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FULL PAPER

The effect of Pregabalin on the pain status of patients with disc and spinal surgeries: A systematic review of drug therapy

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Pain is the physiological response of the body to tissue damage, disease itself, or visceral dilation and can occur intra- or post-operatively. Pregabalin (PGB, δ-[+]-3-isobutylgaba) is structurally similar to gamma-amino butyric acid (GABA), and does not bind to GABA receptors and exerts its effects on the α2δ receptor. Therefore, the aim of the present study was to evaluate the PGB effect on reducing pain in patients with disc and spinal surgeries. The search process was carried out by two researcher (one anesthesiologist and one neurosurgeon) using specific keywords lumbar spinal surgery, pain, lumbar disc herniation (LDH) surgery, lumbar laminectomy, spinal surgery, and PGB in ISI-PUBMED-SCOPUS international databases. In the initial search, 322 articles were found, which after reviewing 16 articles were entered the final stage. Of the articles included in, 6 articles were in the group of patients with spinal surgery, 3 articles were in the group of patients with LDH surgery, 7 articles were in the group of other spinal patients including lumbar discectomy, lumbar laminectomy, and other patients. In most of the reviewed articles, PGB was used to reduce the pain of patients. Due to the positive effect of PGB on reducing pain in patients, it is recommended to prescribe this drug.

KEYWORDS

Pregabalin; pain; spinal fusion.

Introduction

PGB, with a chemical structure displayed in Figure 1, is structurally similar to GABA, but it does not bind to this receptor type. The strong binding of this drug at the end of the presynaptic nerve reduces Ca^{2+} influx at the presynaptic and reduces neurotransmitters such as noradrenaline, serotonin, and glutamate [1,2]. PGB decreased pain by declining cerebral glutaminergic excitatory factor and increasing minergic GABA as an inhibitory agent [3].

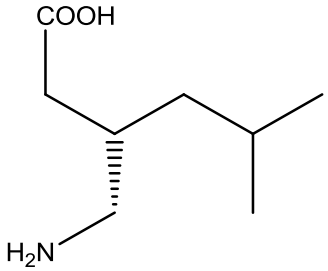

FIGURE 1 Chemical backbone of PGB

One of the pain medicines is PGB that can be used as a pain killer, anticonvulsant, and analgesic, and one of its important uses is to control neuropathic pain. This drug is effective on acute postoperative pain and reduce the excitation of posterior spinal cord neurons

due to tissue damage [4, 5]. PGB can be effective in controlling acute postoperative pain including pain caused by orthopedic, abdominal, and hysterectomy surgeries and can reduce the resulting pain [5, 6].

Pain is the physiological response of the body to tissue damage, disease itself, or visceral dilation and can occur intra- or postoperatively [7, 8]. Pain is considered as a very powerful stressor for all members of society, including patients, families, and health care providers, and can have negative effects on most health-related aspects [9, 10]. In order to improve the health status of patients, various interventions are used, including drug interventions. Various drugs are currently prescribed to reduce pain, one of which is oral PGB tablets [11, 12]. Approximately, 30% of patients experience chronic pain and disability after spine surgery, which can lead to disorders in all aspects of life [13].

Lifestyle changes have caused problems for patients, such as chronic diseases [14]. They also cause many chronic diseases including heart disease [15], diabetes [16], and lumbar disc [17]. Lumbar disc is one of these chronic diseases. In fact, lumbar intervertebral disc herniation is one of the most common problems in today's society, the clinical manifestations of which include pain in the lower back and legs [18]. Diseases related to the nervous and spinal systems are one of the most important and challenging diseases that have negative effects on health status, including imposing health costs, increasing the burden of patient care, reducing quality and life expectancy, as well as inability to perform daily tasks [19-21]. These diseases, especially SCI, affect about 500,000 people per year, and may occur due various types of traumata, including accidents, fights, falls, etc. [22, 23]. In addition, traumatic diseases have caused changes in the tests of the patient and these factors can be effective in causing physiological responses, including pain [24].

Systematic review studies on drug interventions to reduce the pain of patient can be a good patient guide to increase the ability of physicians to identify the appropriate drug to manage and reduce the pain of patient [25]. Considering the importance of the role of pain relief in patients undergoing surgery to help improve the health of the patients, and also the role of physicians in reducing the pain of patient; therefore, the aim of the present study was to evaluate the PGB effect on reducing pain in patients with disc and spinal surgeries.

Methods

Study design and setting

The search process was carried out by two researcher (one anesthesiologist and one neurosurgeon) using specific keywords lumbar spinal surgery, pain, LDH surgery, lumbar laminectomy, spinal surgery, lumbar disc herniation, and PGB in ISI-PUBMED-SCOPUS international databases.

Quality assessment

Inclusion criteria included the use of PGB to reduce pain in patients with disc and spinal surgeries in interventional studies and exclusion criteria included the unrelated articles. In accordance with the inclusion criteria mentioned, both researchers evaluated the quality of the articles completely independently and evaluated the quality of the articles by using the existing checklist.

Measured outcome

The researcher-made checklist, which included the demographic information of the articles, the methodology and the findings of the article, was used as the research checklist.

Statistical analysis

Data were collected by using a researcher-made checklist in the form of a frequency distribution TABLE in Excel, Version 2007.

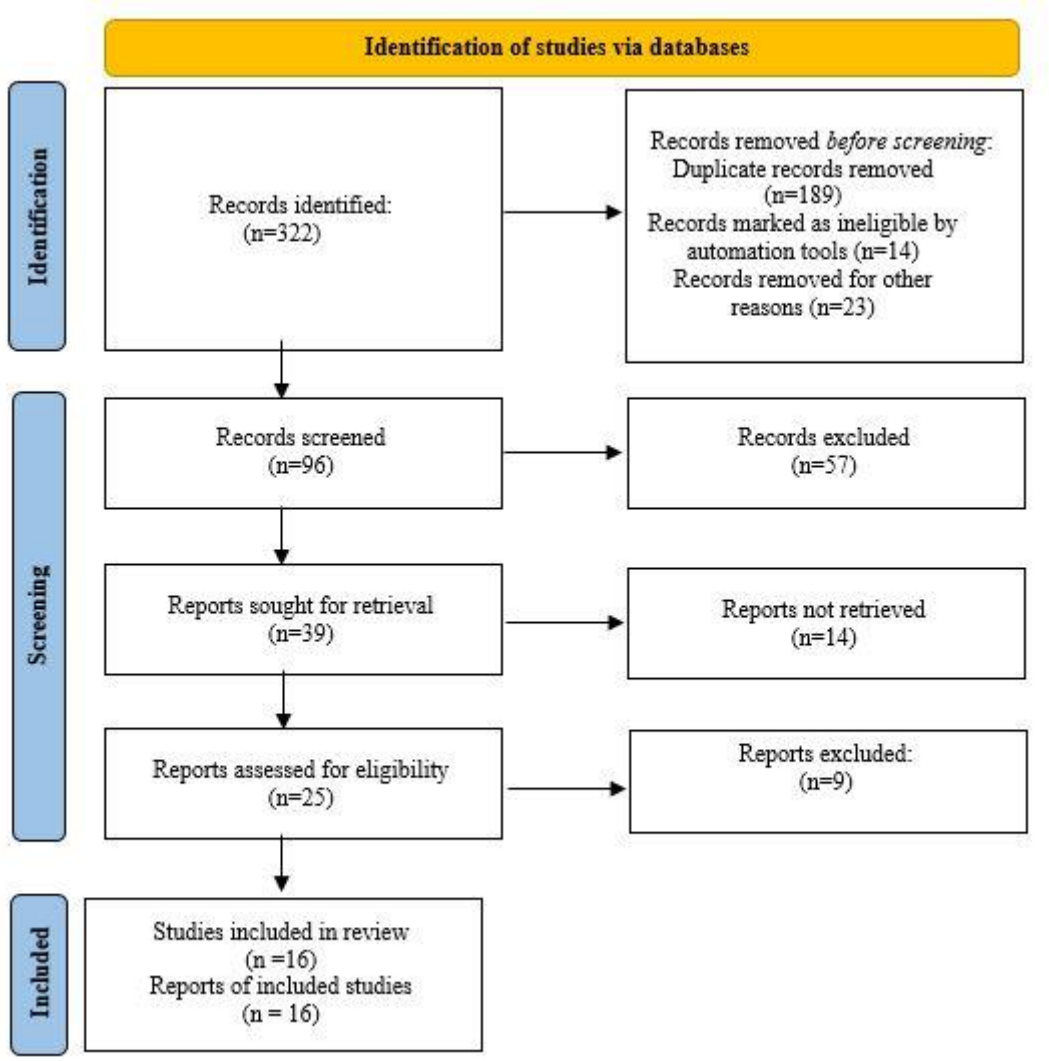

FIGURE 2 Flowchart of the current systematic review

Results

As reported in Table 1, 322 articles were found in the preliminary research, which after reviewing, 16 articles entered the final stage. Of the articles included in, 6 articles were in the group of patients with spinal surgery, 3 articles were in the group of patients with LDH surgery, 7 articles were in the group of other spinal patients including lumbar discectomy, lumbar laminectomy, and other patients. In most of the reviewed articles, PGB was used to reduce the pain of the patients.

TABLE 1 Specifications of articles entered in the systematic review

No.	Author	Country	Study design	N	Mean Age (SD)	Intervention	Outcomes
1	Altıparmak *et al*. (2018)[26]	Turkey	Spinal Surgery	Groups A: 30 Groups B: 31 Groups C:31	Groups A: 54(11) Groups B: 53(11) Groups C:54(11)	Groups A: Tab PGB 75 mg Groups B: Tab duloxetine 60 mg Groups C: Tab placebo	Mean (SD) of pain in the PGB, duloxetine, and control groups before intervention was 26.63 (1.88), 2.87 (1.76), and 26.57 (2), respectively, which reached to 24.80 (2.38), 25.70 (2.10), and 26.09 (2.60) after

							intervention, respectively.
2	Fujita *et al.* (2016)[27]	Japan	Spinal Surgery	Groups A: 30 Groups B: 30 Groups C: 29	Groups A: 59.9(13.7) Groups B: 60.9(9.5) Groups C: 65.4(2.4)	Groups A: Tab PGB 75 mg Groups B: Tab PGB 150 mg Groups C: 5 mg Diazepam	PGB had reduced pain in patients. In the diazepam group, pain was also reduced. However, this rate was higher in the PGB group than in the diazepam group.
3	Khurana *et al.* (2014)[28]	India	Spinal Surgery	Groups A: 30 Groups B: 30 Groups C: 30	Groups A: 49(10.4) Groups B: 46.9(10.1) Groups C: 47.1(10.7)	Groups A: 300 mg gabapentin Groups B: 75 mg PGB Groups C: placebo	The pain level in group B (PGB recipients) was significantly lower than in the other groups 24 hours postoperatively.
4	Sharma *et al.* (2020)[29]	India	Spinal Surgery	Groups A: 40 Groups B: 40 Groups C: 40	Groups A: 38.55(12.44) Groups B: 37.30(11.26) Groups C: 39.88(10.68)	Groups A: 1 gm IV gabapentin Groups B: 1 gm IV PGB Groups C: placebo (Vitamin B complex)	The level of pain reduction and postoperative complications was lower in Group B than the other groups.
5	Ağrı *et al.* (2021)[30]	Turkey	LDH surgery	Groups A: 20 Groups B: 20 Groups C: 20	Groups A: 26–49 years Groups B: 20–48 years Groups C: 20–49 years	Groups A: 75 mg PGB Groups B: 400 mg ibuprofen Groups C: 2 mg/ml betamethasone	The back pain level in groups A, B, and C before intervention was 4.65 (0.33), 4.05 (0.34), and 6 (0.39), respectively. Also, the back pain level in groups A, B, and C after the intervention was 1.20 (0.09), 0.60 (0.11), and 0.95 (0.09), respectively. The leg pain level in groups A, B, and C before the intervention was 6.90 (0.24), 7.10 (0.25), and 7.85 (0.26), respectively. The leg pain level in groups A, B, and C after the intervention was 0.30 (0.11), 0.80 (0.09), and 0.15 (0.08), respectively. The pain level in groups A, B, and C two hours after the surgery was 2.73 (1.63), 2.20 (1.54), and 3.23 (1.73), respectively. The pain level in groups A, B, and C 24 hours after the surgery was 1.73 (0.63), 1.46 (0.62), and 1.96 (0.85), respectively.
6	Boroojeny *et al.* (2021)[31]	Iran	LDH surgery	Groups A: 30 Groups B: 30 Groups C: 30	20-60 years	Groups A: 75 mg PGB Groups B: 150 mg PGB Groups C: Placebo	
7	Dolgun *et al.* (2014)[32]	Turkey	LDH surgery	Groups A: 27 Groups B: 27	Groups A: 46.5(9.8)	Groups A: gabapentin	The amount of pain before the intervention

					Groups B: 44.6(9)	Groups B: 50 mg PGB	was 7 (4-10) in group A and 7 (5-9) in group B. The amount of pain in 3 days after the intervention was 3 (0-6) in group A, and 3 (1-6) in group B. In addition, in 6 months after the intervention in group A is equal to 0 (0-3) and in group B is equal to 0 (0-2).
8	Li *et al*. (2017)[33]	China	lumbar D	Groups A: 30 Groups B: 30 Groups C: 30	Groups A: 48.5(10.2) Groups B: 45.8(13.1) Groups C: 50.4(9.5)	Groups A: Celecoxib (17 days) + PGB (17 days) Groups B: Celecoxib (17 days) + PGB (14 days) Groups C: Celecoxib (17 days)	The pre-intervention pain level was 7.81 (1.59) in group A, 8.15 (1.32) in group B and 8.22 (1.39) in group C. Three months after the intervention, this rate changed to 1.33 (0.78) in group A, 1.37 (0.88) in group B, and 2 (1.33) in group C.
9	Burke *et al*. (2010)[34]	Ireland	lumbar D	Groups A: 18 Groups B: 20	Groups A: 37 (7.8) Groups B: 41 (12.4)	Groups A: 300 mg PGB for preoperatively + 150 mg PGB for postoperatively Groups B: placebo	The pre-intervention pain level in groups A and B was 69 (22.2) and 65.4 (22.7), but this rate decreased to 10.7 (15.6) in group A and 15.4 (19.5) in group B after the intervention.
10	Kumar *et al*. (2013)[35]	India	lumbar laminectomy	Groups A: 25 Groups B: 25 Groups C: 25	Groups A: 45.36(11.04) Groups B: 41.8(12.43) Groups C: 45.64(11.10)	Groups A: 150 mg PGB Groups B: 150 mg capsule tramadol Groups C: placebo	The preoperative pain level was 1.44 (1.44) in group A, 0.8 (1.35) in group B, and 1.68 (1.46) in group C. In the time after the intervention was which was 3.64 (1.28) in group A, 2.32 (1.18) in group B, and 6.04 (0.93) in group C two hours after extubation. The pain level was increased to 4.12 (1.16) in group A, 2.68 (1.22) in group B, and 5.8 (1.08) in group C six hours after extubation.
11	Mohsin *et al*. (2017)[36]	Pakistan	L M	Groups A: 39 Groups B: 39	Groups A: 42(8.9) Groups B: 39(12)	Groups A: gabapentin Groups B: PGB	The pre-intervention pain rate was 1.97 (0.84) in group A and 1.6 (0.87) in group B, which decreased to 0.27 (0.45) and 0.3 (0.46) after the intervention, respectively.

12	Kim *et al*. (2011)[37]	Korea	Spinal Surgery	Groups A: 28 Groups B: 28 Groups C: 28	Groups A: 38(33-48) Groups B: 45(32.5-54.5) Groups C: 48(39-57.5)	Groups A: placebo Groups B: 75 mg PGB Groups C: 150 mg PGB	Preoperative administration of PGB (150 mg) can reduce pain in patients undergoing surgery.
13	Zhuhai1	China	lumbar discectomy	Groups A: 27 Groups B: 27 Groups C: 27	70 (41–91 years)	Groups A: Celecoxib + Pregabalin (preoperative AND postoperative) Groups B: Celecoxib + Pregabalin(postoperative) Groups C: Celecoxib	Preoperative administration of PGB (150 mg) can reduce pain in patients undergoing surgery. Limaprost and PGB reduced pain by 43%, and 7%, respectively, and a combination of the two drugs was administered to 5% of patients undergoing surgery.
14	Choi *et al*. (2013)[38]	Korea	Lumbar Spinal Surgery	Groups A: 36 Groups B: 36 Groups C: 36	Groups A: 54(21-69) Groups B: 53(25-70) Groups C: 52(20-69)	Groups A: placebo+placebo Groups B: pregabalin+placebo Groups C: pregabalin+dexamethasone	PGB alone can reduce pain in patients, but PGB+ dexamethasone co-administration is more effective in reducing pain.
15	Baloch *et al*. (2021)[39]	Pakistan	Microdiscectomy	Groups A: 42 Groups B: 42	27-61 years	Groups A: PGB Groups B: placebo	Pain level decreased from 8.33 to 1.33 in group A and from 7.98 to 2.50 in group B. PBG has also yielded better neuropathic pain management effects.
16	Reuben *et al*. (2006)[40]	Chicago	Spinal Surgery	Groups A: 20 Groups B: 20 Groups C: 20 Groups D: 20	Groups A: 43(14) Groups B: 46(18) Groups C: 42(12) Groups D: 44(160	Groups A: placebo Groups B: placebo + 400 mg celecoxib Groups C: placebo + 150 mg PGB Groups D: 400 mg celecoxib + 150 mg PGB	PGB was used to reduce pain, and PGB + celecoxib had a greater effect on reducing the pain of the patients than PGB alone.

Discussion

In order to improve the condition of patients, attention should be paid to both clinical and laboratory conditions. paying attention to the various aspects of the health of the patients is one of the goals of the treatment team. Health has various aspects, including physical, mental, and spiritual health, which should be given priority in all its dimensions [48,49, 51]. The aim of the present study was to evaluate the effect of PGB on reducing pain in patients with disc and spinal surgeries. Various studies have investigated analgesic properties of PGB. For example, Davari *et al*., reviewed 8 RCT articles (up to 2018) on analgesic properties

of PGB and PBO drugs in SCI patients. They showed that both drugs reduced pain in SCI patients, which is consistent with the results of the present study [41]. Cheng *et al*., also investigated the effect of PGB on shoulder pain. The reviewed three articles (published between 2010 and 2016) with a sample size of 93 patients. They showed that PGB reduced pain for one and two hours but had no effect on reducing pain 24 hours [42]. Likewise, Tong *et al*. reviewed three articles on neuropathic pain. They found that PGB was the most effective drug for reducing neuropathic pain in SCI patients [43]. In addition, the present systematic review study showed that PGB reduced the pain of the patients, which is consistent with the results of the similar studies.

Previous original studies on other groups of patients with different sample sizes and research populations indicated that PGB can also reduce pain. For instance, Sureshkumar *et al*. investigated the effect of antioxidants + PGB for patients with chronic pancreatitis. They found the use of these two drugs increased patient satisfaction and reduced pain [17]. Furthermore, Taguchi *et al*. reported that it was effective in reducing neuropathic pain of patients with spine diseases [44]. Ya Deau *et al*. also investigated the effect of PGB in patients with knee arthroplasty. They stated that although the drug had no effect on reducing pain, it did increase sedation [45].

Although PGB reduced the pain of patients with disc and spinal surgeries in the present study, PGB drug had no effect on reducing patient pain in some systematic review studies. For example, Giménez-Campos et al. performed three RCT articles on PGB and two RCT articles on gabapentin in the sciatica pain group. They found that gabapentin and PGB drugs had no effect on the pain of the patients [46]. Liu *et al*. investigated the effect of gabapentin on spinal surgery pain. They reviewed 16 RCTs, 8 articles for each of gabapentin and PGB. Both gabapentin and PGB were positive effect in reducing the pain of the patients [47, 48].

The innovation and novelty of this study is one of the strengths of this study. Furthermore, due to the fact that in this study it was not possible to report data quantitatively and meta-analysis, it is therefore recommended to conduct a meta-analysis study in this field. The results of this study are also recommended to clinicians to reduce the pain of the patients.

Conclusion

Due to the positive effect of PGB on reducing the pain of the patients, it is recommended to prescribe this drug.

Declarations

Authors' Contribution:

AK, KK did study conception, data analysis, and manuscript writing. AK, KK did data collection and manuscript writing. AK, KK did data collection and manuscript writing. Both authors (AK, KK) contributed to all stages of the article.

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