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Comparative effects of pregabalin and nortriptyline on post-burn neuropathic pain

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ABSTRACT

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This clinical trial evaluates the effectiveness of nortriptyline and pregabalin in managing chronic pain in burn patients after discharge. Current treatments like acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are insufficient, leading to challenges in rehabilitation. This clinical trial is designed to evaluate the effectiveness of two drugs, nortriptyline and pregabalin, in managing chronic post-burn pain and the frequency of their side effects. This double-blind randomized controlled trial involves burn patients experiencing chronic neuropathic pain after hospital discharge, despite standard treatments like acetaminophen and ibuprofen. These patients report pain types such as burning, electric shock, and stabbing, requiring referral to a specialized pain clinic. Pain intensity is measured using the Persian version of the Brief Pain Inventory (BPI-P), where a score of 4 or higher indicates the need for palliative interventions. In this study, 60 patients were treated, 30 with nortriptyline and 30 with pregabalin. The average age was 41.5 years, and the average burn severity was 62%. In the nortriptyline group, the mean pain score decreased from 8.07 to 3.93, while in the pregabalin group, it dropped from 8.07 to 4.47 after treatment. Both groups significantly reduced pain after the intervention ($P<0.05$). This study shows us that both drugs are effective in reducing neuropathic pain in burn patients and that pregabalin is at least as effective as nortriptyline, and this drug can be a special alternative in cases where side effects such as drowsiness or others cause problems.

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1. Introduction

Burns are injuries to the skin or other tissues primarily caused by heat, radiation, radioactivity, electricity, friction, or contact with chemicals [1]. It is estimated that 180,000 people die annually worldwide due to burns. Non-fatal burns are one of the leading causes of disability-adjusted life years (DALYs), especially in low- and middle-income countries [2]. According to the World Health Organization in 2004, nearly 11 million people worldwide were severely burned and required medical care [3]. Despite the advancements in intensive care, pain following burn injuries remains one of the most common complaints of patients, and managing this pain after the acute phase of the burn injury continues to be a challenge for anesthesiologists [4]. One of the primary issues is the chronic pain that persists for years after burn injuries, which can significantly impact the patient's quality of life. This pain is similar to neuropathic pain seen in diabetic patients or post-herpetic neuralgia [5]. During burn treatment, nerve damage leads to spontaneous pain and increased sensitivity to pain. This pain arises from inflammation and nerve injury caused by the burn [6].

Currently, various treatments for managing chronic burn pain, including painkillers, antidepressants, anticonvulsants, and physical therapies, are used. However, common pain medications like acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) are usually ineffective [7]. Tricyclic antidepressants and anticonvulsants such as gabapentin and pregabalin have shown better results. These drugs reduce the excitability of nerves in the damaged tissues [8].

Patients who, after discharge from the hospital, visit the burn clinic for continued treatment of burn injuries, often complain of severe chronic and neuropathic pain. These pains lead to sleep disturbances, daily activity impairments, depression, and issues in rehabilitation processes. Conventional drug treatments have not shown satisfactory results. Therefore, this clinical trial is designed to evaluate the effectiveness of two drugs, nortriptyline and pregabalin, in managing chronic post-burn pain and the frequency of their side effects.

2. Materials and Methods

2.1 Study design

This double-blind, randomized controlled clinical trial approved by the International Center for Clinical Trials Registration (IRCT20100501003844N4) aimed to assess the effectiveness of pregabalin and nortriptyline in managing neuropathic pain in burn patients with healed wounds but persistent pain. These patients, aged 18–65, had burns covering 5% or more of their body and pain scores of 4 or higher, unresponsive to standard pain treatments.

Patients were randomly assigned to receive either pregabalin (75 mg twice daily) or nortriptyline (25 mg twice daily). Pain was assessed using the Brief Pain Inventory (BPI-P), and dosages were adjusted based on pain relief. If pain persisted (BPI-P $\geq$ 4), doses were doubled, and patients were referred to the chronic pain clinic if no significant response occurred.

2.2 Data analysis

At the study's conclusion, data collected by an anesthesia assistant (unaware of the medication given) were analyzed using SPSS version 26. Descriptive statistics were applied: mean and standard deviation for normally distributed variables, and median and interquartile range for non-normally distributed ones. Qualitative data were reported as frequencies and percentages. Normality was assessed with the Shapiro-Wilk test. To compare the Pregabalin and Nortriptyline groups, the Independent t-test (or Mann-Whitney test) was used for quantitative variables, and Chi-square or Fisher's Exact Test for qualitative variables. The McNamara test assessed treatment response changes. Statistical significance was set at $P < 0.05$.

3. Results

This section presents the analysis of data based on the specific objectives of the study. The data pertains to the comparison of the effects of pregabalin and nortriptyline on neuropathic pain in burn patients. The mean age of the patients in this study was 41.5 ± 17.69 years. In the pregabalin group, the mean age was 38.6 ± 14.32 years, and in the nortriptyline group, it was 44.4 ± 20.37 years. According to the Mann-Whitney test, the mean age between the two groups showed no statistically significant difference ($P = 0.395$) (Table 1). Of the total patients, 26 (43.3%) were male and 34 (56.7%) were female. In both the pregabalin and nortriptyline groups, 13 (43.3%) were male, and 17 (56.7%) were female. The gender distribution did not show a statistically significant difference between the two groups.

Of the patients, 40 (66.7%) had underlying comorbidities, and 20 (33.3%) did not. The comorbidities included hypertension, diabetes, hyperlipidemia, and Alzheimer's disease. In both the pregabalin and nortriptyline groups, 20 (66.7%) had comorbidities, and 10 (33.3%) did not. There was no statistically significant difference in comorbidities between the two groups (Table 2).

In this study, 40 patients (66.7%) used concomitant medications, while 20 (33.3%) did not. Both the pregabalin and nortriptyline groups had 20 patients (66.7%) using drugs and 10 (33.3%) not using any. The difference in concomitant medication use between the groups was not statistically significant (Table 3).

The mean burn percentage in the study population was 62.03 ± 9.59%. In the pregabalin group, it was 61.33 ± 9.28%, and in the nortriptyline group, it was 62.73 ± 9.99%. The difference in burn percentage between the

two groups was not statistically significant (P = 0.422) (Table 4). The severity of burns in the patients showed that 36 (60%) had second-degree burns, 23 (38.3%) had third-degree burns, and 1 (1.7%) had fourth-degree burns. There was no statistically significant difference in burn severity between the two groups (Table 5). The mean length of hospital stay in the study population was 9.95 ± 4.05 days. In the pregabalin group, the mean was 10.87 ± 4.32 days, and in the nortriptyline group, it was 9.03 ± 3.61 days. The difference was not statistically significant (P = 0.085) (Table 6). The mean pain intensity score before the intervention was 8.07 ± 0.71. In the pregabalin group, the pain intensity score reduced from 8.07 ± 0.74 before the intervention to 4.47 ± 1.22.

4. Discussion

This study compares nortriptyline, a tricyclic antidepressant, and pregabalin, an anticonvulsant used for neuropathic pain and epilepsy. Nortriptyline works by inhibiting the reuptake of serotonin and norepinephrine, helping manage neuropathic pain, even in non-depressed patients. Pregabalin reduces abnormal brain activity and modulates neurotransmitter release, including glutamate and norepinephrine, to alleviate pain and anxiety. Both drugs are effective in treating neuropathic pain, with pregabalin also having anticonvulsant properties [9].This study found that both pregabalin and nortriptyline effectively reduced neuropathic pain following burns, with no significant difference between the two treatments. These findings are consistent with previous reports, who also considered the use of tricyclic antidepressants and drugs that act by inhibiting sodium channels effective in reducing neuropathic pain [10,11]. Additionally, studies have shown that combination therapy is well-tolerated and leads to improved pain relief in patients who did not achieve optimal pain control with monotherapy [12]. In the study, both pregabalin and nortriptyline significantly reduced pain intensity in patients with neuropathic pain after burn injuries. The response time to treatment showed no significant difference between the two groups. The combination of gabapentin and nortriptyline has been found to be more effective than either drug alone for neuropathic pain, suggesting it could be recommended for patients seeking additional pain relief.

Table 1. Comparison of the Mean Age of Patients in the Pregabalin and Nortriptyline Groups

Group	Mean Age ($\bar{X}$ ± S.D)	Median (IQR)	Min	Max	P-value
Pregabalin	38.6 ± 14.32	(38, 26-50)	17	70	
Nortriptyline	44.4 ± 20.37	(45, 28-62)	14	82	0.395
Total	41.5 ± 17.69	(41, 26-51)	14	82	

Table 2. Comparison of Comorbidities in the Pregabalin and Nortriptyline Groups

Group	Comorbidity (%)	No Comorbidity (%)	Total (%)	P-value
Pregabalin	20 (66.7%)	10 (33.3%)	30 (50%)	
Nortriptyline	20 (66.7%)	10 (33.3%)	30 (50%)	>0.999
Total	40 (66.7%)	20 (33.3%)	60	

Table 3. Comparison of Concomitant Medication Use in the Pregabalin and Nortriptyline Groups

Group	Medication (%)	No Medication (%)	Total (%)	P-value
Pregabalin	20 (66.7%)	10 (33.3%)	30 (50%)	
Nortriptyline	20 (66.7%)	10 (33.3%)	30 (50%)	>0.999
Total	40 (66.7%)	20 (33.3%)	60	

Table 4. Comparison of Burn Percentage in the Pregabalin and Nortriptyline Groups

Group	Burn Percentage ($\bar{X}$ ± S.D)	Median (IQR)	Min	Max	P-value
Pregabalin	61.33 ± 9.28	(65, 55-70)	40	75	
Nortriptyline	62.73 ± 9.99	(65, 55-70)	30	75	0.422
Total	62.03 ± 9.59	(65, 55-70)	30	75	

Table 5. Comparison of Burn Severity in the Pregabalin and Nortriptyline Groups

Group	Second-Degree (%)	Third-Degree (%)	Fourth-Degree (%)	Total (%)	P-value
Pregabalin	18 (60%)	12 (40%)	0 (0%)	30 (50%)	
Nortriptyline	18 (60%)	11 (36.7%)	1 (3.3%)	30 (50%)	>0.999
Total	36 (60%)	23 (38.3%)	1 (1.7%)	60	

Table 6. Comparison of Length of Hospital Stay in the Pregabalin and Nortriptyline Groups

Group	Length of Stay ($\bar{X}$ ± S.D)	Median (IQR)	Min	Max	P-value
Pregabalin	10.87 ± 4.32	(10, 7-14)	5	21	
Nortriptyline	9.03 ± 3.61	(7, 7-10)	5	20	0.085
Total	9.95 ± 4.05	(7, 7-14)	5	21	

Future studies should compare different combinations with their respective monotherapies [13]. The study found that 35% of patients experienced side effects, while 65% did not. There was no significant difference in the frequency of side effects between the pregabalin and nortriptyline groups ($p = 0.787$). Other studies have shown that pregabalin is effective for neuropathic pain (e.g., post-herpetic neuralgia, diabetic neuropathy, partial seizures, and generalized anxiety disorder). The most common side effects reported were drowsiness and dizziness, with few serious adverse effects. It is recommended that pregabalin not be discontinued abruptly. Most clinical trials also report drowsiness (50%), dizziness (49%), and headache (29%) as the most frequent side effects [14,15]. According to the findings of this study, nortriptyline is effective in reducing neuropathic pain, and its effect is at least as significant as pregabalin. Pregabalin is associated with severe side effects like depression and anxiety, which are not present with nortriptyline. Therefore, nortriptyline can be used as a suitable alternative, especially in cases where these side effects might be problematic. Additionally, nortriptyline is more cost-effective and can also be used for treating concurrent depression. Since neither drug was 100% effective in alleviating pain, their combined use might provide better results, though further studies are required.

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Authors' contributions

Conceptualization, Methodology, Funding acquisition, Project administration, Supervision: CEA, SR, HK, MF. Investigation, Data curation, Analysis, Visualization: BBE, MF, AEA, RM, RZ. Writing original draft, Writing review & editing: CEA, HK, MF, RZ. All authors read and approved the final version of manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

This randomized, double-blind clinical trial was approved by the International Center for Clinical Trials Registration (IRCT20100501003844N4). The study design was confirmed by the ethics committee of the Guilan University of Medical Sciences [IR.GUMS.REC.1399.620] and all procedures were performed in strict accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration. All participants gave their written informed consent by signing a form.

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