Prospective Study

Chronic Pregabalin Treatment and Oxycodone Requirement after Spinal Surgery Versus Short Course Perioperative Administration: A Prospective, Nonrandomized Study

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Background: Although being controversial, pregabalin (PGB) is proposed during a short perioperative period to improve pain relief.Comparisons between chronic and short-term users during lumbar spine surgery are lacking.

Objectives: The purpose was to compare opioid requirements and postoperative pain among PGB chronic users and naive patients receiving a 48-hour perioperative administration.

Study Design: Prospective nonrandomized study.

Setting: Tertiary care hospital.

Methods: Chronic users (group PGB, n = 39) continued their treatment, naive patients (group C, n = 43) received a dose of 150 mg preoperatively and 75 mg/12 hours for 48 hours. Anesthesia and analgesia were standardized. The primary outcome was the cumulative oxycodone consumption at 24 hours, other outcomes included pain scores, DN4 (Douleur Neuropathique 4 Questions) scores, and side effects.

Results: Group PGB consumed less oxycodone at 24 hours (median [interquartile range] 10 mg [10–17.5] vs. 20 mg [10–20], $P = 0.013$], at 48 hours (15 mg [10–20] vs. 20 mg [12.5–30], $P = 0.018$), and required less intraoperative remifentanil ($P = 0.004$). Both groups showed similar pain scores during the 48-hour follow-up and at 3 months.Based on multivariate analysis, chronic users of PGB before surgery exhibited lower oxycodone requirements at 24 hours (odds ratio, 3.98; 95% confidence interval, 1.44–7.74; $P = 0.008$]. No differences were noted regarding side effects and DN4 scores.

Limitations: Nonrandomized study.

Conclusions: Patients chronically treated with PGB required less opioid when compared with a short perioperative administration before spinal surgery. Further prospective studies are required to confirm these results in spinal surgeries.

Key words: Spinal surgery, pregabalin, postoperative pain, neuropathic pain

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Patients with low back pain benefiting from spinal surgery are frequently treated with analgesics prior to surgery. The American Pain Society strongly recommends the use of a short period of gabapentinoid initiated preoperatively as a component of multimodal analgesia during major surgery (1). The real benefit of the systematic perioperative use of gabapentinoids on postoperative pain was challenged by recent meta-analyzes, which reported minimal analgesic improvement, greater adverse events, and

a questionable benefit on chronic pain (2,3). However, gabapentinoids have been shown to lower pain intensity, opioid consumption, and opioid-induced side effects when compared with placebo in spinal surgery (4). The main pharmacologic action of gabapentinoids are attributed to its presynaptic binding to $\alpha 2\delta$-1 subunits. Other actions involve a modulation of the serotoninergic descendant facilitating pain system, interactions between presynaptic $\alpha 2\delta$ subunits and NMDA receptors independent of voltage-gated calcium channels, an increase in noradrenaline release from the locus coeruleus, and the trafficking of $\alpha 2\delta$-1 subunits in the superficial and deep layers of dorsal roots (5). The most common side effects are dizziness, somnolence, edema, and visual disturbances (2,3,6). Administration of a short course of pregabalin (PGB) has been shown to be associated with a reduction in the 24-hour morphine consumption, with no improvement in pain scores in a meta-analysis having included trials with low risk of bias (6). Most systematic reviews evaluated gabapentinoids administered for a short period of time, an approach likely to be unusual in the management of patients with chronic pain (2-4,6).

To the best of our knowledge, no study has explored the impact of a prolonged preoperative treatment with PGB in patients scheduled for lumbar spine surgery. We hypothesized that chronic use of PGB could influence the opioid requirement and pain levels following lumbar spine surgery. We tested this hypothesis by evaluating oral oxycodone consumption as the primary outcome, when compared with patients receiving a short-term perioperative administration.

Methods

Ethics, Study Design, and Patient Selection

This single-center prospective nonrandomized study was approved by the Institutional Ethic Committee of the Rennes University Hospital, Rennes, France (Ethical committee number 16.61, Chairperson Vincent Morel, MD) on April 29, 2016. The trial was registered before enrollment on August 15, 2016, at ClinicaTrials.gov (NCT02866396). All patients provided written informed consent before participation. The study was performed in line with the STROBE statement (7) and conducted in accordance with the origin protocol.

The study, conducted in Sevigne Hospital, Cesson Sévigné, France, between September 2016 and December 2017, recruited 83 American Society of Anesthesiologist (ASA) I–III physical status adult patients scheduled for lumbar discectomy and posterior or transforaminal arthrodesis. The exclusion criteria were age > 85 years, a body mass index > 45 kg/m^2, emergency, previous spinal surgery, metastasis, tricyclic antidepressant use, PGB use for another condition, pregnancy, contraindication to the analgesics used perioperatively, and alcohol or drug abuse. The cohort of patients were enrolled prospectively and were divided into 2 groups according to the existence or not of PGB treatment for chronic low back pain, namely chronically treated patients (group PGB) who were consuming PGB for at least 15 days before the surgery, and naive patients (group C), for whom PGB was started preoperatively and maintained for 48 hours according to pain guidelines during painful surgery (1). Treatment-naive patients corresponded to patients who had not been exposed to PGB in the previous 3 months. The attending physicians of each of them were contacted preoperatively to exclude the possibility of PGB prescription. Patients were instructed on the use of the 11-point Numeric Rating Scale (NRS-11) score ranging from 0 (no pain) to 10 (worst pain imaginable), as well as the DN4 (Douleur Neuropathique 4 Questions) score. Patients who were discharged before postoperative day (POD)2 were evaluated during a visit with the surgeon for pain and DN4 scores, as well as for side effects.

Interventions

One hour before surgery, patients received oral analgesia premedication as follows:

- All patients were given acetaminophen 1 g and ketoprofen 100 mg.
- Group PGB: patients received PGB using their home dosing regimen and continued after surgery according to preoperative doses and intervals.
- Group C: patients were given PGB 150 mg followed by 75 mg/12 hours until POD2.

Perioperative Management

General anesthesia was standardized for all patients. Induction was performed with propofol 1.5–2 mg/kg and remifentanil using the Minto model (AlarysTM PK Syringue Pump, CareFusion, San Diego, CA, USA) with an effect-site model and initiated to 4–5 ng/mL (8). Tracheal intubation was facilitated with cisatracurium 0.2 mg/kg. The patients were then positioned prone. Remifentanil was titrated by 0.5 ng/mL to maintain heart rate and blood pressure within 30% of the baseline values. The infusion was progressively reduced 15 minutes before the expected completion of surgery.

Anesthesia was maintained with volatile anesthetic in a 50:50 air-oxygen mixture. Dexamethasone 8 mg, ketamine 0.5 mg/kg, and nefopam 20 mg were also administered intravenously before incision. When surgery was planned to exceed 2 hours, a continuous infusion of ketamine of 0.1 mg/kg/h was started after the bolus and interrupted 20 minutes before skin closure. At the end of surgery, muscular and cutaneous planes were infiltrated with 100 mg of 0.5% levobupivacaine.

Patients were systematically treated with 02 1.5 L/min during the first 24 hours via nasal prongs. In the postanesthesia care unit (PACU), patients received 3-mg boluses of intravenous morphine at 5-minute intervals until NRS-11 score was ≤ 3. Thereafter, all patients were prescribed oral analgesia combining paracetamol 1 g/6 hours, ketoprofen 100 mg/12 hours. Oral immediate-release oxycodone 5 mg for patients ≤ 50 kg or 10 mg for patients > 50 kg was administered not more than once every 6 hours for those having an NRS-11 score > 3. Postoperative nausea and vomiting (PONV) were treated with intravenous ondansetron 4 mg during the first 24 hours and then with oral ondansetron 8 mg.

Perioperative Assessments and 3-Month Follow-Up

Baseline demographics and intraoperative data were collected by the anesthetist in charge of the patient. Postoperative evaluation was performed by an anesthetist and by the nursing staff not involved in the pre- and intraoperative period. Morphine titrated in PACU and oral oxycodone consumption were recorded at 4, 8, 12, 24, and 48 hours after surgery. NRS-11 scores were assessed at rest in PACU, at 4, 8, 12, 24, and 48 hours postoperatively, and during walking at 12, 24, and 48 hours. The DN4 questionnaire was evaluated on POD1 and on POD2. Episodes of PONV, side effects (diplopia, dizziness, confusion, and the maximal sedation score [1: awake; 2: drowsiness, easily awake by appeal; 3: drowsiness, awake to tactile stimulation; 4: drowsiness, awake by pain]) were recorded until POD2. Three months after surgery, the patients were evaluated by a blinded investigator for the pain score during walking and the DN4 questionnaire.

Outcome Measures

The primary outcome was the cumulative oxycodone consumption on POD1. Secondary outcomes were intraoperative remifentanil consumption, postoperative oxycodone request, postoperative NRS-11 and DN4 scores, incidence of PONV, side effects, the length of stay, and the proportion of patients with a DN4 score ≥ 4 or an NRS-11 score ≥ 3 during walking at 3 months.

Sample Size Determination

No previous randomized study has compared the influence on postoperative pain between preoperative chronic users of gabapentinoid and naive patients during spinal surgery. An a priori statistical power calculation was performed using a mean consumption of 26.3 ± 9.4 mg of morphine (9). Assuming a difference of 25% with a type I error rate of 0.05 and a power of 0.85 (2-tailed test), a sample size of 37 patients per group was required (epiR package 0.9–87). With an expected dropout rate of 10%, 83 patients were included.

Statistical Analysis

Statistical analysis was performed using SPSS software version 22.0 (IBM Corp., Armonk, NY). A distribution fitting test was completed using the Shapiro-Wilk test. Continuous data were summarized as mean ± SD or median (interquartile range [IQR]) for normally and nonnormally distributed data, respectively. Categorical variables were expressed as number (%) except for the proportion of patients with a DN4 ≥ 4 and those with an NRS-11 score during walking ≥ 3 at 3 months who were expressed with 95% confidence intervals (CI). Continuous variables normally distributed were compared using the 2-tailed Student t-test, and nonparametric data using the Mann-Whitney U test. Categorical variables were compared using the 2 test or the Fisher exact test as appropriate. The Spearman rank (Rho: rs) correlation was used to evaluate the strength of association between the preoperative DN4 and NRS-11 scores, and between the duration of surgery and the primary end point. The Kaplan–Meier curves and log-rank test examined the difference in the median time of the first intravenous morphine titration during PACU stay. Within-group pain and DN4 scores changes from baseline to postintervention were tested using the Wilcoxon rank-sum test. A multivariate logistic regression was conducted to predict reduced opioid requirement on POD1, defined as lower than the median of 10 mg as the dependent factor. The potential cofounders included in univariate analysis were identified a priori and included male gender, duration of surgery, preoperative NRS-11 and DN4 scores, group (chronic vs. naive users), discectomy (vs. arthrodesis), number of spinal levels, remifentanil dose, and preoperative opioid use. After checking for collinearity by bivariate correlation analysis for each variable, covariables with $P < 0.2$ in

univariate analysis were selected for the multivariate analysis. Model discrimination and calibration were assessed using the C statistic and the Hosmer and Lemenshow goodness-of-fit, respectively. A *P* value < 0.05 was considered statistically significant (2-tailed testing).

Results

Of the 127 consecutive patients screened for eligibility, 83 were enrolled, 82 were analyzed (43 in group C and 39 in group PGB), and all of which were evaluated 3 months after surgery (Fig. 1). Patients in both groups had similar baseline characteristics with the exception of more co-prescription of opioids before surgery in patients scheduled for lumbar fusion in group PGB and a longer duration of surgery in group C (Table 1). In group PGB, the median daily dose of PGB was 150 mg (IQR, 100–162.5, range 50–450), with a mean time from initiation to surgery of 41 ± 13 days. The total dose of intraoperative ketamine did not differ among groups even after excluding patients who received a continuous infusion (6/43 patients in the group C and 3/39 in the group PGB, *P* = 0.91; mean difference 2.5 mg; 95% CI, –1.4 to 6.5, *P* = 0.57; Table 1). In the entire cohort, preoperative pain and DN4 scores were found to be correlated (Spearman rs = 0.40, *P* = 0.0002), as well as for both groups (rs: group PGB, rs = 0.44, *P* = 0.005; group C: rs = 0.34, *P* = 0.02).

Primary Outcome: Cumulative Oxycodone Consumption on POD1

The median cumulative oxycodone consumption on POD1 was significantly reduced in group PGB when compared with group C (10 mg [10–17.5] vs. 20 mg [12.5–20], *P* = 0.013; mean reduction –6 mg [95% CI, –10.26 to –1.74]; Hedge g effect size = 0.62) (Fig. 2). After exclusion of the patients receiving opioids preoperatively, the difference remained significant (10 mg [2.5–10] vs. 20 mg [10–20], *P* = 0.024; mean difference –8.0 mg [95% CI, –12.33 to –3.67]; Hedge g effect size = 0.85). The difference between the 2 groups was the largest at 12 and 24 hours in favor of group PGB (Table 2). There was no relation between the duration of surgery and the 24-hour oxycodone consumption within the groups C (rs = 0.22, *P* = 0.15) and PGB (rs = 0.24, *P* = 0.15). The multivariate analysis found that chronic users of PGB before surgery was associated with a reduction in oxycodone consumption on POD1 (Table 3). Neither duration of surgery, type of surgery, preoperative opioid use, gender, remifentanil dose, preoperative NRS-11 and DN4 scores, and the number of spinal levels influenced the between-groups opioid reduction on POD1.

Secondary Outcomes: Opioid Request, NRS-11 and DN4 Scores, and Side Effects

Patients in group PGB required less intraoperative remifentanil (Table 2) (mean difference –0.03 µg/kg/min, 95% CI, –0.05 to –0.01, *P* = 0.004). No linear relation was found between the duration of surgery and the total dose of remifentanil for the group PGB (R = 0.097, *P* = 0.54) and for the group C (R = 0.15, *P* = 0.24). There was no difference in the amount of morphine titrated and in the proportion of patients not requiring titration in the PACU (Table 2), and the median time to first request of morphine in PACU was comparable in the 2 groups (*P* = 0.78, log-rank test).

There were no significant between-group differences in median pain scores at all time-points (Table 2 and Supplementary Table 1). NRS-11 scores during walking improved on POD2 when compared with preoperative values in group PGB (2 [2–3] vs. 5 [4–6], *P* < 0.0001) and in group C (3 [2–3] vs. 5 [3–6], *P* < 0.0001). The DN4 assessed on POD2 was also reduced when compared with baselines in groups PGB (3 [2–4] vs. 4 [3–5], *P* = 0.0005) and C (2 [2–3] vs. 3 [2–5], *P* = 0.0008). The proportion of patients with a DN4 ≥ 4 on POD2 was similar in groups C and PGB, 8/43 (18.6%; 95% CI, 9.7%–32.6%) and 14/39 (35.9%; 95% CI, 22.7%–51.6%) (*P* = 0.08), respectively.

The incidence of adverse events was similar in both groups (Table 4). Two surgical complications, not related to the study protocol, occurred in the postoperative period: one patient in group PGB was re-operated at POD3 for superficial hematoma, and another patient included in group C was re-hospitalized on POD10 for a pulmonary embolism.

Three-Month Follow-Up: Medication, NRS-11 and DN4 Scores

Four patients (9.3%) in group C and 7 patients (17.9%) in group PGB required at least one analgesic at the 3-month follow-up (*P* = 0.25). No patients needed opioids. In group PGB, 20.5% discontinued PGB after discharge. An improvement from preoperative pain scores during walking was observed at 3 months in group PGB (2 [1–2] vs. 5 [4–6], *P* < 0.0001) and in group C (2 [1–3] vs. 5 [3–6], *P* < 0.0001). At 3 months, no significant difference was noted between the groups C and PGB for NRS-11 score during walking (2 [1–3] vs. 2 [1–2], respectively, *P* = 0.88), as well as for the DN4 score (2

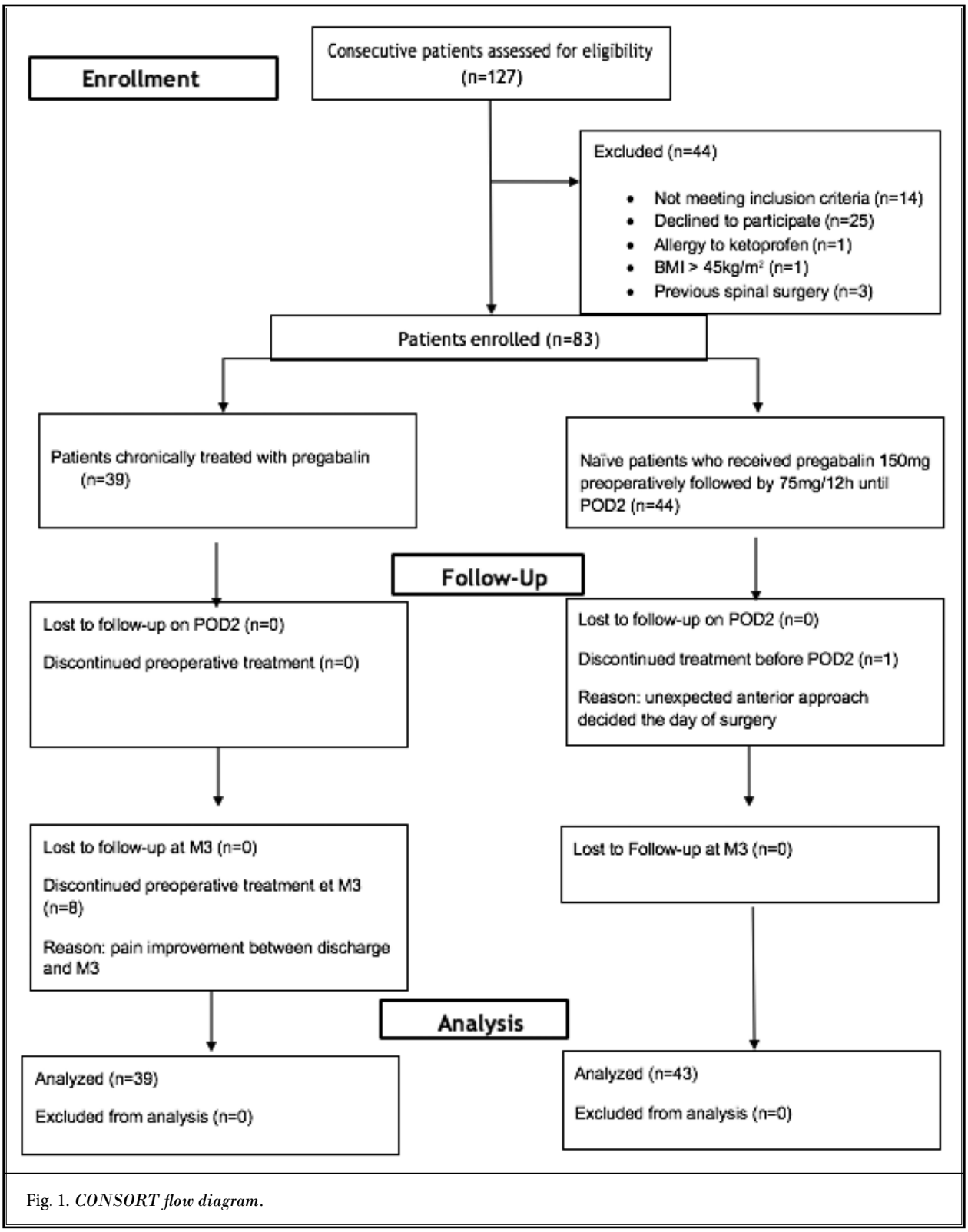

Fig. 1. *CONSORT flow diagram.*

Table 1. *Demographic characteristics*.

Demographic Characteristics	Group C (n = 43)	Group PGB (n = 39)	*P*
Age (y)	51 [43–66]	47 [40–57]	0.15
Female gender	16 (37.2)	17 (43.6)	0.49
BMI (k/m^2)	27.12 ± 7.11	26.92 ± 4.90	0.88
Preoperative PGB daily dose (mg)		150 [100–162.5]	
Lumbar fusion/ discectomy	18 (41.9)/25 (58.1)	13 (33.3)/26 (66.7)	0.43
Preoperative opioid use: total Lumbar fusion Microdiscectomy	1/43 (2.3) 0 1/25 (4.0)	5/39 (12.8) 3/13 (23.1) 2/26 (7.7)	0.07 0.032 0.58
ASA score I ASA score II ASA score III	8 (18.6) 23 (53.5) 12 (27.9)	13 (33.3) 21 (53.9) 5 (12.8)	0.13 0.98 0.93
One-level/two-level surgery	20 (46.5)/23 (54.5)	17 (43.6)/22 (56.4)	0.59
Preoperative NRSw: total Lumbar fusion Discectomy	5 [3–6] 4 [4–5] 5 [3–7]	5 [4–6] 5 [4–6] 5 [3–6]	0.88 0.26 0.61
Site of preoperative pain Back and leg Leg Bilateral	 25 (58.1) 14 (35.6) 4 (9.3)	 23 (58.9) 14 (35.9) 2 (5.1)	 0.28 0.31 0.47
Preoperative DN4: total Lumbar fusion Discectomy	3 [2–5] 4 [3–5] 3 [2–4]	4 [3–5] 4 [4–5] 4 [2–5]	0.16 0.63 0.07
Preoperative DN4 ≥4: total Lumbar fusion Discectomy	18/43 (41.8) 9/18 (50.0) 9/25 (36.0)	25/39 (58.9) 10/13 (76.9) 15/26 (57.7)	0.08 0.14 0.12
Duration of surgery (min): total Lumbar fusion Discectomy	77 ± 44 107 ± 45 54 ± 25	52 ± 26 75 ± 30 40 ± 13	0.008 0.046 0.041
Intraoperative ketamine (mg) Single injection* Bolus + continuous infusion	 37.4 ± 9.3 40.0 ± 11.8	 39.9 ± 7.7 41.5 ± 9.3	 0.57 0.13

Results are expressed as mean ± SD, median [IQR], and n (%).
*n = 36 and 37 in group PGB and in group C, respectively.
ASA, American Society of Anesthesiologist; BMI, body mass index; NRSw, Numeric Rating Scale score during walking.

[1–2] vs. 2 [1–3], respectively, $P = 0.69$). Five patients in group PGB (12.8%; 95% CI, 5.6%–26.7%) and 4 patients in group C (9.3%; 95% CI, 3.7%–21.6%) experienced a DN4 ≥ 4 at 3 months. Overall improvement was also observed for the DN4 scores, when compared with the preoperative period in group PGB (3 [2–4] vs. 4 [3–5], $P < 0.0001$) and in group C (2 [1–2] vs. 3 [2–5], $P < 0.0001$).

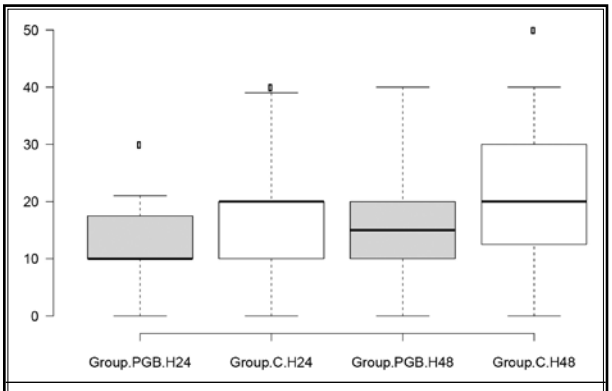

Fig. 2. *Median cumulative oxycodone consumption (in mg, y-axis) on POD1 (H24), primary outcome, and POD2 (H48) between patients included in groups C and PGB. Data are expressed as median (horizontal bar) with 25th to 75th (boxes) and 10th to 90th (whiskers) percentiles and outliers (open circles). Patients in group PGB consumed less oxycodone on POD1 (10 mg [10–17.5] vs. 20 mg [10–20], P = 0.013]) and POD2 (15 mg [10–20] vs. 20 mg [12.5–30], P = 0.018).*

Discussion

In this quasiexperimental study, PGB reduced the opioid requirement by 6 mg (95% CI, –10.26 to –1.74 mg) with a high effect size during the first 48 hours in chronic users when compared with naive patients receiving a 48-hour administration in patients undergoing spinal surgery. Chronic users of PGB before spinal surgery was associated with decreased 24-hour opioid requirements. The NRS-11 and DN4 scores improved within the 2 groups of patients.

PGB possesses a linear pharmacokinetic profile up to 900 mg/day with low variability, a bioavailability greater than 90%, a T^{max} less than 1 hour after a single dose, and a mean elimination half-life of 6 hours. Interactions on CYP450 are rare and without clinical consequences reducing the risk of drug–drug interactions (5). Despite an off-label use, PGB has been proposed in multimodal analgesia to improve pain and reduce opioid side effects during painful surgery (1). However, despite some significant differences in pain and opioid-related adverse effects, the clinical significance regarding the benefit of a perioperative administration of gabapentinoids in mixed surgeries remain controversial (2,3,6,10,11). During spinal surgery, gabapentinoids reduced the opioid request and improved pain scores at rest (4,6,12). The quality of evidence with regard to the

Table 2. *Opioid consumption, pain, and DN4 scores in the perioperative period.*

	Group C (n = 43)	Group PGB (n = 39)	*P*
Remifentanil (μg/kg/min)	0.17 ± 0.05	0.14 ± 0.04	0.004
Morphine in PACU (mg)	6 [0–8]	3 [0–9]	0.53
Time to first request of morphine in PACU (min)	48 ± 27	52 ± 28	0.67
Oxycodone (mg) at: H4 H8 H12 POD1 POD2	 0 [0–0] 0 [0–10] 5 [0–10] 5 [0–10] 0 [0–10]	 0 [0–2.5] 0 [0–10] 0 [0–5] 0 [0–5] 0 [0–10]	 0.93 0.81 0.003 0.029 0.83
Patients who did not require morphine in PACU	15 (34.9)	18 (46.2)	0.29
Patients who did not require oxycodone from PACU to POD2	4 (9.3)	6 (15.4)	0.40
Maximal NRSr during PACU	5 [2–6]	4 [2–5]	0.27
NRSr at H4	2 [1–3]	2 [1–3]	0.15
NRSr at H8	2 [1–3]	2 [1–3]	0.62
NRSr at H12	2 [2–3]	2 [1–3]	0.33
NRSw at H12	4 [3–5]	3 [3–6]	0.54
NRSr at POD1	2 [1–2]	2 [1–2]	0.59
NRSw at POD1	3 [3–4]	3 [2–4]	0.66
NRSr at POD2	1 [1–2]	1 [1–2]	0.44
NRSw at POD2	3 [2–3]	2 [2–3]	0.31
DN4 at POD1	3 [2–4]	4 [3–4]	0.22
DN4 at POD2	2 [2–3]	3 [2–4]	0.16

Results are expressed as mean ± SD, median [IQR], and n (%).
H, postoperative hour; NRSr, Numeric Rating Scale score at rest; NRSw, Numeric Rating Scale score during walking.

Table 3. *Univariate and multivariate analysis for risk factors of oxycodone consumption ≤10 mg 24 hours after surgery.*

	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)	*P* value
Two-level surgery	1.05 (0.38–2.95)	0.86		
Duration of surgery > 64 min	0.99 (0.98–1.02)	0.80		
Preoperative NRS-11 > 5	0.94 (0.69–1.28)	0.71		
Preoperative DN4 > 4	0.96 (0.65–1.41)	0.71		
Male gender	1.19 (0.41–3.43)	0.75		
Discectomy	1.29 (0.36–4.67)	0.70		
Remifentanil > 0.16 μg/kg/min	0.001 (4.7*10-9–214.83)	0.27		
Preoperative use of opioid	0.18 (0.02–1.31)	0.09	0.15 (0.02–1.03)	0.06
PGB group	3.21 (0.98–10.46)	0.05	3.98 (1.44–7.74)	0.008

Hosmer and Lemenshow goodness-of-fit test: $P = 0.41$ and $P = 0.53$.

Table 4. *Side effects and length of stay observed during the first 48 hours after surgery.*

	Group C (n = 43)	Group PGB (n = 39)	*P*
Nausea	9 (20.9)	5 (12.8)	0.33
Vomiting	3 (6.9)	0	0.09
Sedation score	1 [1–2]	1 [1–2]	0.57
Sedation score ≥ 2	11 (25.6)	6 (15.4)	0.26
Diplopia	4 (9.3)	1 (2.6)	0.20
Confusion	0	0	
Dizziness	2 (4.7)	1 (2.6)	0.62
Length of stay	2 [1–3]	2 [1–3]	0.46

Sedation score: maximal sedation score recorded by nurse at H4, H8, H12, H24, and H48 after surgery (1: awake; 2: drowsiness, easily awake by appeal; 3: drowsiness, awake to tactile stimulation; 4: drowsiness, awake by pain). Results are expressed as mean ± SD, median [IQR], and n (%).

effectiveness of short perioperative PGB use, associated to pronociceptive surgery, was high for pain at rest and moderate during movement (13). A repeated administration of PGB has been shown to produce a stable steady-state and less cerebrospinal fluid fluctuation relative to the plasma concentration than a single-dose (14). In an experimental study, the repeated administration of PGB during at least 40 hours before capsaicin application reduced excitatory post-synaptic currents in the dorsal horn, whereas a brief application of a 10-fold higher concentration exerted no significant change (15). PGB 20 mg/kg initiated 7 days before nerve injury has been reported to significantly delay the onset of autotomy behavior by approximately 25 days, and reduced autotomy scores until 63 days when compared with no treatment (16). Initiated after surgery, a dose of 30 mg/kg was required to suppress autotomy behavior (16). The idea of benefits associated with repeated administration of gabapentinoids before surgery on central hyperalgesia has been extracted from animal

models and human data are still lacking. The absence of difference in morphine requirement in PACU can be attributed, at least partly, to the multimodal analgesia. A low correlation between opioid request and pain measures has been already observed in general surgery (6,17), some patients being able to experience a lower pain intensity than expected for scheduled surgery in a context of often disabling preoperative pain. The study was underpowered to detect differences in pain scores, and no quantitative sensory testing was performed. The affinity of noroxymorphone and oxymorphone are 10- to 40-fold higher than oxycodone, respectively. Both genetic polymorphism of CYP2D6 and CYP3A4 influence the pharmacokinetics of oxycodone, but strong evidence for an impact on analgesia, pain scores, and side effects remain to be determined (18). The systematic use of PGB before discectomy, as opposed to spinal fusion, remains questionable given its potential side effects (2,3,6). Current reviews do not support a dose-dependent effect of gabapentinoids on postoperative opioid consumption during a short-term perioperative administration (4,6,12-14). The design of our study does not allow us to determine whether a higher daily dose of PGB could have reduced even more significantly the postoperative consumption of oxycodone or the pain scores.

Although not significant, sedation was more frequent in naive patients. Previous meta-analysis of studies evaluating different spinal surgeries did not find a relation between a short-course use of PGB and the risk of sedation (4,12). Somnolence and dizziness are frequently observed in the absence of progressive and flexible increase in dose regimens (2) in naive patients according to pain relief and adverse events. In the group PGB, the less daily preoperative dose than that usually prescribed for chronic pain and the opioid-sparing effect observed partly explain the reduction in oversedation. Indeed, in a volunteer study, remifentanil combined with PGB potentiated by 62% the end tidal CO^2 at an effect-site target of 2.4 ng/mL without modification in the respiratory rate and minute volume (19). However, ventilatory side effects were assessed only during the infusion of this short-acting opioid, and no information was done after the remifentanil interruption (19). With a context sensitive half time of 3.2 minutes after 3 hours of continuous infusion (20), the ventilatory impact of the association remifentanil/PGB noted in this study (19) is probably limited to the infusion period. In our study, the mean dose of remifentanil was low, and no patients required naloxone during the study follow-up. A retrospective study reported a 6-fold increase in the risk of naloxone requirement when preoperative gabapentinoid is maintained after surgery, but only one of the 128 patients who needed naloxone received remifentanil during surgery, the risk of oversedation being mainly increased by the perioperative continuation of benzodiazepine (21). In our study, the absence of benzodiazepine, the systematic administration of O_2 until POD1, and the multimodal analgesia may have helped to prevent oversedation and respiratory side effects. To avoid potential gabapentinoid overdose, a therapeutic escalation to obtain an opioid-sparing effect should not be the only motivation for prescribing a gabapentinoid preoperatively. No differences in PONV occurred despite the opioid reduction. This could be explained by the multimodal analgesia associated to dexamethasone.

Prolonged infusion of remifentanil during scoliotic surgery was associated with an increase in postoperative morphine consumption by 30% (22). However, the mean hourly dose of remifentanil in this study was twice that used in the present, and the duration of anesthesia was 4-fold longer (23). In contrast, remifentanil infusion up to 0.16 µg/kg/min did not increase postoperative opioid consumption and pain scores during spinal fusion when compared with a placebo (23). In our study, the combination of analgesics and anti-hyperalgesic drugs (24-28) and the gradual reduction of remifentanil during surgery when compared with an abrupt cessation (29) may have been helpful to reduce opioid-induced hyperalgesia.

NRS-11 scores improved at 3 months when compared with preoperative data without between-group differences. We cannot exclude that the effectiveness of surgery performed and the multimodal analgesia used during hospitalization yielded a postoperative and long-term benefit independently of the preoperative use of PGB. One meta-analysis found improvement with PGB during mixed surgery for acute pain at 6 months (13). Conversely, 1 to 4 days administration of PGB 150 to 300 mg/day did not reduce the incidence of pain within 6 months after pronociceptive surgery (11). A recent meta-analysis, including negative unpublished sponsored studies, did not find any significant impact of the short-use of PGB, in the incidence of pain, 6 and 12 months after general surgery (3). Authors reported a low quality of evidence for the reduction in the neuropathic component of pain at 3 months. Recently, a short perioperative use of gabapentinoids did not reduce the risk of chronic pain occurrence when

compared with usual care (2). In mixed surgeries, neuropathic pain affected 13% of patients on POD2 and 33% at 2 months with a protective effect of chronic gabapentinoid therapy (30). We observed a different profile with 27% of patients with a DN4 ≥ 4 on POD2 but only 11% at 3 months without differences between PGB chronic users and naive patients. This suggests that more complex and intense nociceptive mechanisms are implicated in patients scheduled for spinal surgery.

Some limitations have to be considered. Although this study was not randomized, differences in the 2 groups appeared minor, and anesthetic and analgesic management were identical. The opioid reduction was in accordance with the sample-size calculation, and intraoperative opioid consumption was adjusted for baseline differences. Another drawback in our study is that we calculated the sample-size on morphine consumption and not on oxycodone. Using the conversion factor of 1:1.2 between intravenous morphine and oral oxycodone (31), the statistical power remained acceptable. Moreover, the postoperative morphine titration was not included in the main outcome (oral oxycodone consumption), thus not compromising the results. Our study was not powered to detect differences at 3 months in pain and DN4 scores. Finally, postoperative pain can fluctuate according to daily activity, and a multidimensional health-related scale is probably more accurate to test the effectiveness of gabapentinoids in health-related quality of life. The continuation of preoperative chronic treatment remains to be clarified after spinal surgery and analyzed according to major or minor procedures in future prospective studies.

Conclusions

Our study suggests that chronic users of PGB before spinal surgery experienced less opioid consumption when compared with naive patients receiving PGB during to the first 2 PODs. Postoperative oxycodone requirement was positively influenced by the chronic use after controlling for potential cofounding factors. This study reinforces the need for randomized studies, which are needed to further confirm these results during spinal fusion, especially in patients for whom a gabapentinoid has been prescribed for several weeks before scheduled spinal arthrodesis in which pronociceptive mechanisms are stronger than during discectomy.

Author Contributions

CA, ALR, BLT, HLH, and HB contributed to the study design and analysis plan. CA and HLH were involved in the acquisition of data and preparation to data analyses. CA and HB performed data analyses. CA, ALR, BLT, HLH, and HB were involved in the writing of the article. CA and HB wrote the initial draft of the manuscript. All authors critically reviewed and approved submission after redrafting the manuscript to the final version.

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Supplementary Data 1. ***Comparison of NRS-11 scores recorded before and at 48 hours according to groups and surgery.***

	Preoperative NRSw	**48-hour NRSw**	***P***
Spinal fusion (N = 31)	4 [4–6]	3 [2–4]	0.0004
Discectomy (N = 51)	5 [3–6]	2 [2–3]	<0.0001
Spinal fusion: group PGB (N = 13)	5 [4–6]	3 [2–4]	0.009
Spinal fusion: group C (N = 18)	4 [4–5]	3 [3–4]	0.02
Discectomy: group PGB (N = 26)	5 [3–6]	2 [2–3]	0.0001
Discectomy: group C (N = 25)	5 [3–7]	2 [2–3]	0.0001

Results are expressed as median [IQR].
NRSw: Numeric Rate Scale score during walking.