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Clinical efficacy of oral pregabalin in alleviating chronic pain following blunt thoracic trauma

Shiva Bahrehmand[1], Omid Mehrazin[2], Nafiseh Mehri Khotbehsara[2], Firooze Abolhasani Zade[3], Mohammadreza Lashkarizad[4]*

1. Department of General Surgery, Bahonar Hospital, Kerman University of Medical Sciences, Kerman, Iran.
2. Bashkir State Medical University, Ufa, Russia.
3. Cancer & Breast Surgery fellowship, Kerman University of Medical Sciences, Kerman, Iran.
4. Department of Thoracic Surgery, Afzalipoor Hospital, Kerman University of Medical Sciences, Kerman, Iran.

***Corresponding author:** Mohammadreza Lashkarizad; **Email:** Lashkarizadeh@kmu.ar.ir

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Abstract: **Objective:** Chronic pain after blunt thoracic trauma remains a frequent and debilitating problem driven by complex neuropathic mechanisms and insufficient acute pain control. Pregabalin has emerged as a potential non opioid option, though evidence remains inconsistent. Given these gaps, the present study aims to evaluate the therapeutic efficacy of oral pregabalin in managing chronic post traumatic thoracic pain.

Methods: This randomized, double blind clinical trial was conducted from early 2024 to the end of September 2025 at Shahid Bahonar Hospital in Kerman. A total of 50 patients (25 in each group) were enrolled through convenience sampling. Participants received pregabalin or a placebo alongside naproxen for 12 weeks. The primary outcome was chronic pain intensity, while secondary outcomes included changes in pain scores, additional naproxen use, the 30% treatment response rate, adverse events, and quality of life.

Results: Across the 12 week follow up, additional naproxen use remained consistently lower in the pregabalin group, with significant between group differences from week 2 onward (P=0.042 to P=0.001). Pain intensity similarly declined more steeply with pregabalin (repeated measures P=0.001) compared with the control group (P=0.236). Persistent chronic pain was markedly less frequent with pregabalin (8 vs. 19 patients; P=0.001). SF 36 scores improved significantly across all subscales in the pregabalin group (P<0.05) and remained higher than in controls post treatment (P=0.018–0.025).

Conclusion: Adjunctive pregabalin significantly reduced the severity and persistence of chronic post traumatic chest pain when added to naproxen therapy. Its effects are likely mediated through modulation of neuropathic pathways and central sensitization, resulting in decreased analgesic requirements. While no major safety concerns emerged, conclusions regarding tolerability are limited by sample size and warrant confirmation in larger trials.

Keywords: Blunt Thoracic Trauma; Chronic Pain; Efficacy; Pregabalin

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1. Introduction

Chronic pain following blunt thoracic trauma represents one of the major challenges in emergency medicine, trauma care, and pain management, and can lead to considerable clinical and functional consequences for affected patients (1). Despite significant advances in the diagnosis and management of thoracic injuries, a substantial proportion of patients continue to experience persistent or recurrent pain for weeks to months beyond the acute stage (2). The reported prevalence of chronic pain after blunt chest trauma ranges from 20% to 60% across different studies, and is influenced by factors such as injury severity, the presence of multiple rib fractures, associated injuries, and insufficient acute pain control strategies (3). This chronic pain can impair daily activities, quality of life, respiratory function, and rehabilitation, and may ultimately result in substantial medical and socioeconomic burdens (4).

The pathophysiological mechanisms underlying chronic pain after thoracic trauma are complex and involve a combination of neuropathic and neuropathic like pain, persistent tissue inflammation, intercostal nerve injury, alterations in central pain processing, and both peripheral and central sensitization (5,6). Evidence increasingly suggests that neuropathic components play a more prominent role in these patients than previously assumed, underscoring the need for therapeutic agents that target the central nervous system (7). Among such agents, pregabalin—an analog of gabapentinoids and an inhibitor of the $\alpha 2$ subunit of voltage gated calcium channels—has been well established as an effec-

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tive medication for neuropathic pain and has recently attracted significant attention for use in chronic pain following trauma, particularly blunt thoracic trauma (8,9).

Pregabalin reduces central sensitization and decreases the activity of nociceptive neurons in the spinal cord by inhibiting the release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P (10). This mechanism makes it a potentially effective option for managing severe, persistent, and treatment resistant pain in patients with blunt thoracic injuries (11). In addition to its analgesic effects, pregabalin may improve pain related anxiety, sleep disturbances, and functional limitations—factors that are clinically important in the rehabilitation process. Furthermore, given the potential adverse effects of opioids and increasing concerns about dependence and long term opioid use, the incorporation of non opioid agents such as pregabalin into multimodal pain management protocols has become increasingly emphasized (12).

Although several studies have confirmed the efficacy of pregabalin in diabetic neuropathy, fibromyalgia, postherpetic neuralgia, and postoperative pain, evidence regarding its effectiveness in chronic pain resulting from blunt thoracic trauma remains limited, heterogeneous, and sometimes contradictory (13). Some studies have reported significant pain reduction, improved functional capacity, and decreased opioid requirements in patients treated with pregabalin, whereas others have shown only modest or non significant benefits (14). Differences in study design, dosing regimens, timing of treatment initiation, and patient characteristics may partly explain this variability. Therefore, a systematic and rigorous evaluation of the clinical efficacy of pregabalin in this patient population is warranted (15).

Given the substantial burden of chronic pain after blunt thoracic trauma, its detrimental effects on quality of life and respiratory performance, and the growing need for safe and effective non opioid therapeutic options, targeted research in this field is of high importance. The present study was conducted to assess the therapeutic efficacy of oral pregabalin in controlling chronic pain in patients with blunt thoracic trauma.

2. Methods

2.1. Study design

This randomized, double blind clinical trial was conducted from early 2024 to the end of September 2025 at Shahid Bahonar Hospital in Kerman, the trauma referral center of Kerman University of Medical Sciences, in full accordance with the predefined inclusion and exclusion criteria.

2.2. Sampling

The sample size was calculated based on the findings of Sihoe et al. (16), who reported a 30% reduction in pain as a clinically meaningful outcome. Using the mean pain score reported in the reference study (mean=6.0) and a standard deviation of 2.0, an anticipated mean difference of 1.8 points was assumed, corresponding to a large, standardized effect size (Cohen's d=0.9). An a priori power analysis was conducted using G*Power software (version 3.1.9.7) for a two tailed independent samples t test, with a Type I error rate (α) of 0.05, statistical power of 80%, and an allocation ratio of 1:1. Based on these parameters, a total sample size of 50 participants (25 per group) was required. Participants were recruited using convenience sampling, with eligible patients presenting consecutively to the hospital trauma care center until the target sample size was achieved. Longitudinal pain outcomes were analyzed using mixed effects models to account for within subject correlations across repeated measurements, which inherently addresses the issue of multiplicity without the need for Bonferroni correction. For secondary outcomes, including SF 36 subscale scores, effect sizes were reported using partial eta squared (η_p^2), with values of 0.01, 0.06, and 0.14 interpreted as small, medium, and large effects, respectively.

2.3. Inclusion and exclusion criteria

The inclusion criteria consisted of patients aged 18 to 75 years with blunt thoracic trauma, in whom at least 12 weeks had passed since the initial injury, and who continued to experience chronic chest pain with a minimum intensity of 4 out of 10 on the visual analog scale (VAS). Eligible participants were required to have an intact level of consciousness, stable hemodynamic status, and adequate ability to cooperate with clinical assessments. Patients were excluded if they had a history of regular gabapentinoid use, severe cardiopulmonary disease, renal or hepatic failure, untreated neuropsychiatric disorders, or a known hypersensitivity to pregabalin. Additional exclusion criteria included pregnancy or breastfeeding, concurrent use of medications affecting the central nervous system, penetrating chest trauma, a history of seizures or any active neurological disorder, clinical deterioration during the study, unwillingness to continue participation, or failure to complete the prescribed treatment course and follow up evaluations.

2.4. Randomization

In this study, randomization was performed in a 1:1 ratio using a standardized and reproducible procedure. A list of random allocation codes was first generated through the online platform Randomization.com (or another validated random number generator), producing a sequence of assignments with an equal 1:1 distribution for the intervention and control groups. To ensure balanced group sizes and minimize the risk of allocation imbalance, block randomization with fixed or variable block sizes was employed, and the block sizes were not disclosed to the investigators involved in patient assessment to prevent bias. The resulting allocation codes were placed in opaque, identical, sealed, and consecutively numbered envelopes. An allocation officer, blinded to all clinical characteristics of the participants, assigned each

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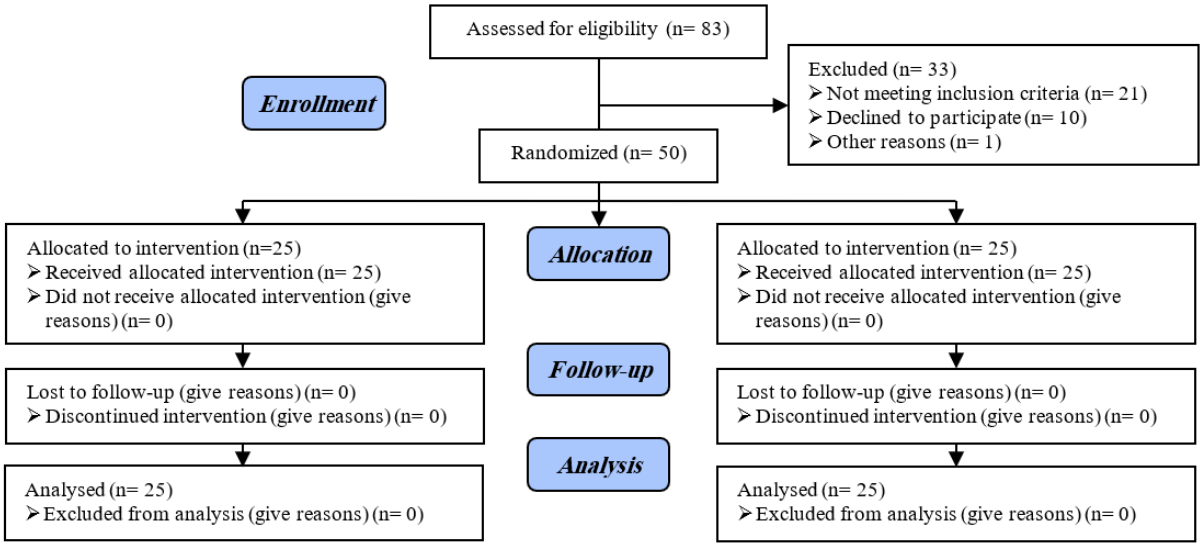


Figure 1 Patient enrollment and follow-up process based on the CONSORT flowchart

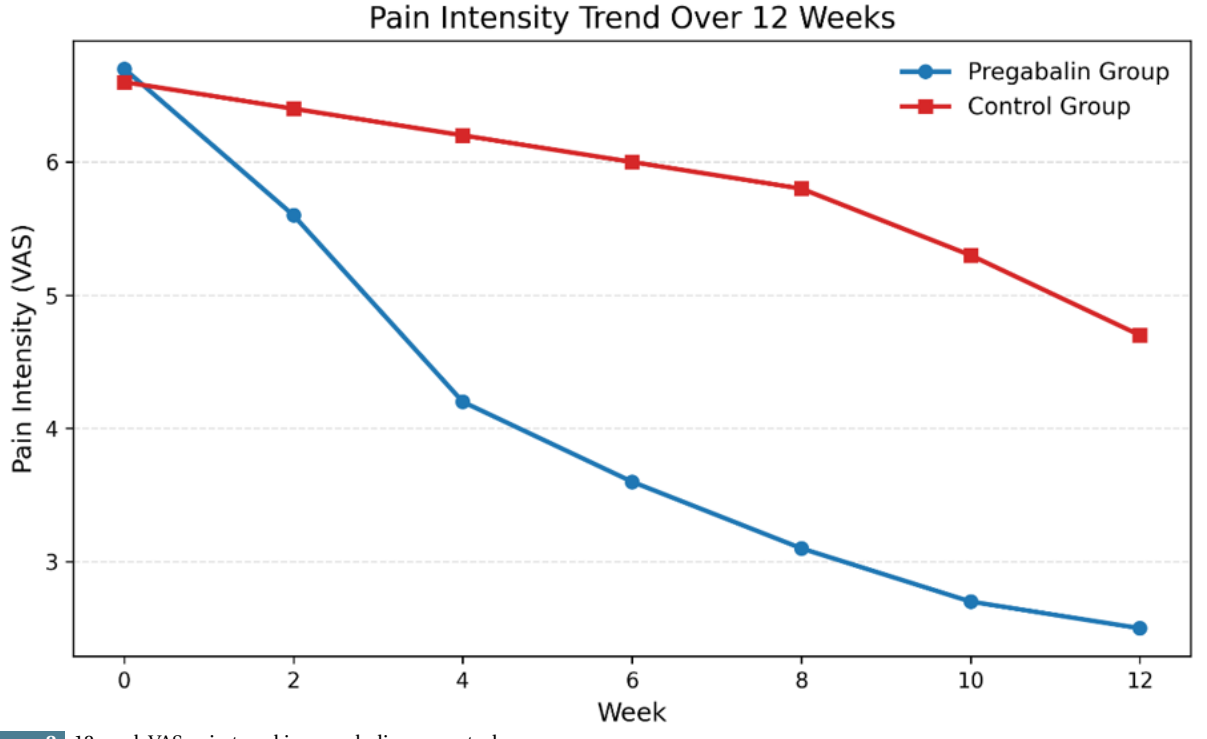


Figure 2 12 week VAS pain trend in pregabalin vs. control groups

eligible patient to one of the two study groups strictly according to the envelope sequence. This approach ensured allocation concealment, prevented prediction of upcoming assignments, and supported the integrity of true randomization within a double blind trial design.

2.5. Blinding

In this study, a double blind design was employed, such that both the participants and the treating physicians—who were also responsible for outcome assessment and statistical analysis—were unaware of the type of intervention administered and the participants' group allocation. Pregabalin and placebo were manufactured and packaged to be identical in appearance, color, size, dosage form, and packaging, thereby preventing any distinguishable differences between the interventions for either the participants or the clinical staff.

2.6. Procedure

In this study, all patients received naproxen 500 mg twice daily to ensure ethical pain management and prevent undertreatment. Participants then received the intervention corresponding to their assigned group. In the intervention group,

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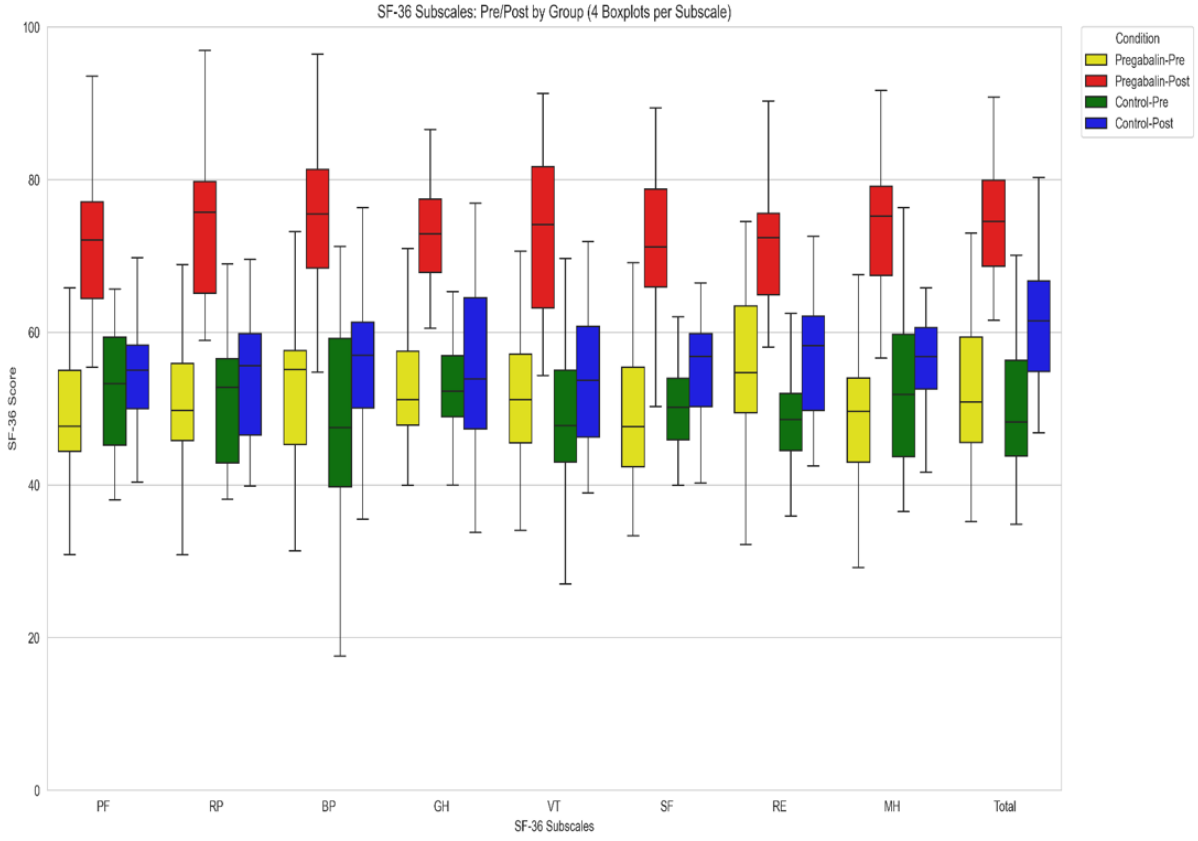


Figure 3 Pre and post intervention comparison of SF 36 subscale scores between the pregabalin and control groups

Table 1 Baseline demographic, clinical characteristics, and trauma etiology of patients in the two study groups

Variable		Study group (n=50)		P-value
		Control group (n=25)	Intervention group (n=25)	
Age (years), mean ± SD		45.8 ± 11.7	46.2 ± 10.9	0.894*
Sex, male n (%)		17 (68%)	19 (76%)	0.752**
Duration of chronic pain (months), mean ± SD		8.3 ± 2.4	8.8 ± 2.7	0.375*
Baseline pain intensity (VAS), mean ± SD		6.7 ± 1.0	6.6 ± 1.1	0.732*
Trauma etiology, n (%)	Motor vehicle collision	14 (56%)	12 (48%)	
	Fall from height	8 (32%)	9 (36%)	0.183**
	Other causes	3 (12%)	4 (16%)	
History of smoking, n (%)		6 (24%)	7 (28%)	0.755**
Injury characteristic	1–2 rib fractures, n (%)	14 (56%)	13 (52%)	
	≥3 rib fractures, n (%)	11 (44%)	12 (48%)	
	Displaced rib fractures, n (%)	9 (36%)	10 (40%)	0.859**
	Non-displaced rib fractures, n (%)	16 (64%)	15 (60%)	
	Flail chest, n (%)	0 (0%)	0 (0%)	

* Independent Samples t-test
** Chi-squared test

patients initiated oral pregabalin at a starting dose of 25 mg per day, which was gradually titrated to 300 mg per day (administered in two divided doses) by the end of the first week. Pregabalin intake continued regularly for 12 weeks, taken twice daily at 12 hour intervals. All tablets were administered with a full glass of water after meals. Patients were also ad-

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Table 2 Weekly additional naproxen use and persistent pain outcomes

Week	Intervention group (n=25) Mean ± SD		Control group (n=25) Mean ± SD		Between group Mean difference (95% CI)	P value*
Week 1	320 ± 90		480 ± 120		160 (219 to 101)	0.091
Week 2	300 ± 85		470 ± 115		170 (226 to 114)	0.042
Week 3	280 ± 80		460 ± 110		180 (234 to 126)	0.015
Week 4	260 ± 75		450 ± 105		190 (241 to 139)	0.001
Week 5	240 ± 70		440 ± 100		200 (249 to 151)	0.004
Week 6	230 ± 68		430 ± 98		200 (248 to 152)	0.003
Week 7	220 ± 65		420 ± 96		200 (247 to 153)	0.006
Week 8	210 ± 63		410 ± 94		200 (246 to 154)	0.009
Week 9	200 ± 60		400 ± 92		200 (245 to 155)	0.011
Week 10	190 ± 58		390 ± 90		200 (244 to 156)	0.014
Week 11	180 ± 55		380 ± 88		200 (243 to 157)	0.017
Week 12	170 ± 52		370 ± 85		200 (242 to 158)	0.001
Outcome	**Intervention (n=25)**	**Control (n=25)**	**ARR**	**RRR**	**95% CI (Risk Difference)**	**P value****
Chronic Pain	8 (32%)	19 (76%)	44%	58%	21% to 67%	0.001

* Independent Samples t test

** Chi squared test

ARR: Absolute Risk Reduction; RRR: Relative Risk Reduction; CI: Confidence Interval

vised that, if they experienced breakthrough pain during the day, they were allowed to take up to two additional doses of naproxen.

In the control group, patients received the same fixed regimen of naproxen 500 mg twice daily, along with placebo tablets identical in appearance, size, and color to pregabalin. To maintain proper blinding and avoid bias, placebo intake began with 1 tablet per day during the first week and increased to 2 tablets per day by the end of that week. The intervention period lasted 12 weeks in both groups. The primary outcome was chronic pain intensity at 12 weeks, reflecting the treatment effect on established chronic pain rather than prevention of pain chronicity, measured using the visual analog scale (VAS) at the end of the study (17). Persistent chronic pain at study completion was operationally defined as a VAS score greater than 4 despite treatment, consistent with commonly used clinical thresholds. Secondary outcomes included changes in pain severity at 4 week intervals, the amount of additional naproxen taken, the treatment response rate (defined as achieving at least a 30% reduction in pain intensity from baseline), quality of life, and all adverse drug reactions documented throughout the study.

Quality of life was evaluated using the validated and widely utilized SF 36 questionnaire. This instrument contains 36 items covering eight core dimensions of physical and psychological health: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality/fatigue, social functioning, role limitations due to emotional problems, and mental health. The scoring system ranges from 0 to 100, with higher scores indicating a better quality of life. Due to its strong validity, reliability, suitability for both individual and study level comparisons, and high sensitivity to clinical changes, the SF 36 is regarded as one of the most standard and robust tools for assessing health related quality of life in interventional research (18).

All pain intensity and quality of life outcomes (VAS and SF 36 questionnaires) were self reported by the participants, and no guidance, explanation, or interpretation was provided by the study personnel, in order to minimize detection bias associated with outcome assessment.

2.7. Statistical analysis

Data were analyzed using SPSS version 25. Normality was assessed using the Kolmogorov–Smirnov test (α=0.05), supplemented by descriptive and graphical methods, including evaluation of skewness and kurtosis values and visual inspection of data distributions, which confirmed that all continuous variables followed a normal distribution. Quantitative variables were summarized as mean±standard deviation, and categorical variables as frequency and percentage. Between group comparisons were performed using the Independent Samples t test for continuous variables (α=0.05) and the chi squared test or Fisher's exact test for categorical variables, depending on cell adequacy (α=0.05). Given the sample size (n=25 per group) and the robustness of parametric tests to moderate deviations from normality, these analyses were considered appropriate.

Longitudinal changes in pain intensity, weekly additional analgesic consumption, and SF 36 scores were evaluated using repeated measures analysis, with a significance level of 0.05 applied to assess both within group changes and between group differences over time. Additionally, non parametric sensitivity analyses were conducted for VAS outcomes, yielding results consistent with the primary parametric analyses. Longitudinal changes in pain intensity, weekly consumption of additional analgesics, and SF 36 questionnaire scores were examined using repeated measures analysis of variance (repeated measures ANOVA). The assumption

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of sphericity was assessed using Mauchly's test, and when this assumption was violated, Greenhouse–Geisser correction was applied to adjust the degrees of freedom. These analyses were conducted to evaluate both within group changes over time and between group differences across measurement time points.

3. Results

During the specified study period, 83 patients were assessed for eligibility, of whom 33 did not meet the inclusion and exclusion criteria and were therefore not enrolled. The study commenced with 50 eligible participants, who were randomly assigned to two equal groups of 25 patients and received their allocated interventions. All participants completed the 12 week follow up, and their data were included in the final analysis. No attrition occurred in this study (Figure 1).

None of the baseline characteristics differed significantly between the two groups, although the comparison pattern shows that some variables were slightly higher in one group than the other; however, these differences were not statistically meaningful (all P values were non significant). The patients' ages were comparable between the two groups, with no observable difference (P=0.894). The proportion of male participants was slightly higher in the intervention group than in the control group, but this increase was not statistically significant (P=0.752). The duration of chronic pain and baseline pain intensity were marginally higher in the intervention group, although these differences were not significant (P=0.375 and P=0.732). Regarding trauma etiology, motor vehicle collisions were somewhat more frequent in the control group, whereas falls from height and other causes were slightly more common in the intervention group; nevertheless, these differences were not statistically significant (P=0.183). A history of smoking was also reported slightly more often in the intervention group, but this difference did not reach statistical significance (P=0.755) (Table 1).

The weekly consumption of additional naproxen was consistently higher in the control group compared with the pregabalin group throughout the follow up period. Except for week 1, the between group differences were evident in all subsequent weeks and statistically significant (week 2: control higher, P=0.042; week 3: P=0.015; week 4: P=0.001; week 5: P=0.004; week 6: P=0.003; week 7: P=0.006; week 8: P=0.009; week 9: P=0.011; week 10: P=0.014; week 11: P=0.017; week 12: P=0.001). According to the repeated measures analysis, the progressive decline in additional analgesic use in the intervention group (P=0.014) compared with the control group (P=0.551) indicates more effective pain control over time. At the end of the study, the prevalence of persistent chronic pain was also markedly lower in the pregabalin group than in the control group (8 vs. 19 patients; P=0.001) (Table 2).

The trajectory of pain intensity based on VAS demonstrated clear differences between the pregabalin and control groups over time. At baseline, pain scores were statistically comparable between the two groups (P=0.732). However, from week 2 onward, the pregabalin group exhibited significantly lower pain levels, beginning with a marked reduction at week 2 (P=0.042). This advantage persisted through week 4 (P=0.001) and continued in week 6 (P=0.003). A similar pattern was observed at week 8 (P=0.009), with the pregabalin group maintaining significantly greater pain reduction. The superiority of pregabalin remained evident at weeks 10 (P=0.014) and 12 (P=0.019), with consistently lower VAS scores compared to the control group. In the repeated measures analysis, the pregabalin group showed a pronounced and progressive decline in pain intensity over time (P=0.001), whereas the control group demonstrated only a minimal reduction with a much flatter trajectory (P=0.236) (Figure 2).

The analysis of SF 36 quality of life scores showed that the pregabalin group experienced significant improvements across all subscales and in the overall score compared with baseline (P<0.05), whereas most changes observed in the control group were small and statistically non significant (P>0.05). Between group comparisons at the end of the intervention further demonstrated that post treatment scores for physical functioning (P=0.021), role limitations due to physical problems (P=0.025), bodily pain (P=0.018), general health (P=0.023), vitality (P=0.024), social functioning (P=0.020), role limitations due to emotional problems (P=0.018), mental health (P=0.021), and the overall quality of life score (P=0.019) were all significantly higher in the pregabalin group compared with the control group (Figure 3).

No severe adverse events or treatment discontinuations occurred during the study. The most frequently reported adverse effects were dizziness, somnolence, dry mouth, mild peripheral edema, and transient nausea. Dizziness was slightly more common in the pregabalin group, whereas somnolence and dry mouth were reported somewhat more frequently in the control group; peripheral edema occurred marginally more often in the pregabalin group, and nausea was slightly more frequent in the control group. Statistical analysis using the chi squared test for events with adequate counts and Fisher's exact test for less common events showed that none of these between group differences reached statistical significance: dizziness (P=0.276, χ^2 test), somnolence (P=0.318, χ^2 test), dry mouth (P=0.442, χ^2 test), peripheral edema (P=0.391, Fisher's exact test), and nausea (P=0.527, Fisher's exact test). No cases of skin rash, clinically meaningful hemodynamic changes, or neurologic complications were observed. Overall, both groups exhibited comparable safety and tolerability profiles, and all differences in adverse event rates between the pregabalin and control groups remained statistically non significant (P>0.05).

4. Discussion

The findings of this study indicate that the addition of pregabalin as an adjuvant therapy in patients with chronic pain following blunt chest trauma leads to substantial improvements in pain control, reduced need for supplemental anti inflam-

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matory medication, and marked enhancement in overall quality of life. The trajectory of pain intensity and the pattern of additional analgesic use clearly demonstrated that patients receiving pregabalin experienced a faster and more sustained reduction in pain and required fewer rescue medications throughout follow up. Concurrently, the prevalence of persistent chronic pain at the end of the study was noticeably lower in the pregabalin group, underscoring the drug's potential role in mitigating long term pain after thoracic trauma. These observations align with existing literature and support the notion that pregabalin is particularly beneficial in managing neuropathic or mixed nociceptive–neuropathic pain associated with chest wall injury (19,20)

Blunt thoracic trauma frequently results in microscopic injury to intercostal nerves, persistent soft tissue inflammation, and maladaptive neuroplastic changes (21). These mechanisms can give rise to chronic neuropathic pain or a mixed pain phenotype that is difficult to control with standard anti inflammatory agents alone, as such medications primarily address nociceptive pathways and exert limited influence on abnormal neuronal signaling (22). Consequently, introducing a pharmacologic agent with a distinct mechanism of action—such as pregabalin—can address this therapeutic gap and reduce the likelihood of acute pain evolving into chronic pain (23).

The observed improvements in quality of life domains further strengthen the clinical significance of these findings. Enhanced physical functioning, reduced role limitations due to physical and emotional factors, improved vitality, better sleep patterns, and decreased anxiety related to chronic pain suggest that pregabalin's impact extends beyond analgesia alone (24). These effects are consistent with previous studies involving neuropathic pain populations following peripheral nerve injury or major surgery, highlighting the close interplay between effective pain control and broader functional and psychological outcomes (25).

Another key aspect is the safety and tolerability profile of pregabalin. Although adverse events such as dizziness, somnolence, dry mouth, mild edema, and transient nausea occurred in both groups, none showed statistically meaningful differences, and no serious events were reported. This favorable tolerability is clinically important, especially in trauma patients who often require multiple concomitant medications(26). Taken together, the study indicates that a combined therapeutic approach incorporating standard care and pregabalin offers meaningful advantages over routine management alone in preventing pain chronicity and improving functional outcomes (27). Given that chronic post traumatic pain remains a major cause of disability and reduced quality of life in patients with chest trauma, employing a medication that specifically targets neuropathic pain pathways is of substantial clinical value (28).

Overall, pregabalin appears to mitigate pain progression through modulation of excitatory neurotransmission, attenuation of central sensitization, and reduced reliance on supplemental analgesics (26). These findings provide a foundation for future multicenter studies with larger sample sizes to further evaluate the long term efficacy and safety of pregabalin in this patient population (29).

5. Limitations

This study has several limitations. It was conducted at a single trauma center with a relatively small sample size, which may affect the generalizability of the findings. The single blind design introduces the possibility of performance or reporting bias. Additionally, a longer follow up was not available to evaluate sustained long term outcomes beyond the study period. Future multicenter trials with extended follow up are warranted to confirm the long term efficacy and safety of pregabalin in post traumatic chronic pain.

6. Conclusion

Adjunctive pregabalin significantly reduced the severity and persistence of chronic post traumatic chest pain when added to naproxen therapy. Its effects are likely mediated through modulation of neuropathic pathways and central sensitization, resulting in decreased analgesic requirements. While no major safety concerns emerged, conclusions regarding tolerability are limited by sample size and warrant confirmation in larger trials.

7. Declarations

7.1. Acknowledgement

The authors gratefully acknowledge the support of Kerman University of Medical Sciences and sincerely thank the parents of the infants and children who participated in this study.

7.2. Authors' contribution

All authors contributed to the study design, data collection, manuscript preparation, and final revision.

7.3. Conflict of interest

There are no financial, personal, or professional conflicts of interest related to this study.

7.4. Funding

This study was financially supported by Kerman University of Medical Sciences.

7.5. Human Ethics and Consent to Participate declarations

Written informed consent was obtained from all participants after they were fully informed about the aims, procedures, and potential implications of the study. Participant confidentiality was strictly preserved throughout the research process, and no personal or identifiable information was disclosed at any stage. All interventions performed in this

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study were part of standard therapeutic care, and participation in the study did not impose any additional financial burden on the patients. Participants and, when applicable, their legal guardians were informed that the treatment approaches used in the study were clinically equivalent and associated with no differences in cost. The study protocol was reviewed and approved by the Ethics Committee of Kerman University of Medical Sciences (Ethics Code: IR.KMU.AH.REC.1404.129). The trial was prospectively registered in the Iranian Registry of Clinical Trials (IRCT) under the registration number IRCT20251205068217N1 (https://irct.behdasht.gov.ir/trial/87992). All study procedures were conducted in full compliance with the ethical standards of the Declaration of Helsinki and relevant institutional guidelines. As the authors are non native English speakers, a large language model (LLM), such as ChatGPT, was used to refine the language for clarity and grammatical accuracy. The authors confirm that this tool was utilized exclusively for linguistic and stylistic improvement and was not involved in data analysis, interpretation, study design, or scientific decision making.

7.6. Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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