Perioperative Pregabalin for Postoperative Pain Control and Quality of Life After Major Spinal Surgery

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Background: Adequate management of postoperative pain after major spine surgery is often difficult to achieve. We investigated the efficacy of an antineuropathic pain drug, pregabalin (PG), on postoperative pain control and on improvement of quality of life (QoL).

Methods: Sixty patients scheduled for elective decompressive spine surgery were enrolled. One hour before surgery patients received 300 mg of either oral PG or placebo (PL) and 150 mg of PG or PL twice a day for 48 hours postoperatively. During the first 48 postoperative hours, a continuous infusion of morphine 0.01 mg/kg/h and ketorolac tromethamine 2.5 mg/h was administered. Intravenous morphine in 2-mg aliquots up to a maximum of 10 mg was used as rescue therapy. Pain was measured at rest and during movement using a visual analog scale (VAS score), and side effects were recorded in the first hour and at 4, 8, 12, 24, and 48 hours. Three months and 1 year after discharge, patients were contacted by telephone by 1 of the authors to obtain follow-up information using the EuroQoL questionnaire.

Results: During the first 8 postoperative hours, VAS scores at rest were significantly lower in the PG group than in the PL group ($P < 0.05$), whereas VAS scores on movement were significantly lower up to 12 hours after the operation in the PG group ($P < 0.05$). The morphine consumption in the PG group was 3 ± 2 mg, whereas in the PL group it was 9.5 ± 2.5 mg ($P < 0.05$). Postoperative incidence of constipation and nausea/vomiting was higher in the PL group than in the PG group. No significant differences between the 2 groups were observed with regard to other adverse effects. QoL measures revealed an improvement in outcome, especially in movement and in pain dimensions in both groups; however, at 3 months, subjective qualification of overall QoL was better in the PG group than in the PL group. There were no differences in QoL after the 1-year follow-up period.

Conclusions: Perioperative PG administration reduces early postsurgical pain at rest and particularly during movement after major spine surgery with less opioid consumption, and it seems to influence the improvement of overall QoL 3 months after surgery.

Key Words: major spine surgery, postoperative pain control, pregabalin

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Major spinal surgery causes severe postoperative pain, which can persist for up to 3 days, thus hampering reconvalescense.[1,2] Patients often have chronic pain and the area of surgery can be large when multiple levels are operated on.[3] Opioid treatment is recommended as the first choice of medication for the management of postoperative pain but is associated with a number of adverse effects.[4]

Increasing emphasis has been placed on the use of nonopioid analgesic drugs as part of a multimodal regimen for preventing pain in the perioperative period.[5,6] Documented benefits of multimodal therapy include improved pain relief, reduction in perioperative stress response, shorter hospital stays, decreased hospital costs, improved patient satisfaction, and a reduction in postoperative morbidity and mortality.[7,8]

Pregabalin (PG) is a structural analog of γ-aminobutyric acid, which was synthesized over a decade after gabapentin. It inhibits Ca(2+) currents through high-voltage—activated channels containing the α2-δ1 subunit, reducing neurotransmitter release and attenuating postsynaptic excitability. PG is rapidly absorbed when consumed orally, with more than 90% bioavailability, and it achieves peak plasma levels within 30 minutes to 1.4 hours.[9] Pharmacological studies have demonstrated stereo-specific effects of PG in neuropathic and inflammatory pain models.[10,11]

Recently, a large number of clinical trials indicated that PG could be effective in early postoperative pain.[12,13] Two of them investigated the efficacy of perioperative PG administration on postoperative pain[14,15] in spinal surgery, assessing a positive effect on postoperative opioid consumption.

The objectives of the present study were to investigate the effects of perioperative PG administration on different aspects of postoperative pain and on short-term and long-term quality of life (QoL).

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MATERIALS AND METHODS

This prospective, randomized, double-blind, and placebo (PL)-controlled clinical study was designed to include 60 adult patients of either sex, having American Society of Anesthesiologists physical status I-II, scheduled for elective decompressive lumbar laminectomy with spinal fusion for degenerative spinal stenosis between February 2009 and January 2010. Approval of the Local Research Ethics Committee was sought and obtained, and written, informed consent was obtained from all patients. Patients receiving chronic opioid treatment or sedatives or anticonvulsants, had known allergy to PG or morphine, had a history of alcohol abuse, presented with diabetes, or had impaired kidney function were excluded from the study.

One day before surgery, all patients completed the EuroQoL questionnaire,[16] (EQ-5D) to evaluate their QoL. The EQ-5D is a generic health assessment instrument developed by the International EuroQol group as a standardized measure for a description of health status. It consists of 2 parts: the EQ-Visual Analog Scale (EQ-VAS), a subjective qualification of overall QoL (score 0 = worst imaginable state to 100 = best imaginable state), and a questionnaire consisting of 5 items (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression). Respondents rate each item on a 3-level scale from 1 (no problem) to 3 (extreme problem).

Patients were randomly assigned to 2 equal groups of 30 each using a computer-generated table of random numbers to receive either a matching PL or PG 300 mg (Lyrica; Pfizer) and PL or PG 150 mg, twice a day for 48 hours postoperatively.

All of the medications were identical, were provided by the hospital pharmacy, and were administered orally 1 hour before induction of anesthesia by a staff nurse who was not involved in the study.

The general anesthetic technique was standardized. After preanesthesia with midazolam (0.04 mg/kg), patients underwent standard induction with propofol 2 mg/kg and fentanyl 2 μg/kg, and orotracheal intubation was facilitated by cisatracurium 0.15 mg/kg. Anesthesia was maintained with sevofluorane and air in oxygen. Intraoperative analgesia was provided by remifentanyl 0.1 to 0.25 μg/kg/min. During the surgery, 4 mg of ondansetron and 8 mg of dexamethasone were given for prophylaxis of nausea and vomiting. The patient received morphine intravenously (0.1 mg/kg) before sevofluorane closure, and remifentanyl was stopped after completion of the last surgical suture. At the end of surgery, neuromuscular block was antagonized with 0.04 mg/kg neostigmine and 0.02 mg/kg atropine.

The total introperative remifentanil consumption for each patient was noted.

Postoperative analgesia was performed with a continuous morphine infusion of 0.01 mg/kg/h and ketorolac tromethamine infusion of 2.5 mg/h, which started 30 minutes before the end of surgery and continued until 48 hours after surgery.

After tracheal extubation, the patients were transferred to the postanesthesia care unit.

Patients were questioned during the first 1 hour in the postanesthesia care unit and were later evaluated in the ward at 4, 8, 12, 24, and 48 hours by an independent observer blinded to group allocation about pain at rest (static) and during movement (dynamic) and incidence of side effects. Pain with movement was recorded after the patient completed a 90-degree logroll for a while during the first 8 postoperative hours and 12 hours after, when stand-up position was required by the surgical protocol.

Postoperative pain was assessed by a VAS ranging from 0 mm (no pain) to 10 mm (worst pain imaginable). If the VAS pain score was ≥ 3 mm, 2-mg aliquots of intravenous morphine, as required and up to a maximum of 10 mg, were administered as rescue therapy.

The Ramsay sedation scale[17] (1: anxious, agitated, or restless; 2: cooperative, oriented, tranquil; 3: responds to command; 4: brick response; 5: a sluggish response; and 6: no response) was used to assess the sedation. Patients with a sedation scale of ≥ 4 were considered sedated. Respiratory depression was defined as respiratory frequency ≤ 8 and oxygen saturation $< 90\%$ without oxygen administration. Hypotension (mean of arterial blood pressure was $< 80\%$ of baseline) and other adverse effects including dizziness, pruritus, headache, diarrhea, constipation, nausea, vomiting, peripheral edema, dry mouth, and blurred vision were recorded postoperatively.

Three months and 1 year after hospital discharge, telephonic interviews were conducted for all patients by a blinded author (I.G.) to assess their QoL using the EuroQoL questionnaire. The "perceived current health status" was evaluated with the question: "compared with my general level of health before surgery my health state today is better/the same/worse?"

Statistical Analyses

Statistical analyses were performed using the Statistical Package for Social Sciences software, version 11.5. Continuous variables are presented as mean ± SD. Categorical variables are expressed as actual numbers and percentages and are compared using the χ^2 analysis. Comparison between means of continuous variables was carried out with a 2-tailed Student t test. The incidence of side effects was analyzed with the Fischer exact test. A P-value < 0.05 was considered statistically significant.

A sample size of 25 patients per group was calculated to detect a significant difference of 15% or more in morphine consumption with a power of 85% and a significance level of 5%. In order to account for any dropouts, we enrolled 30 patients in each group.

RESULTS

A total of 60 patients were included in the study and randomly assigned to their treatment groups. The baseline demographic and clinical characteristics of each group appear in Table 1. No significant differences were observed between the 2 groups regarding preoperative clinical characteristics, anesthesiological technique,

TABLE 1. Patient and Surgical Characteristics

	PG Group (n = 30)	PL Group (n = 30)
Age (y)	66.2 ± 10.8	63.5 ± 9.9
Male/Female (n)	9/21	14/16
Height (cm)	166.5 ± 10.7	177 ± 5.9
Weight (kg)	80 ± 27.9	85.2 ± 16.7
BMI (kg/m^2)	28.7 ± 9.1	27.0 ± 4.4
ASA physical status (I/II) (n)	12/18	10/20
History of PONV, n (%)	3 (10)	2 (6.6)
Spinal levels fused, n (%)		
1	4 (13.4)	3 (10)
2	13 (43.3)	12 (40)
3	13 (43.3)	15 (50)
Duration of anesthesia (min)	164.5 ± 88.4	155.6 ± 83
Duration of surgery (min)	133.7 ± 84.5	110 ± 95
Intraoperative remifentanyl consumption (μg)	2983 ± 1676	2885 ± 1789
Postoperative rehabilitation (d)	55.2 ± 36.2	58.2 ± 32.4

Values are means ± SD or number of patients (n) and percentages.
There were no significant differences between the 2 groups.
ASA indicates American Society of Anesthesiology; BMI, body mass index; PG, pregabalin; PL, placebo; PONV, postoperative nausea and vomiting.

and postoperative rehabilitation, whereas postoperative length of stay was longer in the PL group than in the PG group (8.5 ± 1.0 vs. 6.3 ± 0.5 d, $P < 0.01$). Despite the fact that there was no statistical difference between the 2 groups regarding sex, the overall number of female patients was higher in the PG group than in the PL group.

During the first 8 postoperative hours, VAS score for pain at rest was significantly lower in the PG group when compared with the PL group; moreover, VAS during movement continued to be lower for 12 hours in the PG group than in the PL group. The PG group experienced less pain during movement compared with the PL group when stand-up position was required ($P < 0.05$) (Figs. 1, 2).

The total 48-hour morphine consumption in the PG group was 3 ± 2 mg, whereas in the PL group it was 9.5 ± 2.5 mg ($P < 0.05$) (Table 2). The number of patients who required morphine during the postoperative period

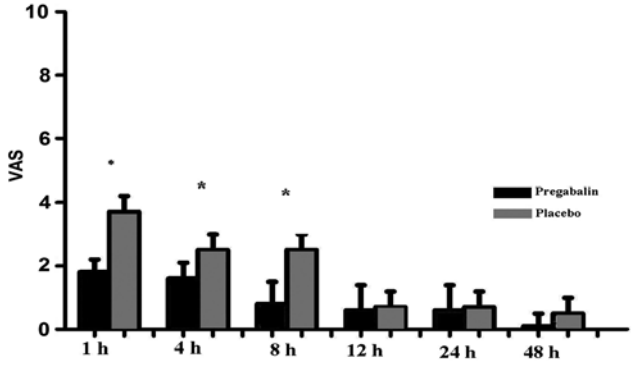

FIGURE 1. Postoperative pain score (VAS) at rest in the pregabalin and placebo groups. Values are means ± SD, *$P < 0.05$. VAS indicates visual analog scale.

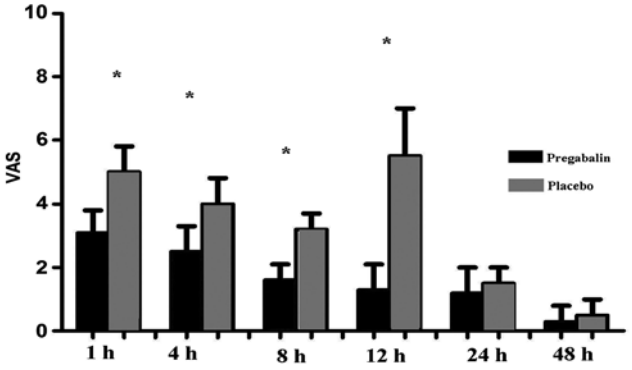

FIGURE 2. Postoperative pain score (VAS) during movement in the pregabalin and placebo groups. Values are means ± SD, *$P < 0.05$. VAS indicates visual analog scale.

was higher in the PL group than in the PG group ($P < 0.001$).

Postoperative nausea, vomiting, and incidence of constipation were higher in the PL group than in the PG group. No significant differences were observed between the 2 groups regarding sedation, respiratory depression, and other adverse effects (Table 3).

The EuroQoL measures showed significant improvement in mobility and in pain dimension 3 months and 1 year after surgery in both groups. At the time of the interviews, perceived current health status of all patients was better than before surgery. However, at 3 months, the subjective qualification of overall QoL (EQ-VAS) was better in the PG group than in the PL group (Table 4).

DISCUSSION

The main finding of our study was that, in patients undergoing major spinal surgery, preoperative administration of a 300 mg dose of PG and a dose of 150 mg twice a day for 48 hours postoperatively resulted in a significant reduction in VAS scores for pain at rest during the first 8 postoperative hours and for 12 postoperative hours for pain evoked by movement in stand-up position. These beneficial effects of PG were not accompanied by

TABLE 2. Morphine Consumption

Hours	PG Group (n = 16/30)	PL Group (n = 30/30)†
1	2.3 ± 1.5	3.5 ± 1.0*
4	0.6 ± 1.0	2.5 ± 1.0*
8	0	2.5 ± 1.0*
12	0	1.0 ± 1.1*
24	0	0
48	0	0
Total	3.0 ± 2.0	9.5 ± 2.5*

Values are means ± SD.
*$P < 0.05$.
†Number of patients requiring additional morphine during the study period, $P < 0.001$.
PG indicates pregabalin; PL, placebo.

TABLE 3. Incidence of Side Effects

	PG Group (n = 30)	PL Group (n = 30)
Dizziness	2	3
Pruritus	0	1
Nausea	1	4*
Vomiting	0	6*
Sedation	3	5
Respiratory depression	2	3
Hypotension	2	2
Headache	0	0
Constipation	1	5*
Diarrhea	0	0
Peripheral edema	1	0
Dry month	0	0
Blurred vision	0	0

Values are number of patients.
*$P < 0.05$.
PG indicates pregabalin; PL, placebo.

increased side effects. Kim et al[14] investigated the intensity of pain in the same setting for 48 postoperative hours, but the efficacy of treatment of pain at rest and during movement was not investigated. The study by Burke and Shorten[15] has demonstrated less morphine consumption during the first 24 postoperative hours in a less painful setting (lumbar discectomy).

In our study we had a higher number of female patients in the PG group than in the PL group; however, this difference was not statistically significant. The fact that women have a higher pain threshold is the subject of discussion in the literature.[18,19] Age and female sex could influence the incidence of nausea and vomiting; however, in our study, the decreased opioid consumption was effective in preventing this adverse effect.

Among the gabapentinoids, PG would be a better option when compared with its congener gabapentin because of its greater analgesic efficacy[20] and better pharmacokinetic profiles.[19] PG exhibits highly predictable and linear pharmacokinetics across its therapeutic dose range with low intersubject variability.[21]

Biochemical studies have hypothesized that the analgesic action of PG depends on the reduction of calcium influx at nerve terminals with a reduction in the release of neurotrasmitters, including glutamate, noradrenaline, calcitonin gene-related peptide, and substance P.[22,23]

Although parenteral opioids are still considered the foundation of treatment for moderate-to-severe pain, the opioid doses necessary for complete relief of spontaneous pain at rest (tonic pain) have no effect on movement associated (phasic pain).[24]

Despite its theoretical advantages, perioperative use of PG to manage acute postoperative pain yielded contradictory results in previous studies, which might be associated with different doses, timing of administration, and also the type of surgery.[12,13]

Many experimental studies have suggested that "protective premedication"[25] with PG such as gabapetin, administered before inflammatory trauma or surgical stimulation, may reduce the degree of central sensitization[21] with analgesic efficacy. In the first trial investigating the postoperative analgesic effects of PG, a dose of 300 mg demonstrated significant pain-relieving properties for patients in dental surgery.[26]

TABLE 4. Quality of Life (EuroQoL-5D) Scores Before Surgery, 3 Months, and 1 Year After Surgery

	PG Group			PL Group		
	Presurgery	3 mo	1 y	Presurgery	3 mo	1 y
Mobility*						
No problems	5	28	29	4	25	28
Moderate problems	20	2	1	18	5	2
Extreme problems	5	0	0	8	0	0
Self-care						
No problems	27	29	29	26	27	27
Moderate problems	3	1	1	4	3	3
Extreme problems	0	0	0	0	0	0
Usual activities						
No problems	20	25	26	23	25	28
Moderate problems	10	5	4	7	5	2
Extreme problems	0	0	0	0	0	0
Pain/discomfort*						
None	0	15	25	0	16	22
Moderate	20	15	5	19	14	8
Extreme	10	0	0	11	0	0
Anxiety/depression						
None	23	28	28	22	25	25
Moderate	7	2	2	8	5	5
Extreme	0	0	0	0	0	0
EQ-VAS (0-100)*	65 ± 13.7	80 ± 9.5†	87.5 ± 4.8	68 ± 10.3	70 ± 8.2†	87 ± 4.2

Data are number of patients or mean ± SD.
*Between presurgery and 3 months after surgery in the PG and PL groups, $P < 0.05$.
†Between the PG and PL groups 3 months after surgery, $P < 0.05$.
EQ-VAS indicates EQ-visual analog scale; PG, pregabalin; PL, placebo.

A clinical study conducted by Reuben et al[27] investigated the perioperative analgesic effect of PG (150 mg, 1 hour before and 12 h after surgery) and of a combination of PG and celecoxib in patients undergoing spinal surgery. The researchers demonstrated that the combination of PG and celecoxib was superior to PL and to either drug alone for the reduction of postoperative pain; however, excessive sedation was found in the PG group and in the PL group, probably linked to increased use of morphine. In our study we demonstrated a better control of postoperative pain in the PG group than in the PL group with less morphine use and a significant reduction in opioid-related adverse events. The larger dose amount of morphine in the study by Reuben may be because of the fact that the investigators did not use a background infusion of opioid plus nonsteroidal anti-inflammatory drug to maintain stable target concentrations of the analgesic, but only patient-controlled analgesia on demand. In both our patient population and Reuben's population the incidence of nausea and vomiting was lower in the PG group compared with the PL group. In our study, no more incidence of sedation was noticed in the PG group, although we used a higher dose of PG (300 mg). Similar results were found by Kim et al[14] with a 150 mg dose.

In the current literature, PG has demonstrated good efficacy in terms of QoL after major spine surgery. A recent study[15] has reported that perioperative PG administration may benefit patients undergoing lumbar discectomy in terms of pain and 3-month functional outcome. The results of our study indicate that PG does not influence long-term QoL; both groups, PL and PG, have a better QoL overall in mobility and pain/discomfort than before surgery. However, at 3 months, the perception of participants' overall health status was better in the PG group than in the PL group. This result could be explained by 2 hypotheses: (1) A good memory and less perioperative stress in patients who received PG because of better pain control in the postoperative period compared with the PL group, especially during movement, may have led to greater self-confidence, which continued over time. (2) The ability of PG to block chronic allodynia suggests a possible effect in preventing chronic pain. Some studies have shown that PG can block hyperalgesia and allodynia in rat models of neuropathic pain or postoperative pain.[28–30] Moreover, PG has been shown to decrease central sensitization (reduction in the area of punctate mechanical hyperlagesia and dynamic touch allodynia) in the electrical hyperalgesia model in human volunteers,[31] and so the same antihyperalgesic effect of PG may occur during and immediately after surgery. A recent study[32] suggests that a single 300-mg dose of PG in patients has sufficient central nervous system bioavailability to be useful under acute conditions when brain or spinal cord excitability may lead to long-term disease such as chronic pain.

We can suggest that less postoperative opioid need can also influence the length of hospital stay. The PG group reached up-site position and started spontaneous nutrition earlier than the PL group. Our results confirm that a multimodal approach to perioperative care can result in an overall improvement in recovery.[33]

The limitations of this study include the relatively small numbers of patients studied, failure to record separate VAS pain back and VAS pain leg scores for each patient, and lack of information about the use of analgesic drugs 3 months and 1 year after surgery.

The strengths of this study include the performance of the surgical procedure by a single center, collection of the questionnaire by a single blinded investigator, and length of follow-up up to 12 months after surgery.

CONCLUSIONS

The results of this study indicate that perioperative PG administration may benefit patients undergoing lumbar spinal fusion surgery in terms of pain and functional outcomes.

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