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Pregabalin versus Gabapentin Efficacy in the Management of Neuropathic Pain Associated with Failed Back Surgery Syndrome

Laith Thamer Al-Ameri,[1] Mohammed Emad Shukri,[1] Ekhlas Khalid Hameed,[1] Ahmed Abed Marzook[2]

Al-Kindy College of Medicine,[1] University of Baghdad, Baghdad, Iraq
Dijlah University College,[2] Baghdad, Iraq

Objective : Failed back surgery syndrome (FBSS) is a common long-term complication following spine surgeries characterized by chronic persistent pain; different strategies of management were employed to deal with it. This clinical trial aims to compare the efficacy of Pregabalin and Gabapentin in the management of this condition.

Methods : A double-blind, randomized, comparative study (clinical trial registry NCT05324761 on 11th April 2022) with two parallel arms with Pregabalin and Gabapentin were used in arms one and two, respectively. Visual analog scale was used for basal and endpoint assessment of pain. T-test and analysis of covariance were used to deal with different variables. A pairwise test was used to compare pairs of means.

Results : Of 66 patients referred to the trial, 64 were eligible, with 60 patients completing the 30 days trial. Both pregabalin and gabapentin effectively reduce pain, with significant *p*-values of 0.001 for each group. However, the pregabalin group was superior to gabapentin in pain reduction (p=0.001). Gender was an insignificant factor (p=0.574 and p=0.445 for the pregabalin and gabapentin groups, respectively, with a non-significant reduction (p=0.393) for both groups in total. Location of stenosis before surgery and type of surgery performed show non-significant effect on pain reduction for both groups.

Conclusion : Both pregabalin and gabapentin effectively and safely relieve neuropathic pain associated with FBSS; pregabalin was significantly more effective irrespective of the patients' gender.

Key Words : Pregabalin · Gabapentin · Neuropathic pain · Clinical trial.

INTRODUCTION

In neurosurgical practice, spine surgeries are common procedures with a prevalence of 37% and a lifetime prevalence equal to 85[7,23]. Failed back surgery syndrome (FBSS) is a chronic back pain issue that significantly impacts patients and primary health care centers[7]. FBSS is possible to be categorized as follows : non-fulfillment of getting satisfactory improvement following spine surgery with the ensuing necessity of analgesics and not being able to return to work; additionally, it might be defined as patients with chronic persistent pain or new pain emergence succeeding spinal surgery for low back

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• Address for reprints : **Laith Thamer Al-Ameri**
Al-Kindy College of Medicine, University of Baghdad, Nahdha square, Risafah, Baghdad 10045, Iraq
Tel : +964-7705343467, E-mail : laith.thamer@yahoo.com, ORCID : https://orcid.org/0000-0002-5863-1564

pain with or without sciatica with failure to achieve the preoperative anticipation of pain relief[12].

In recent decades, the frequency of spine procedures has significantly climbed[6,15]. Notwithstanding surgical advancements and improved diagnostic tools, FBSS is a common condition being hard to deal with[22]. It is well known that spine surgery may comprise bone removal (laminectomy, foraminotomy), disc material removal (microdiscectomy, formal discectomy), or instrumentation of the spine using transpedicular screws with fusion by posterior lumbar interbody fusion, transforaminal lumbar interbody fusion or anterior lumbar interbody fusion[19].

Few management solutions are planned for patients with FBSS since it is a complicated condition sharing multiple underlying causes[9,13,21]. Neuropathic pain is the furthermost problematic agony to manage and is usually unyielding to opioid and nonsteroidal anti-inflammatory drugs[20]. Additionally, numerous aspects are tangled in pain development, like biological, psychological, and social, necessitating an integrative management tactic[1,26]. Recently, numerous clinical studies have been intended to report the effectiveness and suitability of treatment plans. Comparisons of specific treatment types have also been the objective of different studies.

Following surgery, pain signals are received by the somesthetic area of the brain via peripheral sensory fibers, primarily Ab-type fibers (fast myelinated fibers associated with temperature and mechanical nociceptors) and C fibers (slow unmyelinated fibers associated with polymodal nociceptors)[28]. In response to pain stimulus, a complex adaptive processes activation starts in the dorsal horn of the medulla, as it is the first synaptic station for pain signals, with glutamate and substance P, which are the primary neurotransmitters involved[27].

The European Federations of Neurological Societies have recommended gabapentinoids and tricyclic antidepressants as first-line medicines for neuropathic pain except for trigeminal neuralgia[3], with clinical evidence for the efficacy of gabapentin monotherapy in reducing pain plus functional recovery[5]. The foremost analgesics used for neuropathic pain are those which act by lessening action potentials in A and C fibers by blocking voltage-dependent ion channels or hindering pain transmission along the spine[11].

Pregabalin is thought to reduce neuropathic pain feelings by decreasing glutamate release in the spinal cord horn[16]. Pregabalin is one of the famous drugs for neuropathic pain and is marketed under the brand name Lyrica with an oral route of administration with low liability for addiction[14]. Common side effects that could be encountered are sleepiness, drowsiness, confusion, memory impairment, impaired motor coordination, dry mouth, and weight gain. The potential serious adverse effects include angioedema, drug misuse, and elevated suicide risk[17]. Once pregabalin is administered at high doses over a long period, addiction may develop. However, usual doses show a low risk of addiction[2]. Pregabalin blocks voltage-dependent calcium channels and is selective in binding to the $\alpha 2\delta$ subunit. Even though pregabalin is a gamma-aminobutyric acid (GABA) analog, it does not bind to the GABA receptors, does not convert into GABA, and is not a GABA-A or GABA-B receptor agonist[17]. Nevertheless, pregabalin has been discovered to enhance the expression of L-glutamic acid decarboxylase, the enzyme responsible for GABA production, in the brain dose-dependent manner, suggesting that it may have indirect GABAergic effects by boosting GABA levels in the brain. Ataxia, diplopia, and back discomfort are common adverse effects similar to those of gabapentin[2].

Gabapentin is an anticonvulsive medicine that was first used as a muscle relaxant and anti-spasmodic. Still, it was later discovered that it could also be used as an anticonvulsive and as an adjunct to other anticonvulsants. Gabapentin belongs to the gabapentinoid group used to treat partial seizure and central neuropathic pain[29]. It has the trade name neurontin, gabatrex, neuroplex, nurona, and others. It has a structure similar to GABA, but its action is mediated by inhibiting voltage-gated calcium channels[4]. It was recommended as a first-line treatment for central pain by the 2010 European Federation of Neurological Societies with a similar pain relief achieved by all doses with the same effect of pregabalin for neuropathic pain with less cost[29]. Gabapentin was found to have a greater pain-relieving effect as early as 2 weeks after starting medication. Other moods, depression, anger-hostility, fatigue, and physical functioning assessments were better handled with gabapentin than with a placebo. Suicide, despair, Steven-Johnson syndrome, allergy, angioedema, erythema multiforme, rhabdomyolysis, and withdrawal seizure are all major adverse effects[10].

This study aims to assess the efficacy of pregabalin and gabapentin in the management of pain associated with FBSS and to compare them.

MATERIALS AND METHODS

The Ethical and Scientific Committee at Al-Kindy College of Medicine approved the proposal for the study. Then, each participant was asked to sign a written consent form after thoroughly explaining the study's objectives.

This is a double-blind, randomized, comparative study (clinical trial registry NCT05324761 on 11th April 2022, US National Library of medicine) with two parallel assignments arms and an active medication for each arm. Eligible participants were at least 18 years of age, with previous spine surgery with or without fixation and subsequent chronic back pain for at least 3 months. Each patient was diagnosed with FBSS by two neurosurgeons or orthopedic surgeons who have been well-experienced with spine surgery for at least 5 years. Patients with connective tissue diseases and those with psychiatric illnesses were excluded from the study. Additionally, patients with any medical condition that may affect the outcome as a possible cofounder were excluded. All participants were then allocated by simple randomization into the two study groups using a random number generator.

In addition to similar measurements for all participants, including lifestyle changes, each participant received an active medication according to the arm group. Arm one received pregabalin 75 mg twice daily, while arm two received gabapentin 300 mg twice daily.

A baseline pain assessment was done for each participant using the Analogue visual scale (VAS), with a minimum score of the scale of 0 and a maximum of 10; the higher the score, the more severe pain from the patient perspective.

All participants were provided a direct phone number with the contact investigator for any inquiry and to record any possible adverse effects. Additionally, each of them was contacted regularly to ensure compliance with treatment and to record and deal with any adverse effects. Safety assessments were ensured before and during the study through physical examination and observing the renal and liver function parameters.

Endpoint assessment was done on day 30 of the study using the VAS for all participants who succeeded in finishing the time of management.

Data were collected and assembled in Axel sheets, then statistically analyzed through SPSS software version 22 (IBM Corp., Armonk, NY, USA); two-sample t-test and analysis of covariance were used to deal with different variables. A pairwise test was used to compare pairs of means. Significance was defined with a *p*-value less than 0.05.

RESULTS

Between the 12th of April and the 1st of June, 66 participants were referred for the clinical trial; 64 were eligible to enroll in the study, and were randomized into two parallel groups (32 for each group, age, and gender-matched). Sixty participants completed the 30 days trial (30 for each group). The main cause of discontinuation was poor adherence to treatment. Of the remaining participants, 28 were male, with a 1 : 1.2 male to female ratio. Age ranges between 36 and 68 years (mean age, 50±2.7). At day 0 (baseline assessment), there was no significant change in pain score between the two

Table 1. Significance of difference in pain score according to group of medication at day 0 (baseline assessment) and day 30 (endpoint assessment) of trial for each group using two sample t-test

Group	Baseline assessment	Endpoint assessment	*p*-value
Pregabalin (n=30)	6.27±1.41	2.63±1.54	0.001*
Gabapentin (n=30)	6.33±1.52	3.97±1.52	0.001*

Values are presented as mean±standard deviation. *Significant at 95% confidence interval

Table 2. Effect of medications on pain score according covariance analysis

Group	Endpoint assessment	95% confidence interval	*p*-value
Pregabalin	2.65±0.25	2.16–3.14	0.001*
Gabapentin	3.95±0.25	3.46–4.44	0.001*

Values are presented as mean±standard error unless otherwise indicated. *Significant at 95% confidence interval

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Table 3. Effect of gender on pain score according to the covariance analysis

Group	Mean baseline assessment	Endpoint assessment	95% confidence interval	*p*-value
Pregabalin	6.27			0.574*
Male (n=14)		2.80±0.40	1.99–3.61	
Female (n=16)		2.49±0.37	1.73–3.25	
Gabapentin	6.33			0.445*
Male (n=14)		4.16±0.34	3.46–4.86	
Female (n=16)		3.80±0.32	3.15–4.45	
Total	6.30			0.393*
Male (n=28)		3.48±0.28	2.91–4.05	
Female (n=32)		3.14±0.27	2.61–3.68	

Values are presented as mean±standard error unless otherwise indicated. *Non-significant at 95% confidence interval

Table 4. Effect of location of stenosis whether predominantly central versus foraminal on pain score according to the covariance analysis for each group

Group	Mean baseline assessment	Endpoint assessment	95% confidence interval	*p*-value
Pregabalin	6.27			0.301*
Central		3.03±0.46	2.09–3.97	
Foraminal		2.43±0.32	1.77–3.10	
Gabapentin	6.33			0.874*
Central		3.99±0.31	3.36–4.63	
Foraminal		3.92±0.35	3.20–4.64	

Values are presented as mean±standard error unless otherwise indicated. *Non-significant at 95% confidence interval

Table 5. Effect of type of surgery on pain score according to the covariance analysis for each group

Group	Mean baseline assessment	Endpoint assessment	95% confidence interval	*p*-value
Pregabalin	6.27			0.755*
Laminectomy with fixation		2.55±0.38	1.76–3.33	
Laminectomy without fixation		2.72±0.38	1.93–3.51	
Gabapentin	6.33			0.073*
Laminectomy with fixation		3.68±0.30	3.07–4.29	
Laminectomy without fixation		4.34±0.34	3.64–5.04	

Values are presented as mean±standard error unless otherwise indicated. *Non-significant at 95% confidence interval

Table 6. Adverse effects recoded through the trial*

Group	Dizziness	Drowsiness	Nausea or vomiting	Headache	Vertigo	Total no. of affected participants	*p*-value
Pregabalin	8 (27.0)	8 (27.0)	3 (10.0)	1 (3.3)	0 (0.0)	12 (40.0)	0.793†
Gabapentin	7 (23.0)	9 (30.0)	2 (6.7)	1 (3.3)	1 (3.3)	13 (43.3)	0.793†

Values are presented as number (%). *The same participants may record more than one adverse effect. †Non-significant

groups, with a *p*-value of 0.43. At day 30 (endpoint assessment), both groups show a significant change in pain scores with *p*-values of 0.001 for each (Table 1).

In Table 2, covariance analysis shows that the estimated pain scores at endpoint assessment with adjustment of baseline assessment were 2.65±0.25 and 3.95±0.25 for pregabalin and gabapentin groups, respectively. Pain score was lower in pregabalin group with a significant *p*-value of 0.001.

According to covariance analysis and after adjustment of baseline assessment, the estimated mean pain scores at endpoint assessment were non-significant related to gender for each of the two groups and total participants with *p*-values of 0.574 and 0.445 for pregabalin and gabapentin groups, respectively, and 0.393 for both groups as total (Table 3).

Depending on the location of the stenosis, whether predominantly central or foraminal, and according to covariance analysis with adjustment of baseline assessment, the effect of location on pain score change was non-significant for both groups, with *p*-values of 0.301 and 0.874 for pregabalin and gabapentin groups, respectively (Table 4).

Additionally, according to covariance analysis and after adjustment of baseline assessment, the effect of the type of surgery performed, whether with or without fixation, was non-significant for each of the two groups, with *p*-values of 0.755 and 0.073 for the pregabalin and gabapentin groups, respectively (Table 5).

Participants from both groups showed few self-limiting adverse effects that required no treatment discontinuation. Accordingly, pregabalin and gabapentin were considered safe, with no serious adverse effects recorded (Table 6). The total number of participants who showed adverse effect were 12 and 13 for pregabalin and gabapentin groups, respectively; each affected participant may show one or more adverse effect. The difference between both groups was non-significant, with a *p*-value of 0.793.

DISCUSSION

Current guidelines prescribe pregabalin and gabapentin as the first line of management for neuropathic pain of different etiologies. However, to our knowledge, although there are different studies published, including clinical trials and systematic reviews evaluating and comparing the effectiveness of pregabalin and gabapentin, there is a lack of trials comparing their efficacy in the management of neuropathic pain associated with FBSS. Therefore, and as FBSS is frequently seen in daily neurological practice, a head-to-head comparative trial is required to bring attention towered the preferable primary management regarding both efficacy and safety.

In several recent years, different studies have been published showing different results regarding the efficacy of pregabalin and gabapentin in neuropathic pain management of etiologies rather than FBSS, including spinal cord injury, diabetic neuropathy, sciatica, etc. However, although many studies confirm that both pregabalin and gabapentin were effective in neuropathic pain relief, there was a controversy regarding the significance of comparing their effectiveness.

In a meta-analyses done by Tong et al.[25], eight clinical trials were included and analyzed, in which pregabalin and gabapentin with the addition of carbamazepine and amitriptyline were compared for their efficacy toward neuropathic pain following spinal cord injury. The pain was assessed by either VAS (similar to our study) or Numerical rating score; the final analysis results show that pregabalin is superior and more effective than gabapentin and other drugs used. This result was consistent with our study. However, gabapentin performed better regarding safety. In our study, data were limited regarding adverse effects and safety.

In another meta-analyses study done by Davari et al.[8], another eight clinical trials were included and analyzed. Pregabalin and gabapentin were compared regarding efficacy in neuropathic pain following spinal cord injury. Final analyses show that both were effective in pain relief, similar to this study; however, the difference between their efficacies was not significant and thus disagreed with this study.

In another study by Mishra et al.[18], pregabalin and gabapentin were compared regarding their efficacy toward neuropathic pain related to cancer. This was consistent with the present study; pregabalin was superior to gabapentin; additionally, pregabalin shows a morphine-sparing effect significantly more than gabapentin for cancer-related pain.

Disagreeing with our study, in their clinical trial, Robertson et al.[24] show a different picture; gabapentin was significantly more effective than pregabalin in reducing pain in patients with chronic sciatica. A different picture may be related to the small number of patients enrolled in the above clinical trial; however, the crossover method used in the above trial adds

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strength to it, making their results more considerable. Moreover, both pregabalin and gabapentin were significant in relieving pain, similar to the present and all above studies.

Limitations to our study include a small sample size and short follow-up time, making it difficult to assess long-term safety and efficacy. Additionally, functional and quality of life evaluations are recommended for future studies.

CONCLUSION

Pregabalin and gabapentin effectively relieve neuropathic pain associated with FBSS; pregabalin is significantly more effective, with no significant difference related to gender, in reducing pain in both groups. Location of stenosis before surgery, central or foraminal, type of surgery performed, with or without fixation, showed a non-significant effect on pain reduction. Long follow up study is needed to assess long-term safety and efficacy.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Author contributions

Conceptualization : LTAA; Data curation : EKH; Formal analysis : AAM; Methodology : AAM; Project administration : LTAA; Visualization : EKH, MES; Writing - original draft : MES, LTAA; Writing - review & editing : EKH, LTAA

Data sharing

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ORCID

Laith Thamer Al-Ameri https://orcid.org/0000-0002-5863-1564
Mohammed Emad Shukri https://orcid.org/0000-0001-7864-8702
Ekhlas Khalid Hameed https://orcid.org/0000-0002-0068-3329
Ahmed Abed Marzook https://orcid.org/0000-0002-2179-4773

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