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A retrospective clinical trial of gabapentin combined with duloxetine for the treatment of neuropathic pain after maxillofacial fracture

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Abstract

Background & Objectives: Neuropathic pain (NPP) following a maxillofacial fracture can decrease patients' quality of life and lead to numerous mental and psychological issues. However, using gabapentin alone for neuralgia only yields moderate results. Consequently, this study's primary objective was to examine the effectiveness and safety of combining gabapentin and duloxetine to alleviate NPP subsequent to a maxillofacial fracture. *Methods:* In this retrospective study, we examined patients diagnosed with NPP following maxillofacial fractures from January 2017 to December 2023 at our hospital. All patients received a combination of gabapentin and duloxetine for a 12-week period. We evaluated the effects of this combination on patients using the Visual Analog Scale (VAS), the Pittsburgh Sleep Quality Index (PSQI), the Self-Assessment Scale for Anxiety (SAS), the Hamilton Assessment of Depression (HAMD), and the 36-item Short-Form Survey (SF-36). *Results:* This study included a total of 63 patients. After treatment combining gabapentin and duloxetine, there was a significant decrease in VAS, SAS, HAMD, and PSQI scores ($P<0.001$). There was also a significant improvement in life quality ($P<0.05$). Sleep staging results showed improved sleep quality post-treatment. Patients experienced longer total sleep time ($P<0.001$), fewer awakenings ($P<0.05$), and reduced awakening duration ($P<0.05$). Furthermore, stress duration six months post-treatment was significantly shortened ($P<0.05$).
Conclusions: This study indicated that the combined treatment of gabapentin and duloxetine was highly effective for post-maxillofacial fracture NPP. This combination notably improved patients' pain levels, overall quality of life, sleep patterns, and levels of anxiety and depression.

Keywords: Neuropathic pain, maxillofacial fracture, gabapentin, duloxetine

INTRODUCTION

Oral and maxillofacial surgeons often result in trigeminal nerve injuries caused by trauma to the facial region, with areas like the inferior alveolar nerve being particularly vulnerable during incidents such as mandibular fractures and surgical repairs. Damage can occur through a variety of mechanisms including severance from fractures near nerve entry points, shearing from displaced fractures, or direct injury from drills and screws during surgical fixation.[1-3] Neuropathic pain (NPP) is widely recognized as the most common, enduring, and difficult type of chronic pain, impacting 6-8% of the world's population.[4,5] The fundamental damage to the nervous system is the root cause of this condition, resulting in both physical and functional impairments. The persistence of severe pain can give rise to a variety of mental and psychological challenges, such as anxiety, depression, insomnia, and suicidal ideation and behaviors. These complexities can significantly diminish the overall quality of life for individuals affected by this condition.[6,7]

The most effective pharmacotherapy options for managing NPP include gabapentin, tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRIs).[8,9] Gabapentin is a type of antiseizure medication that exerts its effects on the peripheral and central nervous systems, targeting the spinal

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cord pain conduction pathway, peripheral nerve nociceptors, cerebral cortex, and other sites, ultimately blocking NPP and providing therapeutic benefits.[10] In Europe, gabapentin has received approval for the treatment of NPP, while in the United States it is approved for the management of postherpetic neuralgia, a specific type of NPP.[11] Duloxetine, on the other hand, functions as a norepinephrine and serotonin reuptake inhibitor, enhancing the descending inhibitory control pathway in the central nervous system to help manage pain.[12,13] Duloxetine is a medication that is commonly used in clinical settings to treat a number of conditions, including major depression, fibromyalgia, generalized anxiety disorder, chronic musculoskeletal pain, and diabetic peripheral neuropathy.[14]

Based on long-term observations, it has been found that the effectiveness of single-use gabapentin therapy for patients with post-fracture neuralgia in the maxillofacial region is only moderate.[15,16] However, there is potential for enhancing pain management and improving the quality of life for patients through the combination of gabapentin with other medications. As of now, there exists a paucity of studies assessing the effectiveness of combining gabapentin with duloxetine for managing neuralgia subsequent to maxillofacial fractures. Consequently, the primary objective of this investigation is to delve into the efficacy and safety profile of utilizing gabapentin in conjunction with duloxetine for alleviating NPP post-maxillofacial fracture. This endeavor seeks to augment our knowledge base regarding therapeutic modalities employed in addressing this condition.

METHODS

Study design

Participants in this retrospective clinical study were selected from patients who received treatment at the Department of Oral Surgery of the 910th Hospital of PLA Joint Logistic Support Force between January 2017 and December 2023. All data were obtained from the clinical database of our hospital. The study was conducted in compliance with Chinese Good Clinical Practice and the Declaration of Helsinki. All study-related procedures and documents were approved by the Institutional Review Board of the 910th Hospital of PLA Joint Logistic Support Force. Individuals diagnosed with NPP were included in the study. The diagnostic criteria was based on the European Academy of Neurology Guideline on NPP.[17] Additionally, based on history and clinical experience, the participants were diagnosed with NPP due to maxillofacial fracture.

The primary endpoint was the change in pain intensity score from baseline to week 1, month 1, 3 and 6, measured using a visual analogue scale (VAS). Secondary endpoints included change from baseline to month 3 and 6 in modified MacNab assessment, Pittsburgh Sleep Quality Index (PSQI), Self-rating anxiety scale (SAS), Hamilton Depression Rating Scale (HAMD) and 36-Item Short Form Survey (SF-36). Safety assessments consisted of monitoring and recording all adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. NPP occurs infrequently in maxillofacial fracture, and the sample size was determined *a priori* without power calculation.

Participants

All NPP patients feeling anxious and depressed were included. No limit was applied in terms of age, gender, nationality and ethnicity. Inclusion criteria were: (1) Gender unlimited, age 18-60 years old; (2) Accurate diagnosis of neuralgia after maxillofacial fracture; (3) Complete clinical data records of patients; (4) No cerebrovascular diseases; (5) No history of gabapentin and duloxetine allergy; (6) No history of tobacco and alcohol addiction. Exclusion criteria were: (1) co-morbid serious infectious diseases; (2) Withdrawal of treatment due to various reasons; (3) Allergic constitution; (4) Dysfunction of liver, kidney and other organs; (5) Pregnancy and lactation; (6) Patients with epilepsy, head injury, or other related neurological diseases.

As shown in Figure 1, from January 2017 to December 2023, 63 consecutive patients with NPP after maxillofacial fracture received gabapentin combined with duloxetine in our hospital. Gabapentin capsule was taken orally, 0.3g each time, three times a day. Duloxetine hydrochloride enteric-coated capsule was taken orally once a day, 60mg each time. The duration of administration in all participants was 12 weeks.

Outcomes assessments

Visual analogue scale (VAS)

Improvement in pain was assessed both prior to treatment and at intervals of 1 week, 1, 3, and 6 months post-treatment, with corresponding VAS measurements documented. A 10-centimeter ruler

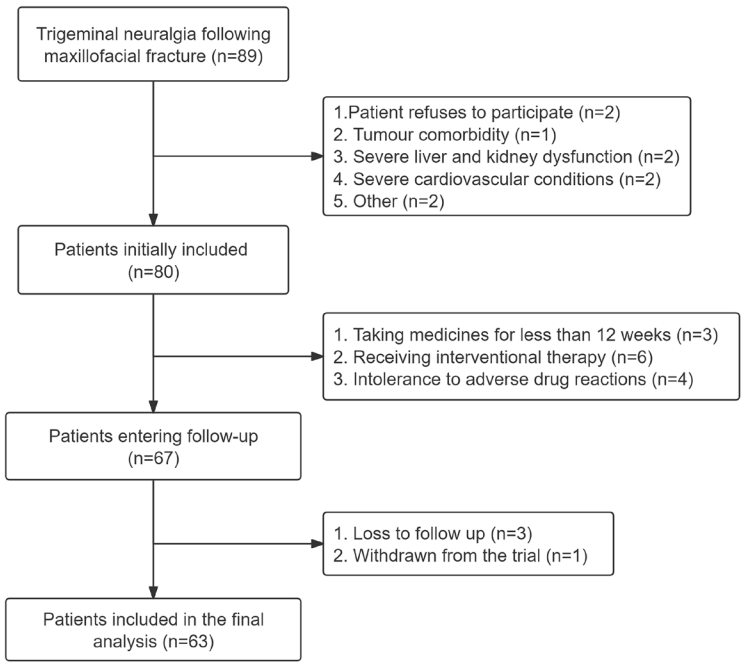

Figure1. Study design and procedure

was utilized for VAS assessment, with the leftmost point indicating 0, signifying absence of pain, and the rightmost point indicating 10, signifying excruciating pain. Intermediate points along the ruler denote varying degrees of pain. Patients were instructed to mark the point on the scale that best reflects their own level of pain. Pain levels were categorized as follows: 0-3 denoting mild pain, which does not significantly interfere with sleep; 4-6 indicating moderate pain, with mild disruption to sleep patterns; and 7-10 representing severe pain, characterized by an inability to fall asleep due to pain or frequent awakening from sleep.[18]

Pittsburgh Sleep Quality Index (PSQI)

The sleep parameters of the subjects were meticulously monitored prior to the commencement of medication, as well as at the intervals of 4, 8, and 12 weeks post-medication, employing the PSQI for evaluation. This comprehensive tool encompasses seven dimensions, with scores ranging from 0 to 3 points per dimension. A cumulative score equal to or exceeding 5 points is indicative of suboptimal sleep quality, with higher scores correlating with increasingly compromised sleep patterns.[19]

Self-rating Anxiety Scale (SAS)

Prior to and following the 12-week treatment period, anxiety evaluations were conducted within both cohorts. The SAS served as the instrument for appraising the anxiety levels among participants. Comprising 20 inquiries, each item was rated on a scale of 1 to 4, thereby establishing a cumulative score range of 20 to 80 points. As per established Chinese norms, a SAS standard score of 50 points delineated the threshold, with scores falling within the range of 50 to 59 indicative of mild anxiety, 60 to 69 suggestive of moderate anxiety, and scores exceeding 69 indicative of severe anxiety.[20]

Hamilton Depression Rating Scale (HAMD)

The HAMD was utilized to assess the level of depression both prior to and 12 weeks subsequent to treatment administration across the two cohorts. A HAMD score below 7 denotes an absence of depression, while scores ranging between 7 and 17 signify mild depression. Moderately depressed individuals are characterized by scores between 17 and 24, while scores exceeding 24 indicate severe depression. It is imperative to note that there exists a positive correlation between the severity of depression and the corresponding HAMD score.[21]

36-Item Short Form Survey (SF-36)

The SF-36, devised by the U.S. Bureau of Medicine Research Group, stands as a ubiquitous

scale employed for evaluating health-related quality of life. Comprising eight dimensions meticulously designed, it delineates an assessment framework bifurcated into two cardinal categories: the Physical Health Summary Score (PCS) and the Mental Health Summary Score (MCS). These dimensions encompass Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), and Mental Health (MH).[1] Its efficacy has been substantiated through validation studies, affirming its reliability in the assessment of chronic illnesses within the Chinese context.[22] Scoring adheres to the guidelines delineated in the SF-36 Physical and Mental Health Summary Scale User's Manual.[23]

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 26.0 (SPSS IBM Corporation, Chicago, IL, USA). Measurement data were expressed as mean ± standard deviation, and compared using the single factor repeated measures analysis of variance test, and subsequently, multiple comparisons were analyzed by Dunnett-t test. Enumeration data were expressed as percentage, and compared using Chi-square test. P<0.05 considered as statistically significant.

RESULTS

Baseline of study population

A total of 89 patients presenting with neuralgia resulting from maxillofacial fractures were enrolled in the study. The patients were treated with a combination of gabapentin and duloxetine for an average of 6 months (range: 3 to 8 months). Two patients withdrew from the study, citing a desire to discontinue the medication. One patient was excluded from the study due to the identification of a tumor during the course of treatment. Subsequently, four patients encountered complications, and an additional two withdrew for unrelated reasons, thereby precluding their inclusion in the final analysis. Ultimately, a cohort of 80 patients, receiving a combined regimen of gabapentin and duloxetine, met the stringent inclusion criteria. Regrettably, three patients failed to complete the prescribed 12-week medication regimen, six underwent interventional therapy, and four demonstrated intolerance to the medication, necessitating their exclusion from the study. Consequently, the study proceeded with a refined cohort of 67 patients. Within this group, three patients were lost to follow-up, and one voluntarily withdrew from the study, resulting in a final cohort of 63 patients for comprehensive analysis (Figure 1, Table 1).

Therapeutic efficacy of combination therapy

The efficacy of combining gabapentin with duloxetine in alleviating NPP following maxillofacial fractures was evaluated utilizing VAS scores. A notable reduction in pain severity, as indicated by VAS scores, was observed from an initial value of 7.57±1.25 to 5.89±1.28 during the first postoperative week. Subsequently, the scores decreased to 2.94±0.62 at 1 month, 1.83±0.55 at 3 months, and 1.43±0.59 at 6 months after the combination Therapy (Figure 2A). Follow-up was evaluated using the MacNab efficacy evaluation criteria, and the number of excellent, good and poor cases after one week of treatment was 46, 15 and 2, respectively; and the number of good and poor cases after 6 months of treatment was 12, 25 and 26, respectively (Table 2). Opioid administration was required in 9 patients (14.3%). Following treatment, there was a significant decrease in mean opioid consumption (in mg oral morphine equivalents) compared to pre-treatment levels (16.67±10.00 *vs.* 2.22±3.63, $P<0.001$). The pre- and 24-hour post-treatment opioid consumption for these 9 patients is detailed in Table 3. The effectiveness of gabapentin combined with duloxetine in ameliorating anxiety and depression in patients with NPP following maxillofacial fracture was assessed utilizing SAS and HAMD scores. Notably, a marked reduction in both SAS and HAMD scores was observed at the 3-month mark post-treatment in comparison to pre-treatment levels (SAS: 65.83±2.46 *vs.* 54.89±2.87; HAMD: 23.86±2.45 *vs.* 12.08±2.00; $P<0.001$, Figure 2B and C). However, no significant disparities were noted between scores recorded at the 6-month and 12-month intervals following treatment initiation (6M *vs.* 12M; SAS: 54.89±2.87 *vs.* 51.60±2.55; HAMD: 12.08±2.00 *vs.* 10.51±2.12; $P>0.05$, Figure 2B and C).

We evaluated the quality of life among patients experiencing post-maxillofacial fracture NPP following treatment with a combined regimen of gabapentin and duloxetine, utilizing the SF-36 questionnaire (Figure 2D). The average score for each domain of the SF-36 post-treatment demonstrated a marked increase compared to baseline ($P<0.05$). Notably, a statistically significant disparity was observed in the mean scores across all SF-36 domains at the 3 and 6-month intervals post-initiation of combined

Table 1: Descriptive Analyses of 63 patients with trigeminal neuralgia following maxillofacial fracture

Variables	All patients (n=63)
Age (years), mean ± SD	51 ± 0.8
Gender, female, number (%)	36 (57.1)
Duration of pain (year), median, IQR	1.5, (0.5 - 3)
BMI (kg/m^2), mean ± SD	21.7±2.63
Symptoms associated with nerve damage besides to neuropathic pain, number (%)	
Allodynia	10 (15.9)
Analgesia	13 (20.6)
Dysesthesia	5 (7.9)
Hyperalgesia	4 (6.3)
Hyperpathia	10 (15.9)
Hypoesthesia	6 (9.5)
Spontaneous pain	12 (19.0)
Paresthesia	3 (4.8)
Fracture site, number (%)	
Mandible	21 (33.3)
Maxilla	17 (27.0)
Zygomatic arch	8 (12.7)
Cheekbone	3 (4.8)
Naso orbital region	2 (3.2)
Others	1 (1.6)
More than two compound injuries	12 (19.0)
Location of nerve injury, number (%)	
Supraorbital nerve	11 (17.5)
Infraorbital nerve	28 (44.4)
Inferior alveolar nerve	16 (25.4)
lingual nerve	6 (9.5)
Others	3 (4.8)
Pain at the terminal branches, number (%)	
1 branch	28 (44.4)
2 or more branches	35 (55.6)
Base VAS scale, number (%)	
4-6	11 (17.5)
7-10	52 (82.5)
Base PSQI scale, mean ± SD,	17.62 ± 0.19
Base SAS scale, mean ± SD,	65.98 ± 0.28
Base HAMD scale, mean ± SD	23.89 ± 0.33
Diabetes history, number (%)	10 (15.9)

Allodynia: painful response to an innocuous stimulus; **Analgesia:** absence of pain to a noxious stimulus; **Dysesthesia:** Unpleasant abnormal sensation (spontaneous or evoked)-descriptors include: tender, pricking, stinging, burning, electric, cold; **Hyperalgesia:** increased painful response to a noxious stimulus; **Hyperpathia:** explosive abnormal pain that outlasts a noxious stimulus; **Hypoesthesia:** reduced sensation to stimulation-descriptors include: numb, rubbery, swollen, wooden; **Spontaneous pain:** spontaneous pain caused by a lesion or disease of the somatosensory nervous system-involves sharp paroxysmal pain not associated with painful stimuli-descriptors include: throbbing, electric shock, burning, excruciating, wrenching; **Paresthesia:** abnormal sensation (spontaneous or evoked) that is not unpleasant --descriptors include: tingling, tickling, itching, crawling. **VAS:** visual analogue scale; **PSQI:** Pittsburgh sleep 1uality index; **SAS:** self-rating anxiety scale; **HAMD:** Hamilton depression rating Scale.

Table 2: Assessment of modified MacNab among 63 patients at each timepoint

Postoperative		1 Week n (%)	1st month n (%)	3rd month n (%)	6th month n (%)
Neuropathic pain patients (n=63)	Excellent	46 (73.0)	29 (46.0)	19 (30.2)	12 (19.0)
	Good	15 (23.8)	19 (30.2)	22 (34.9)	25 (39.7)
	Poor	2 (3.2)	15 (23.8)	22 (34.9)	26 (41.3)

gabapentin and duloxetine therapy relative to pre-treatment levels (P<0.05). Moreover, there was a discernible enhancement in sleep quality among patients at the 6-month follow-up compared to pre-treatment levels (P<0.05; Figure 2E).

Sleep monitoring indicators

Sleep staging, encompassing awake, light, deep, and REM stages, was meticulously monitored in patients both before and six months post-surgery (Figure 3A). Following the administration of gabapentin in conjunction with duloxetine, noteworthy extensions were observed in both total sleep time and the duration of each sleep stage, in stark comparison to pre-treatment measures (6M *vs*. Pre, total sleep time: 5.32±1.49h *vs*. 3.66±1.19h, deep sleep: 1.5±0.3h *vs*. 0.8±0.2h, light sleep: 3.0±0.3h *vs*. 4.2±0.3h, REM sleep: 0.5±0.3h *vs*. 0.3±0.3h, P<0.001; Figure 3B). Moreover, a marked reduction in both the frequency of awakenings (6M *vs*. Pre, P<0.001; Figure 3C) and the duration of wakefulness (6M *vs*. Pre: 1.1±0.4h *vs*. 2.3±0.4h, P<0.001; Figure 3D) was evident prior to surgery compared to the corresponding figures at the six-month post-treatment mark. Furthermore, an evaluation of emergency intensity, gauged through heart rate fluctuations as indicative of patients' stress levels, was conducted both pre-treatment and six months post-treatment. It was discerned that the duration of stress experienced pre-treatment significantly lagged behind that witnessed at the six-month post-treatment juncture (6M *vs*. Pre: 4.3±0.2h *vs*. 8.21±0.2h, P<0.001; Figure 3E), while the interval required for recuperation exhibited a notable extension (6M *vs*. Pre: 1.8±0.2h *vs*. 1.3±0.2h, P<0.001; Figure 3E).

Adverse events

In the 63 patients who received the combination of gabapentin and duloxetine, a total of 11 adverse events were documented (Table 4). Importantly, no major drug-related complications occurred during the follow-up period. The adverse events included vomiting in two patients, dizziness in five patients, and headache in two patients. These side effects were mild, transient, and did not necessitate specific treatment. Notably, two patients experienced constipation during the medication period.

DISCUSSION

Trauma to the oral and maxillofacial region is the most common cause of nerve injury in the practice of oral and maxillofacial surgeons. The inferior

Table 3: Daily consumption of morphine in 9 patients

Patient NO.	Morphine equivalent before treatment (mg/24h)	Morphine equivalent at 6 months after treatment (mg/24h)
1	10	0
2	10	0
3	20	5
4	20	5
5	10	0
6	40	10
7	10	0
8	20	0
9	10	0

alveolar nerve is particularly vulnerable to injury in cases of mandibular trauma.[2] Fractures near the mandibular foramen can result in nerve dissection, leading to permanent sensory abnormalities. Displaced fractures of the mandibular body or angle can also cause shearing or traction injury to the inferior alveolar nerve. Gunshot wounds to the mandible can be highly destructive, potentially severing the inferior alveolar nerve and causing irreversible damage.[24] Fractures of the zygomatico-mandibular complex often result in infraorbital rim injury, extending into the infraorbital foramen and canal, potentially leading to infraorbital nerve injury.[25] Similarly, fractures of the frontal bone above the supraorbital foramen can result in injury to the supraorbital nerve.[26] Surgical repair of maxillofacial fractures also poses a risk of trigeminal nerve injury, as the nerve may be pierced by drills and screws during internal fixation. Additionally, manipulation or exposure of the fractured segment during surgery may also pose a risk of nerve injury.[3]

Patients with post maxillofacial fracture often suffer from NPP due to nerve damage, manifesting as abnormal sensations, dysesthesia, and loss of normal sensation.[27,28] A less common consequence of nerve injury is NPP. NPP is defined by the International Association for the Study of Pain (IASP) as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system." NPP is a clinical description that requires a demonstrable lesion or known trauma of the involved nerve. NPP is commonly described as a burning sensation, although it may be perceived as throbbing, wrenching, excruciating, and electric shocks.[29,30] NPP occurs in conjunction with hypoesthesia and paradoxical hypersensitivity. Thus, patients with NPP experience sensory loss and the so-called positive phenomena, which include distinct findings of spontaneous pain, dysesthesia (spontaneous or evoked), allodynia, hyperalgesia, and hyperpathia.[31] Allodynia is pain evoked by an innocuous stimulus that usually does not elicit pain, such as light touch, pressure,

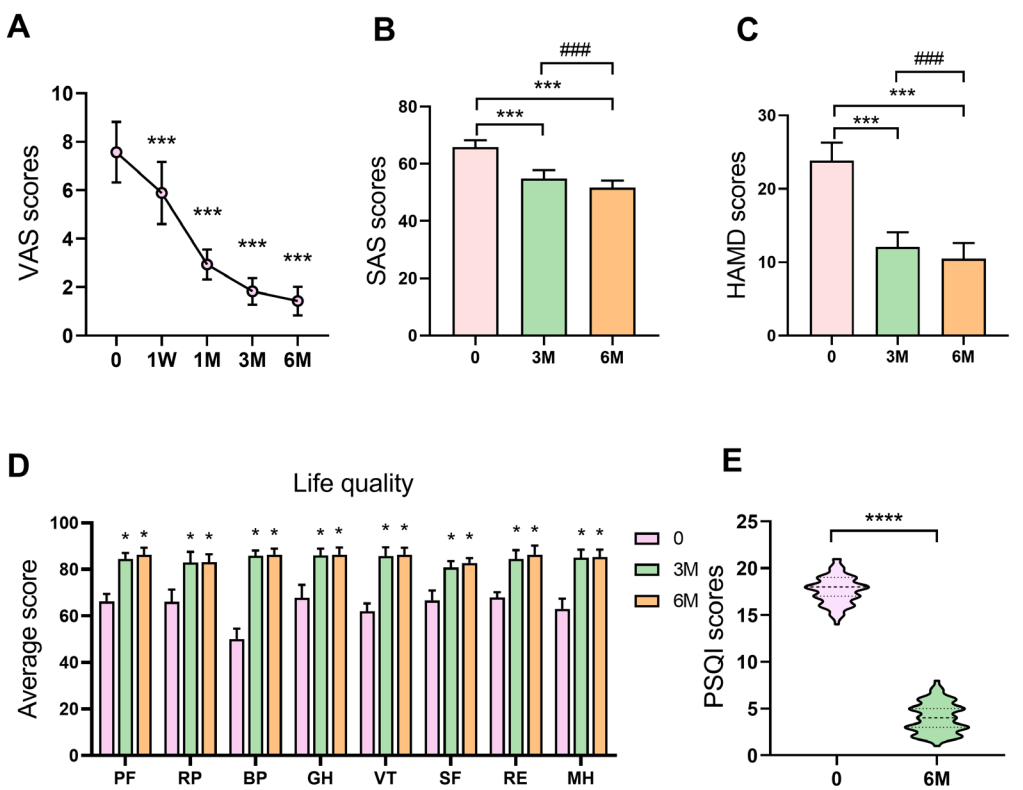

Figure 2. Clinical changes after treatment with gabapentin combined with duloxetine, including VAS, SAS, HAMD, Life quality and PSQI. (A) VAS scores of patients at various time points. (B) SAS assessments of patients at different time points. (C) HAMD assessments of patients at various time points. (D) Quality of life scores of patients at different time points. (E) HAMD assessment at pre-treatment and month 6 post-treatment. Values are expressed as Mean ± SD. $^{*}P < 0.05$, $^{***}P < 0.001$, $^{****}P < 0.0001$, vs. the baseline; $^{\#\#\#}P < 0.0001$, vs. the month 3.

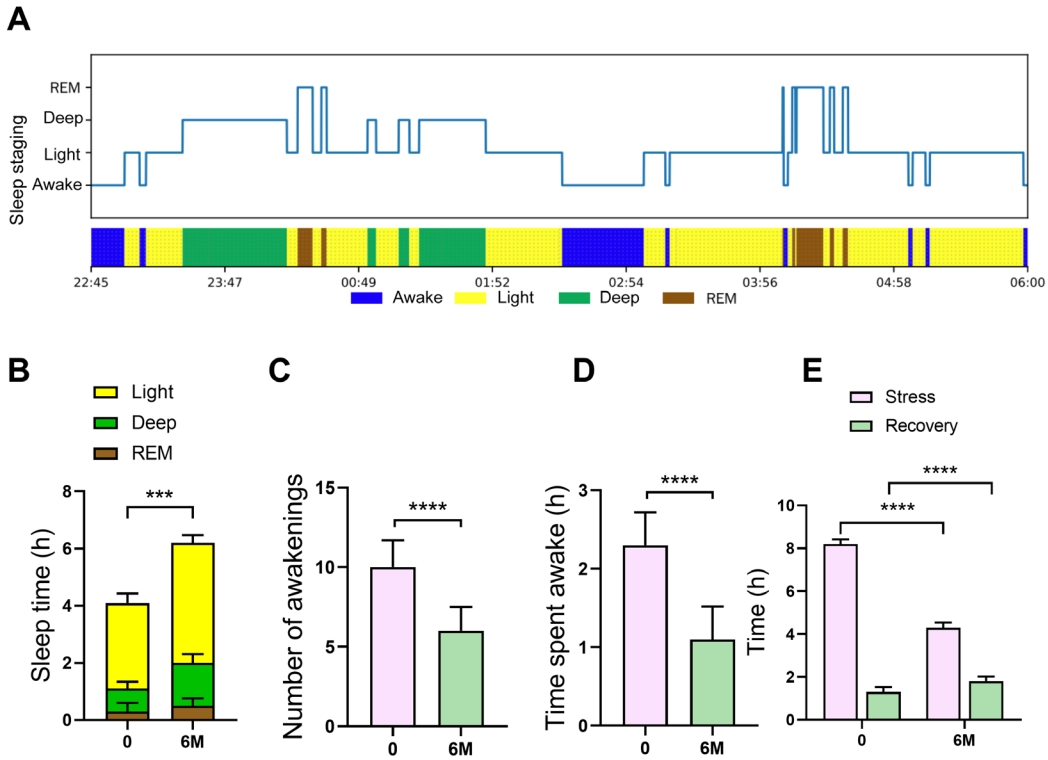

Figure 3. The combined treatment of gabapentin and duloxetine improves sleep quality in patients suffering from post-maxillofacial fracture NPP. (A) Sleep staging in patients after gabapentin combined with duloxetine treatment. (B) Changes in the sleep times of patients, categorized by different sleep stages, before and after six months of treatment. (C) Changes in the number of awakenings in patients before and after 6 months of treatment. (D) Changes in patients' awakening times before and after 6 months of treatment. (E) Changes in patients' stress levels before and after 6 months of treatment.

or cold, whereas hyperalgesia is an increased response to a noxious stimulus.[31] Hyperpathia is an explosive abnormal pain that outlasts the stimulus. NPP can be episodic or continuous, and severe episodes of pain can be seen followed by total pain remission.[29-31] Paroxysmal pain also can occur, defined as "spontaneous, sudden, jabbing pain of seconds".[32] There is usually no pain between the episodes of paroxysmal pain, but, if frequent episodes are present, persistent pain can occur. The patients included in this study were diagnosed with NPP following maxillofacial fracture in accordance with the aforementioned diagnostic criteria, in addition to clinical experience.

Table 4: Adverse events

Description	No.
Vomiting	2
Dizziness	5
Headache	2
Constipation	2
Total No.	11

The results of this study suggest that a combination of gabapentin and duloxetine can provide excellent pain relief and some control of neuropathic symptoms in patients experiencing post-maxillofacial fracture NPP. Patients in this study experienced significant and clinical meaningful reductions in SAS, HAMD, and PSQI scores compared with preoperative baseline values over 12 weeks of study treatment. The improvements observed in life quality were also reflected in the average score for each domain of the SF-36 post-treatment demonstrated a marked increase compared to baseline. We also found that combining gabapentin and duloxetine significantly increased total sleep time and the duration of each sleep stage, while reducing awakenings and wakefulness duration, when compared to pre-surgery sleep patterns six months after treatment. The medication side effects of the

drug combination of gabapentin and duloxetine in patients undergoing treatment for NPP following maxillofacial fracture are generally well tolerated.

Medication is the primary treatment for post-maxillofacial fracture NPP, but monotherapy's limited efficacy and severe side effects at higher doses hinder its effectiveness. Drug tolerance further complicates matters, as higher doses are needed for optimal relief.[33] Monotherapy's inadequacy can lead to impaired functioning, disrupted sleep, reduced quality of life, and increased economic costs. In clinical practice, combination therapy is often employed, and NPP management is no exception. Studies indicate that at least 45% of patients use multiple medications.[34] Research shows that combining two drugs is more effective than single-drug therapy, enhancing pain relief while minimizing side effects.[35] The synergistic effect allows for reduced medication dosages. The combination of ketoprofen lysine salt (KLS) and gabapentin has shown efficacy in treating chronic pain, potentially enhancing the synergistic effects of the component drugs.[36] Duloxetine and gabapentin are preferred for pregnant patients with NPP due to cancer, particularly chemotherapy.[37] Our findings suggest that the gabapentin-duloxetine combination alleviates neuralgia after maxillofacial fracture, reducing pain, improving sleep quality, and mitigating anxiety and depression. However, the superiority of combination therapy over monotherapy remains unproven and requires validation in higher-quality clinical studies.

Anti-seizure medications, such as gabapentin, and antidepressants, such as duloxetine, are commonly utilized in the management of NPP. In contrast to traditional pain medications, such as acetaminophen, NSAIDs, and opioids, anti-seizure medications and antidepressants have a slower onset of action and may require up to two weeks for patients to experience their full therapeutic effects. To comprehensively assess the efficacy of the combination of gabapentin and duloxetine, we exclusively enrolled patients who completed a 12-week course of medication in this study. Gabapentin is excreted through the kidneys. In order to achieve the necessary concentrations for effective pain management, it may be necessary to increase the dosage. Nevertheless, this may place an additional burden on the patient's kidneys. This has resulted in the imposition of clinical dose limitations on the utilization of gabapentin.[37] Previous study has indicated that duloxetine exhibits high selectivity and does not bind to many neurotransmitter receptors, including dopamine, adrenergic, cholinergic, opioid, glutamate, and GABA receptors. This selective binding profile also extends to sodium, potassium, and calcium channels.[38] In comparison to gabapentin, duloxetine has a lower incidence of adverse effects due to its lack of monoamine oxidase inhibition.[37] Previous studies have suggested that gabapentin and/or duloxetine may be effective in treating NPP.[38-40] The data from this trial indicate that the combination of gabapentin and duloxetine may be a potential treatment option for neuralgia following maxillofacial fractures. The combination of gabapentin and duloxetine may offer additional benefits, as duloxetine exerts noradrenergic effects at lower doses. Prior investigations have demonstrated that duloxetine enhances the availability of endogenous norepinephrine in the spinal cord, potentially improving pain relief.[41,42] However, it is crucial to vigilantly monitor patients for potential side effects and make necessary adjustments to the dosage.

To date, there is a paucity of comprehensive documentation in scientific literature regarding the use of this particular combination for the treatment of NPP, especially in the context of maxillofacial fractures. Furthermore, the implementation of trials with this combination will facilitate the development of evidence-based guidelines for post-maxillofacial fracture neuralgia, thereby enhancing clinical practice and ultimately elevating the standard of care for individuals affected by this condition. As research on post-maxillofacial fracture neuralgia progresses, collaboration and knowledge-sharing within the dental community will be essential in addressing existing gaps and refining treatment strategies.

This study has several limitations. First, there are the inherent constraints of retrospective studies. Second, the sample size was small due to the limited number of patients included, which may have affect the study's results. Third, no control group was established for comparison. Despite these limitations, the study indicates that dual therapy with gabapentin and duloxetine is a highly effective treatment for neuralgia following maxillofacial fractures. In order to substantiate these findings on a broader scale, additional prospective studies with larger sample sizes and appropriate control groups are necessary.

In conclusion, this study indicated that the combined treatment of gabapentin and duloxetine was highly effective for post-maxillofacial fracture neuralgia. This combination improved patients'

pain levels, overall quality of life, sleep patterns, and levels of anxiety and depression.

DISLOSURE

Ethics: This study was approved by the Institutional Review Board (IRB) of the 910th Hospital of PLA Joint Logistic Support Force. The IRB was not required to obtain informed consent from patients because all data were retrospective.

Data availability: Data available on request from the authors.

Financial support: None

Conflict of interest: None

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