; to answer this question, a controlled study comparing pre- vs postoperative application of pregabalin should be considered. Unfortunately, until now this was only investigated in a single animal study. Although these results were convincing, they cannot be transferred to humans. In our study, we decided against this highly interesting approach, as we aimed to focus on the effect on opioid consumption and hyperalgesia.

Contrary to the findings in hyperalgesia, our results for the mechanical pain threshold do not show any significant effect. Partially, this can be explained by the small sample size. Additionally, assessing mechanical pain threshold at a distance of 50 mm from the incision resulted in several

Table 2 Results [mean (SD)]. *Statistically significant

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Pregabalin</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Mean NRS score at rest during the first 48 h after operation</td>
<td>1.81 (0.49)</td>
<td>1.83 (0.50)</td>
<td>0.4596*</td>
</tr>
<tr>
<td>Mean NRS score during mobilization during the first 48 h after operation</td>
<td>3.69 (0.69)</td>
<td>3.77 (0.54)</td>
<td>0.3680</td>
</tr>
<tr>
<td>Summative piritramide consumption (mg) during the first 48 h after operation</td>
<td>77.37 (15.88)</td>
<td>51.49 (16.25)</td>
<td>0.0004*</td>
</tr>
<tr>
<td>Pain threshold before operation [log(g)]</td>
<td>1.97 (0.29)</td>
<td>1.99 (0.24)</td>
<td>0.6738</td>
</tr>
<tr>
<td>Pain threshold 48 h after operation [log(g)]</td>
<td>1.20 (0.56)</td>
<td>1.05 (0.58)</td>
<td></td>
</tr>
<tr>
<td>Normalized area of hyperalgesia (cm²) measured 48 h after operation</td>
<td>143 (87)</td>
<td>84 (54)</td>
<td>0.0497*</td>
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Fig 3 Time course of postoperative piritramide (mg) consumption via a PCA device after preoperative administration of placebo or 300 mg pregabalin in patients undergoing transperitoneal nephrectomy [mean (SD), *P<0.025].
patients, in whom these points were located outside their individual area of hyperalgesia. Therefore, any conclusions drawn from these data should be critically scrutinized.

The NRS scores did not differ between the groups, neither in rest nor during mobilization. This is in accordance with a recent meta-analysis.\(^7\)

The most common side-effects of pregabalin in chronic pain treatment are somnolence and dizziness. Several trials reported an increase in these side-effects, but mainly in groups with high doses.\(^{18} \, 21 \, 22 \, 24\) In our study, we could neither find a significant difference in sedation, nor a single case of a severely sedated patient after operation. The incidence of PONV did not differ significantly.

A possible weakness of our study is choosing opioid sparing as the primary parameter, and not focusing on patient-related data such as hyperalgesia, mechanical pain threshold, or additional factors such as reduction in opioid-induced side-effects. We admit that these questions are of high clinical importance; however, at the time our study was planned, the literature was inconclusive about the effect of pregabalin on postoperative pain, we primarily wanted to demonstrate whether there was a reduction in postoperative opioid consumption or not. This also explains why we did not apply a complete set of quantitative sensory tests, which would be a promising approach for future studies.

In conclusion, our study has shown that preoperative administration of 300 mg pregabalin in patients undergoing transperitoneal nephrectomy reduces postoperative opioid consumption by 33% within the first 48 h. Moreover, we could demonstrate that pregabalin significantly decreases the area of hyperalgesia. Further research in this field should focus on pregabalin’s effect on the development of persistent postoperative pain, the reduction in opioid-related side-effects, and its attributability to be ‘preemptive’.

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Declaration of interest
None declared.

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