Observational Study

Outcomes and Predictors of Response to Pregabalin for the Treatment of Post-Traumatic Trigeminal Neuropathic Pain Following Neuroablative Procedures: A Retrospective Observational Study

Lu Liu, MD, Zhe Sun, MD, Yan Zhang, MD, Guofeng Ma, MD, and Fang Luo, MD

From: Beijing Tiantan Hospital, Capital Medical University, Pain Management, Beijing, China

Address Correspondence:
Fang Luo, MD
Department of Pain Management
Beijing Tiantan Hospital
Capital Medical University
Beijing 100050, China
E-mail: 13611326978@163.com

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Background: Post-traumatic trigeminal neuropathic pain (PTNP) following trigeminal neuralgia (TN)-related neuroablative procedures is relatively rare. Due to the fear of debilitating complications, its treatment has been generally suboptimal. Pregabalin (PGB) has been reported to relieve neuropathic pain. However, the potential role of PGB and the predictors of response of PGB use as a strategy in the treatment of PTNP following TN-related neuroablative procedures have not been identified yet.

Objectives: To report the efficacy and safety of PGB and the identification of predictors of PGB for PTNP following TN-related neuroablative procedures.

Study Design: Monocentric, retrospective, observational study.

Setting: This study consecutively enrolled patients with PTNP following TN-related neuroablative procedures who were prescribed PGB at Beijing Tiantan Hospital.

Methods: From January 2018 to June 2022, a total of 112 patients were included in this study, of whom 10 were excluded because of incomplete follow-up data and side effects immediately after taking PGB. Final analysis included 102 patients. Demographic data, pain-related baseline data, efficacy of patients with PTNP after one month of PGB evaluated by the Barrow Neurological Institute (BNI) scores for pain, and side effects of PGB were extracted and analyzed. The predictors of pain-relieving effects of PGB were identified by logistic regression analysis.

Results: Within one month after the use of PGB alone, 29 out of the 102 (28.4%) patients achieved pain relief with a significant reduction in the BNI scores ($P < 0.01$). All of the 73 patients who did not respond to PGB monotherapy either switched to other medications (n = 8) or combined additional oral medications to the existing PGB therapy (n = 65). The main side effect of PGB in our study was dizziness. Binary logistic regression analysis showed that longer disease durations (Adjusted odds ratio [OR] = 0.55, 95% confidence interval [CI] 0.43 to 0.72, $P = 0.000$) and higher Hospital Anxiety and Depression Scale (HADS) scores (Adjusted OR = 0.29, 95% CI 0.10 to 0.87, $P = 0.022$) were poor predictors of response to PGB.

Limitations: This was a retrospective observational study. Long-term efficacy and safety of PGB in the treatment of PTNP patients were not evaluated.

Conclusions: This study confirms that PGB monotherapy is not a very effective treatment for PTNP following TN-related neuroablative procedures. PGB was more beneficial in patients with shorter disease durations and lower HADS scores.

Key words: Post-traumatic trigeminal neuropathic pain, efficacy, safety, predictor of response, pregabalin

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Post-traumatic trigeminal neuropathic pain (PTNP), previously termed anesthesia dolorosa (AD), is a facial or oral pain caused by trauma to the trigeminal nerve(s) (1). PTNP is a relatively rare but dreaded, debilitating complication in the oral and maxillofacial field, that is partly caused by trigeminal neuralgia (TN)-related neuroablative procedures, such as partial sensory rhizotomy (PSR), radiofrequency thermocoagulation (RFT), percutaneous balloon compression (PBC), glycerol rhizotomy (GR), gamma knife radiosurgery (GKRS), and so on (2). It is a chronic condition where patients experience numbness and constant severe pain, simultaneously, in the areas innervated by the TN involved (3). The cause of PTNP is still unknown, but animal studies have implicated various biological processes, such as inflammation, enhanced neuropeptide-mediated pain signal transmission, endothelial receptor activity, and glial cell dysfunction causing trigeminal hyperexcitability (4). In general, good estimates of the prevalence of PTNP are lacking, probably at least in part due to shifting diagnostic terms and criteria (5). Tatli et al (6) reported the incidence of this troublesome dysesthetic sensory disturbance following TN-related neuroablative procedures is highly variable, ranging from 0.3% to 2%, depending on the reports. Although PTNP is rather uncommon, once it occurs, this severe chronic pain syndrome can greatly compromise patients' quality of life and disrupt basic daily activities. Moreover, ineffective treatments impose serious health-economic burden on patients (7).

The interventions of PTNP are challenging, and consensus on treatment to resolve this kind of neuropathic pain (NP) has yet to be standardized. PTNP treatment typically involves medications and surgery. The mainstays of pharmacologic treatment of painful traumatic trigeminal neuropathy remain antiepileptic drugs and tricyclic antidepressants. In contrast to the traditional 50% pain reduction for clinical significance, research has shown that about a 30% reduction represents meaningful pain relief (8). For patients who do not respond to pharmacological regimens, there are a number of surgical treatment options available, including mesencephalotomy, thalamic or periaqueductal deep brain stimulation, dorsal root entry zone (DREZ) lesion (DREZ procedure), etc. Despite these numerous medical and surgical interventions, symptoms remain persistent in many patients (9).

As early as 1999, Rozen et al (10) reported the use of gabapentin, as an anticonvulsant and analgesic, for the treatment of patients with AD, more recently known as PTNP. Gabapentin is a structural analog of gamma-aminobutyric acid (GABA), which binds to the α protein subunit of voltage-gated calcium channels widely distributed in the central and peripheral nervous system. The action of gabapentin in alleviating the symptoms of PTNP probably relates to its ability to enhance neuronal inhibition and suppress central deafferentation hypersensitivity (11). Unfortunately, the pharmaceutical therapy of gabapentin for PTNP is often insufficient.

Pregabalin (PGB), similar to gabapentin, belongs to the gabapentinoids family and is classically used as an antiepileptic and an analgesic (12). However, unlike gabapentin, PGB has an amino acid substitution at the third position, which enhances lipid solubility and diffusion across the blood-brain barrier, and has an overall better pharmacokinetic profile. PGB acts as a better ligand for the α protein subunit and has shown superior analgesic potency than gabapentin (13). The US Food and Drug Administration has approved PGB for the management of NP associated with diabetes mellitus (DM), postherpetic neuralgia, partial onset seizures, and fibromyalgia (13-15). So far, few investigators have examined the potential role of PGB as a strategy to treat PTNP, including PTNP following neuroablative procedures. With this background in mind, we designed this study to determine the effects and identify the predictors of response of PGB on PTNP following neuroablative procedures.

Methods

Study Design and Ethical Approval

This study involving human patients is in accordance with the 1964 Declaration of Helsinki. After obtaining approval from the Medical Ethics Committee of Beijing Tiantan Hospital, we retrospectively reviewed the clinical database for the medical records of patients with PTNP following TN-related neuroablative procedures between January 2018 to June 2022, at the Department of Pain Management of Beijing Tiantan Hospital. Written informed consent from patients was exempted because of the retrospective nature of this study. Patients who fulfilled the following eligibility criteria were included for analysis: (1) age $\geq$ 18 years; (2) diagnosed with PTNP in accordance with the criteria of Section 4.1.2.3 in the International Classification of Orofacial Pain, First Edition (1); (3) a history of TN-related neuroablative procedures (e.g., PSR, RFT, PBC, GR,

GKRS, etc. within 6 months before the onset of pain; and (4) started analgesic treatment for PTNP with PGB as a monotherapy for the first time. Exclusion criteria for the study included: (1) patients who had previously undergone surgeries for PTNP, such as mesencephalotomy, deep brain stimulation, DREZ procedure, and so on; (2) patients who had received PGB for other reasons; (3) patients undergoing simultaneously combined therapy with other medications; and (4) patients with incomplete baseline data or follow-up data.

Patient Population and Data Collection

This retrospective study was based on the data from the hospital information system's medical records and the department follow-up database. Patients' baseline characteristics included age, gender, body mass index (BMI, weight in kilograms divided by the square of height in meters), duration of disease (time interval between symptom onset and first visit in our clinic), a history of smoking, a history of sleep disorder, comorbidities, such as hypertension, DM, cardiac disease, cerebrovascular disease or autoimmune disease, pain laterality (left/right), and etiology of TN (16), including classical or idiopathic TN (caused by arterial compression or unknown etiology), secondary TN (caused by tumor compression or multiple sclerosis, etc), previous TN-related neuroablative procedures, such as PSR, RFT, PBC, GR, GKRS, baseline Barrow Neurological Institute (BNI) scores (I: no pain, no medication; II: occasional pain, not requiring medication; III: some pain, adequately controlled with medication; IV: some pain, not adequately controlled with medication; and V: severe pain/no pain relief), baseline BNI facial hypesthesia scores (I: no facial numbness; II: mild facial numbness and not bothersome; III: facial numbness and somewhat bothersome; and IV: facial numbness and very bothersome), baseline Hospital Anxiety and Depression Scale (HADS) scores (used for evaluation of the potential mood of patients, 0 to 7 scores for normal or no anxiety/depression, 8 to 10 scores for mild, and 11 to 21 scores for moderate or severe anxiety/depression) (17), and prescribed medications for PTNP previously (i.e., drug type, quantity, and days of drug supply). Based on whether PGB monotherapy was effective within one month of use or not, the patients were divided into the responsive group and the nonresponsive group. Routine follow-ups were conducted from the initial prescription of PGB via outpatient visits every month. Any possible side effects, such as dizziness, somnolence, weight gain, edema, or vertigo and their severity, were evaluated and recorded every month at outpatient clinics by experienced pain physicians. BNI scores, BNI facial hypesthesia scores, and HADS scores were recorded during each monthly follow-up visit.

Prescription of PGB and Evaluation of the Effectiveness

After being diagnosed with PTNP, oral PGB (Pregabalin Capsules, Pfizer Pharmaceutical Co. Ltd, New York, NY) was prescribed. For each PGB prescription, the information on quantity, frequency of administration, and days of drug supply were collected and analyzed. Treatment was initiated with 150 mg of PGB, divided into 2 or 3 doses per day, and increased to 300 mg per day after 3 to 7 days, then increased by 150 mg per day, every 3 to 7 days, depending on individual patient response and tolerability (18). The maximum dose of PGB did not exceed 600 mg per day. Once side effects occurred with the increase in PGB dosage, the dose of PGB was reverted back to the last tolerable dose (19).

Pain relief within one month of PGB use was evaluated with BNI scores (20). Complete pain relief was defined as being pain free without medication (BNI I) after PGB monotherapy. Satisfactory pain relief was defined as a BNI score of II or III. Meanwhile, BNI scores that reached from I to III one month after PGB was defined as responsive treatment; whereas, BNI score that still remained IV or V one month after PGB was considered nonresponsive. When PGB treatment was rated as responsive, the prescribed dose was continued. Dose adjustments were not allowed during this maintenance period. Then, PGB was gradually decreased up to the point where the symptoms recurred, with the aim of finding the minimum effective dose without any side effects. Inversely, when PGB treatment was evaluated as nonresponsive, other medications in addition to PGB were prescribed, or PGB was either switched to other medications or surgical treatment options were considered (Fig. 1). The onset time was recorded when pain relief was observed for the first time after PGB monotherapy. Patients who had responded to PGB with BNI ranging from I to III within one month, but had increased BNI to IV or V later, were defined as pain recurrence. The response rate after PGB was calculated as follows: [the number of (BNI I+II+III) patients]/total number of patients)*100%.

Statistical Analysis

All data were collected retrospectively and analyzed with SPSS Statistical Software Version 24 (IBM

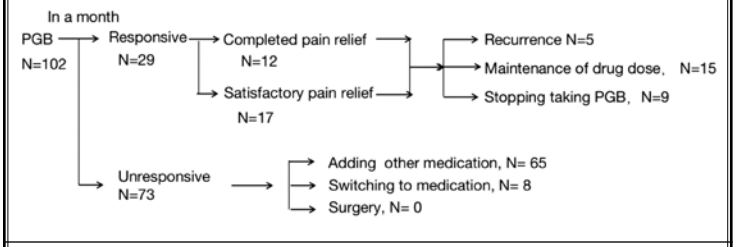

Fig. 1. *The patient outcome and the final treatment choice.*

Corporation, Armonk, NY). Descriptive statistics for all variables of interest were computed. Normally distributed continuous data were presented as means ± standard deviations (SDs) and analyzed by independent t tests. Nonnormally distributed continuous data were presented as medians and interquartile ranges and analyzed by the Mann-Whitney U test. The categorical data were described as frequencies and percentage values, and were tested using the chi-square test or Fisher's exact test (when the expected values were < 5). The baseline variables with $P < 0.1$ were included as the potential predictors for response to PGB monotherapy in the preliminary screening. Multivariate logistic regression analyses were then conducted to examine the predictors for response to PGB for patients with PTNP. We identified the final multivariate model for using a backward stepwise approach with $P < 0.05$ of the likelihood ratio test for the exclusion of excess factors. Unadjusted and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated separately. All tests were 2-tailed, and a P value of < 0.05 was considered statistically significant.

Results

Baseline Characteristics of Patients Enrolled

A total of 112 patients were prescribed PGB as a single agent for the treatment of PTNP following TN-related neuroablative procedures, between January 2018 to June 2022. Five patients were excluded because their follow-up data were incomplete. In total, 107 patients were included in this study. Ninety-six out of one hundred and seven (89.7%) patients who received medications, such as nonsteroidal anti-inflammatory drugs, antidepressants, or gabapentin before taking this PGB monotherapy, did not achieve good analgesic effect. Forty-one (38.3%) patients underwent TN-related neuroablative procedures at our hospital, and the rest, at other hospitals. The demographics and baseline data of the 107 enrolled patients are shown in Table 1. The mean age was 71.6 years with a median duration of disease of 5 months; 25.2% of patients suffered from hypertension. Almost half of the patients had a history of sleep disorder (48.6%), and 63.6% had HADS scores > 7.

Comparison of the Data Between the Responsive Group and the Nonresponsive Group

Five (4.7%) patients suffered from intolerable side effects immediately after taking PGB, which was discontinued right away. After excluding the aforementioned 5 patients, 29 (28.4%) out of the remaining 102 patients achieved pain relief and 73 (71.6%) patients stopped PGB monotherapy because of weak efficacy (Table 2). There were no significant differences between the 2 groups with regards to age, gender, BMI, pain laterality, a history of smoking, hypertension, DM, cardiac disease, cerebrovascular disease, autoimmune disease, etiology of TN, previous TN-related neuroablative procedures, baseline BNI scores, baseline BNI facial hypesthesia scores, and prescribed medications for PTNP previously. The duration of disease and the incidence of sleep disorder were all significantly lower in the responsive group than those in the nonresponsive group ($P < 0.05$). And the percentage of patients with HADS scores ranging from 8 to 21 in the nonresponsive group was much higher than that in the responsive group (72.6% vs 41.4%, $P = 0.003$) (Table 2)

Efficacy and Outcome

The BNI scores after PGB alone within one month in the responsive group were much lower than those in the nonresponsive group [2 (range: 1, 3) vs 4 (range: 4, 5), $P = 0.00$]. The patient outcome and the final treatment choice are shown in Fig. 1. One month after prescription of PGB during the first visit, PGB significantly alleviated pain in 29 patients (28.4%), which included 12 (41.4%) patients with complete pain relief and 17 (58.6%) patients with satisfactory pain relief. The effective dose of PGB was maintained for 6 to 8 weeks and then gradually decreased to the minimum effective dose, without recurrence (275 mg per day). Within one month after using PGB monotherapy, the median effective dosage without having side effects in the responsive group was 375 mg per day. Whereas, the median dose of PGB in the nonresponsive group was 425 mg per day. Fortunately, 9 patients did not require any

Table 1. *Baseline characteristics of patients enrolled.*

Variables	Total
Number, n	107
Age , mean ± SD (y)	71.6 ± 11.3
Women, n (%)	73 (68.2%)
BMI, mean ± SD (kg/m^2)	22.8 ± 2.8
Duration of Disease, median (IQR) (mo)	5.0 (3.0, 8.0)
Right Laterality, n (%)	46 (43.0%)
A History of Smoking, n (%)	37 (34.5%)
A History of Sleep Disorder, n (%)	52 (48.6%)
Comorbidities, n (%)	
Hypertension	27 (25.2%)
DM	19 (17.8%)
Cardiac Disease	10 (9.3%)
Cerebrovascular Disease	8 (7.5%)
Autoimmune Disease	7 (6.5%)
Etiology of TN, n (%)	
Classical or Idiopathic TN	97 (90.7%)
Secondary TN	10 (9.3%)
Previous TN-Related Neuroablative Procedures, n (%)	
PSR	21 (19.6%)
RFT	49 (45.8%)
PBC	19 (17.8%)
GR	7 (6.5%)
GKRS	11 (10.3%)
Baseline BNI Scores, n (%)	
IV	82 (76.6%)
V	25 (23.4%)
Baseline BNI Facial Hypesthesia Scores, n (%)	
II	3 (2.8%)
III	71 (66.4%)
IV	33 (30.8%)
Baseline HADS Scores, no (%)	
≤ 7	39 (36.4%)
8-21	68 (63.6%)
Prescribed Medications for PTNP Previously, no (%)	
None	11 (10.3%)
Oral NSAIDs (inclusive of COX-2 inhibitors)	69 (71.9%)
Antidepressants	12 (12.5%)
Gabapentin	28 (29.2%)

Data are expressed as mean ± SD, standard deviation, or median (IQR, interquartile range); n, number (%); y, year; mo, month. BMI, body mass index; DM, diabetes mellitus; TN, trigeminal neuralgia; PSR, partial sensory rhizotomy; RFT, radiofrequency thermocoagulation; PBC, percutaneous balloon compression; GR, glycerol rhizotomy; GKRS, gamma knife radiosurgery; {AU: not in table} PTNP, post-traumatic trigeminal neuropathic pain; BNI, Barrow Neurological Institute ({AU: not in table} IV: some pain, not adequately controlled with medication; V: severe pain/no pain relief). The degree of ipsilateral facial numbness was assessed by the BNI Facial Hypesthesia Scale (II: mild facial numbness and not bothersome; III: facial numbness and somewhat bothersome; IV: facial numbness and very bothersome); HADS, Hospital Anxiety and Depression Scale scores (0 to 7 scores for normal or no anxiety/depression, 8 to 21 scores for possible anxiety/depression); NSAIDs, nonsteroidal anti-inflammatory drugs.

medication after 12 weeks of successful treatment with PGB monotherapy. Five out of the twenty-nine patients in the responsive group experienced recurrence at 4, 7, 8, 10, and 11 months after the initial prescription of PGB because of reducing drug dosage or patient compliance. Among these 5 patients, 3 titrated the dose of PGB and gradually achieved pain relief again. The remaining 2 were prescribed an additional dose of 40 mg duloxetine, due to insufficient pain relief from the maximum dose of PGB as monotherapy. Inversely, in 73 out of 102 patients (83.6%), there was no significant decrease in BNI scores within one month after PGB alone, and none of these patients opted for surgical interventions. Among the 73 patients, 65 underwent combination therapy with PGB and other oral medications and 8 patients switched to other medications alone. Out of the 65 patients who were on combined therapy, 38 were prescribed duloxetine in combination with PGB, 21 were prescribed venlafaxine, 4 were prescribed olanzapine, and 2 were prescribed oxycodone. The remaining 8 had to switch to other drugs, such as duloxetine alone (n = 2), olanzapine alone (n = 2), quetiapine alone (n = 1), a combination of duloxetine and oxycodone (n = 2), and a combination of olanzapine and oxycodone (n = 1), for satisfactory pain relief.

Univariate and Multivariate Analysis for PTNP Outcome After PGB

Univariate and multivariate logistic regression analysis was carried out to identify the predictors of the effect of PGB monotherapy on PTNP following neuroablative procedures (Table 3). In univariable regression analysis, risk factors with *P* values (i.e.,a history of hypertension, duration of disease, a history of sleep disorder, and baseline HADS score) were < 0.1. All of these 4 variables were selected for multivariate regression analysis, which revealed that the duration of disease (Adjusted OR = 0.55, 95% CI 0.43 to 0.72, *P* = 0.000) and the baseline HADS scores (Adjusted OR = 0.29, 95% CI 0.10 to 0.87, *P* = 0.027) were significant

Table 2. *Univariate comparison analysis of the data between the responsive group and the nonresponsive group.*

Variables	Total	Responsive Group	Nonresponsive Group	*P* value
Number, n	102	29	73	
Age, median (range) (y)	71.6 ± 11.3	72.8 ± 11.0	71.2 ± 11.5	0.53
Women, n (%)	70 (68.6%)	19 (65.5%)	51 (69.9%)	0.67
BMI, mean ± SD (kg/m^2)	22.8 ± 2.8	23.1 ± 2.6	22.7 ± 2.9	0.39
Duration of Disease, median (IQR) (mo)	5.0 (3.0, 8.0)	3.0 (2.0,.4.0)	7.0 (5.0, .8.0)	-0.00
Right Laterality, n (%)	44 (43.1%)	9 (31.0%)	35 (47.9%)	0.12
A History of Smoking, n (%)	35 (34.3%)	9 (31.0%)	26 (35.6%)	0.98
A History of Sleep Disorder, n (%)	49 (48.0%)	9 (31.0%)	40 (54.8%)	-0.03
Comorbidities, n (%)				
Hypertension	26 (25.5%)	11 (37.9%)	15 (20.5%)	0.07
DM	18 (17.6%)	5 (17.2%)	13 (17.8%)	0.95
Cardiac Disease	9 (8.8%)	3 (10.3%)	6 (8.2%)	0.71
Cerebrovascular Disease	7 (6.9%)	1 (3.4%)	6 (8.2%)	0.67
Autoimmune Disease	6 (5.9%)	1 (3.4%)	5 (6.8%)	0.67
Etiology of TN, n (%)				
Classical or Idiopathic TN	93 (91.2%)	26 (89.7%)	67 (91.8%)	0.73
Secondary TN	9 (8.8%)	3 (10.3%)	6 (8.2%)	
Previous TN-Related Neuroablative Procedures, n (%)				
PSR	20 (19.6%)	5 (17.2%)	15 (20.5%)	0.49
RFT	47 (46.1%)	13 (44.8%)	34 (46.6%)	
PBC	18 (17.6%)	8 (27.6%)	10 (13.7%)	
GR	7 (6.9%)	1 (3.4%)	6 (8.2%)	
GKRS	10 (9.8%)	2 (6.9%)	8 (11.0%)	
Baseline BNI Scores, n (%)				
IV	77 (75.5)	23 (79.3%)	54 (74.0%)	0.57
V	25 (24.5)	6 (20.7%)	19 (26.0%)	
Baseline BNI Facial Hypesthesia Scores, n (%)				
II	3 (2.9%)	2 (6.9%)	1 (1.4%)	0.32
III	68 (66.7%)	18 (62.1%)	50 (68.5%)	
IV	31 (30.4%)	9 (31.0%)	22 (30.1%)	
Baseline HADS Scores, n (%)				
≤ 7	37 (36.3%)	17 (58.6%)	20 (27.4%)	0.00
8-21	65 (63.7%)	12 (41.4%)	53 (72.6%)	
Prescribed Medications for PTNP Previously, n (%)				
None	9	3 (10.3%)	6 (8.2%)	0.73
Oral NSAIDs (inclusive of COX-2 inhibitors)	68	18 (62.1%)	50 (68.5%)	0.54
Antidepressants	12	4 (13.8%)	8 (11.0%)	0.69
Gabapentin	26	8 (27.6%)	18 (24.7%)	0.76

Data are expressed as mean ± SD, standard deviation, or median (IQR, interquartile range); n, number (%); y, year; mo, month. BMI, body mass index; DM, diabetes mellitus; TN, trigeminal neuralgia; PSR, partial sensory rhizotomy; RFT, radiofrequency thermocoagulation; PBC, percutaneous balloon compression; GR, glycerol rhizotomy; GKRS, gamma knife radiosurgery; {AU: Not in table} PTNP, post-traumatic trigeminal neuropathic pain; BNI, Barrow Neurological Institute (IV: some pain, not adequately controlled with medication; V: severe pain/no pain relief). The degree of ipsilateral facial numbness was assessed by the BNI Facial Hypesthesia Scale (II: mild facial numbness and not bothersome; III: facial numbness and somewhat bothersome; IV: facial numbness and very bothersome); HADS, Hospital Anxiety and Depression Scale scores (0 to 7 scores for normal or no anxiety/depression, 8 to 21 scores for possible anxiety/depression); NSAIDs, nonsteroidal anti-inflammatory drugs.

predictors of poor outcome for PTNP following PGB (Table 3).

Complications

Five patients experienced intolerable dizziness immediately after taking PGB and had to discontinue it. No serious complications occurred from PGB monotherapy, throughout the study period. There were no significant differences in incidence of somnolence, weight increase, edema, and vertigo between the responsive group and the nonresponsive group (Table 4). Thirty-five patients (47.9%) in the nonresponsive group and 6 (20.7%) in the responsive group (P = 0.011) suffered from dizziness (Table 4). All patients experienced a slight dizziness because of PGB treatment during the first few weeks of administration; however, these side effects were transient and tolerable, thus patients continued taking PGB as prescribed.

Discussion

To our knowledge, this is the largest scale observational study to access the efficacy of PGB in PTNP patients following TN-related neuroablative procedures until now. We found that PGB monotherapy could only notably alleviate pain in less than one-third of the patients, which was not clinically feasible. This conclusion means that we should immediately combine PGB with other drugs or switch to other drugs for treatment, once patients fail to respond to PGB monotherapy. Meanwhile, we also confirmed that longer duration of disease and higher HADS scores were significant predictors of poor outcomes for PTNP following PGB monotherapy. These results will help make clinical decisions regarding the treatment of PTNP patients.

PTNP is currently considered extremely difficult to manage (21). The recommendations of pharmacological treatment of PTNP generally involve tricyclic antidepressants and antiepileptic drugs (22). However, the tricyclic antidepressants have a number of side effects, such as tiredness, weight gain, and mouth dryness. The antiepileptic drugs, including PGB and gabapentin, have emerged as the most effective drugs to manage various NP states. Clinical trials for comparative efficacy and safety of PGB and amitriptyline have projected PGB as a better treatment option in diabetic neuropathy due to a lesser proportion of side effects (25%) than amitriptyline (65.4%) (23). In a previous study (24), PGB has turned out to be 2- to 4-fold more potent than gabapentin as an analgesic in treating NP. Saldaña et al (25) reported suggesting PGB as a valid treatment alternative for the management of patients with gabapentin-refractory peripheral NP. Hence, we explored whether PGB could become a promising candidate for PTNP patients following TN-related neuroablative procedures.

A great number of studies are available regarding the efficacy of PGB on central NP (26) along with a broad range of peripheral NP etiologies (27). A review involving 45 studies, including a total of 11,906 patients, with a follow-up period ranging from 2 to 16 weeks, reported that oral PGB for postherpetic neuralgia, painful diabetic neuropathy, and mixed NP could achieve almost 85% pain relief. Unlike their study, the pain relief rate of PGB on PTNP following TN-related neuroablative procedures in our study was < 30%. Our result is consistent with that of Derry et al (28), who were unable to establish the benefits of 600 mg PGB in HIV neuropathy. Hence, although PGB is the first-line recommended drug for treating NP, its efficacy for PTNP, as a particular type of NP, is limited.

Table 3. *Univariate and multivariate logistic analysis of response to PGB monotherapy for PTNP.*

Variables	Univariate Logistic Analysis		Multivariate Logistic Analysis	
	OR (95% CI)	*P* value	Adj OR (95% CI)	*P* value
A History of Hypertension	2.36 (0.92-6.05)	0.073		
A History of Sleep Disorder	0.43 (0.18-1.06)	0.067		
Duration of Disease	0.56 (0.43-0.73)	0.000	0.55 (0.43-0.72)	0.000
Baseline HADS scores	0.29 (0.12-0.70)	0.006	0.29 (0.10-0.87)	0.027

Abbreviations: OR, odds ratio; CI, confidence interval; Adj OR, adjusted odds ratio; PGB, pregabalin; PTNP, post-traumatic trigeminal neuropathic pain; HADS, Hospital Anxiety and Depression Scale scores.

Table 4. *Side effects*.

	Responsive Group	Nonresponsive Group	*P* value
Number, n (%)	29 (28.4%)	73 (71.6%)	
Side Effects, n (%)			
Dizziness	6 (20.7%)	35 (47.9%)	0.011
Somnolence	9 (33.3%)	15 (20.5%)	0.260
Weight increase	6 (22.2%)	11 (15.1%)	0.492
Edema	4 (13.8%)	6 (8.2%)	0.464
Vertigo	3 (10.3%)	4 (5.5%)	0.402

Abbreviation: n, number.

Drug combination with various modes and targets on NP theoretically leads to improved efficacy (21). That was because the mechanism of NP involves multiple and complex molecular interactions (29). In our retrospective study, PTNP patients who did not respond to PGB monotherapy were prescribed PGB in addition to antidepressants or opiates and so on. Although our study was not designed as a comparison of monotherapy vs combination treatment, our data provides a reference for the recommendation of combination treatment with PGB for PTNP patients with suboptimal response to a monotherapy. Similarly, in the reports by Tesfaye et al (30), PGB monotherapy resulted in significant pain relief in only 34% of patients with painful diabetic peripheral NP (i.e., responders, who reached Numeric Rating Scale < 3) after 6 weeks. Patients who started combination therapy (i.e., had inadequate response to monotherapy) saw a further reduction of 1.0 (SD 1.3) point (98.3% CI 0·6 to 1.3, $P < 0.0001$). Currently, most guidelines do not recommend combination treatment modalities for the treatment of PTNP due to insufficient evidence, despite widespread use by clinicians (29). Further investigation is expected to improve clinical strategies for the use of combination therapy with PGB in the treatment of PTNP.

In our study, the disease duration of patients in the responsive group was 3 months, while that in the nonresponsive group was nearly 7 months. A longer disease duration may be one of the causes for poor pain control. We infer that PGB may be more effective when applied in the early stages of PTNP following TN-related neuroablative procedures. This is consistent with the results of Tarrio et al (31), who reported of a greater response to PGB in NP patients with shorter disease duration (≤ 3 months). Conversely, studies have also shown that patients respond equally well to PGB treatment regardless of disease duration. A pooled analysis of PGB for peripheral NP conditions, such as diabetic peripheral neuropathy, postherpetic neuralgia, and post-traumatic/postsurgical pain, revealed that patients benefit from treatment with PGB regardless of their duration of pain (32). Vadivelu et al (33) proposed that once a peripheral NP condition is established, there is no clear evidence why it becomes more difficult to treat over time. Based on the different conclusions mentioned above, more high-quality clinical evidence is needed to assess the treatment effect of PGB in different pain duration categories.

In our study, multivariate regression analysis reveals that high HADS scores before the prescription of PGB are definitely related to poor PGB outcomes. As is known to us all, chronic pain in general, and NP specifically, are frequently associated with anxiety, depression, and sleep disorders (34). Patients with these negative emotions tend to respond worse to PGB treatment. Therapies should therefore treat these concomitant symptoms along with pain. Nevertheless, these results are not consistent with the results reported by Arnold et al (35), which presented that PGB was likely to be similarly efficacious in reducing pain in patients with or without anxiety or depressive symptoms. In summary, PGB for the treatment of PTNP patients with high HADS scores remains to be verified further. Our study suggests that PGB monotherapy is suitable for PTNP patients with low HADS scores. Those who do not respond to PGB monotherapy require other agents, such as serotonin and noradrenaline reuptake inhibitors or tricyclic antidepressants, added as combination therapy. However, the optimized treatment strategy needs to be further confirmed. In our univariate analysis, a history of sleep disorder was a negative predictor for the efficacy of PGB monotherapy for PTNP. However, multivariate analysis did not prove this result. That may be due to the rather small sample size of this study and there was an indirect relationship between the history of sleep disorder and the efficacy of PGB. This indirect relationship became insignificant after the adjustment of regression variables.

In this study, 5 (4.7%) out of 107 patients suffered from intolerable side effects shortly after taking PGB and PGB was discontinued in these patients immediately. It can be established that very few patients showed intolerance for PGB. However, overall adverse effects were generally mild or moderate in intensity. The majority of clinical studies involving administration of PGB for the treatment of various types of NP states have shown dizziness, somnolence, weight gain, edema, and vertigo as common side effects (15). Consistent with previous studies (36), the main side effect of PGB in our study was dizziness. The occurrence of dizziness can be directly attributed to its primary mechanism of action. It inhibits various types of calcium channels and N-type located in different areas of the brain to decrease the release of depolarization-dependent neurotransmitters (37). The highest level of expression of these channels has been found in the cerebellum and in the hippocampus, and their dysfunction/decreased activity affects the vestibulocerebellar/brainstem structures and higher cortical functions leading to dizziness (38). Thirty-five patients (47.9%) presented with dizziness in the non-

responsive group, which was much higher than those in the responsive group (20.7%, $P = 0.01$) (Table 4). The dosages of PGB in the nonresponsive group were much higher than those in the responsive group. This shows that the adverse effects of PGB were dose-dependent. The result was similar to that of a previous study by White et al (39). On the contrary, another review (40) regarding the results of dizziness stratified by PGB dose was not significant, indicating that PGB had no dose effect on the incidence of dizziness. In our study, we also did not find any significant differences in the incidence of somnolence, weight increase, edema, and vertigo between the responsive group and the nonresponsive group. The exact relationship between PGB dosage and side effects needs to be explored in the future.

Limitations

Several limitations were detected in the current analysis. First, this is a retrospective single-center study, hence, a prospective multicenter-controlled study will be expected to avoid inherent bias and provide a higher level of evidence. Second, most of the enrolled patients have shorter courses of disease. That was because we started PGB treatment as early as possible in 38.3% of patients who suffered from PTNP after undergoing TN-related neuroablative procedures at our hospital. And due to the relatively small sample size, we did not analyze the result stratified according to the course of the disease. Hence, a stratified study on the duration of disease needs to be conducted further. Third, we did not differentiate the classification (HADS-anxiety or HADS-depression) and severity (mild, moderate, or severe) of HADS to assess the mental state of patients. Fourth, the follow-up period was relatively short. The effect of combination therapy on PTNP was uncertain. Long-term efficacy and side effects of PGB on PTNP need a longer patient follow-up period. Certainly, all these patients will be continuously monitored, and further reports will undoubtedly provide an even clearer picture regarding PGB for PTNP.

Conclusions

In this study, PGB monotherapy was not a very effective treatment for PTNP following TN-related neuroablative procedures. The prescription of PGB monotherapy may be more appropriate in PTNP patients with a shorter duration of disease and lower HADS scores.

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