Tropical Journal of Pharmaceutical Research November 2022; 21 (11): 2473-2478
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i11.29

Original Research Article

Efficacy of the combination of carbamazepine and pulsed-radiofrequency in the treatment of trigeminal neuralgia

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Sent for review: 25 May 2022 *Revised accepted: 29 October 2022*

Abstract

Purpose: *To investigate the effect of the combination of carbamazepine and pulsed-radiofrequency therapy on trigeminal neuralgia (TN) and changes in inflammation status in vivo.*
Methods: *Ninety-seven trigeminal neuralgia patients treated in Wuhan Fourth Hospital from January 2018 to January 2021 were analyzed retrospectively. Forty-five patients treated with pulsed-radiofrequency therapy alone were designated as the control group (CG), while 52 who underwent carbamazepine and pulse-radiofrequency combination therapy were enrolled in the study group (SG). Changes in serum inflammatory factors, viz, interleukin (IL)-6, IL-1β, and tumor necrosis factor α (TNF-α), were recorded before and after treatment. Similarly, changes in pain visual analog scale (VAS) score, quality of life score, and oxidative stress index were assessed before and after treatment; so also were changes in clinical efficacy and incidence of adverse reactions.*
Results: *After treatment, VAS score, and levels of IL-6, IL-1β, and TNF-α in SG were lower than those in CG, while the score of quality of life in SG was higher ($p < 0.05$). The clinical efficacy of SG was higher than that of CG, but there was no significant difference in incidence of adverse reactions ($p < 0.05$).*
Conclusion: *The therapeutic combination of carbamazepine and pulsed-radiofrequency is more effective than pulsed-radiofrequency alone in the short-term treatment of TN in patients. It produces better relief of pain, reduces inflammation and improves patients' quality of life. However, it does not affect the incidence of adverse reactions.*

Keywords: *Carbamazepine, Pulsed-radiofrequency therapy, Trigeminal neuralgia*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Trigeminal neuralgia (TN) is a representative neurofacial pain disorder that is characterized by unilateral paroxysmal pain in one or more branches of the trigeminal nerve, described as tingling or electric shock-like pain, triggered by harmless stimulation [1]. It is a stubborn facial disease that is relatively difficult to treat and has a very low cure rate. It has been called the "immortal cancer" [2]. Statistics reveal that the annual incidence of TN is 3 to 5 per 100,000 people, mostly in those over 50 years old, and more common in women [3]. The incidence of TN in China is about 182 million. As living standards continue to improve and human life expectancy

continues to increase, the elderly population is also increasing year by year [4]. Now that China has entered an aging society, the incidence of TN is also on the rise [5]. The main drugs for TN treatment are antiepileptic and other non-antiepileptic drugs, mainly to relieve symptoms, with serious side effects after long-term use [6]. Carbamazepine, a familiar drug for TN treatment, can effectively improve the clinical symptoms of patients, and it is the first drug of choice [7]. By stabilizing the abnormal nerve cell membrane, the permeability of Na^+ and Ca^{2+} is decreased, and the transmission excitation is reduced to improve the neurological function of patients [8]. Clinical studies have found that the effect of a single drug in TN treatment is not very efficient, hence it is often combined with other regimens [6-9]. The use of pulsed-radiofrequency modulation in treatment has long been documented and widely accepted [9]. This is because, it is minimally invasive, safe, and does not damage the nerves. When the pain recurs, the treatment can be repeated without affecting neuromotor function, and there are no complications such as skin numbness [9]. There is still controversy regarding the combination of carbamazepine with pulsed-radiofrequency for the treatment of TN. In this study, the efficacy of the combination of carbamazepine and pulsed-radiofrequency therapy in the management of TN was compared with pulsed-radiofrequency therapy alone and analyzed retrospectively. The outcome of this investigation is expected to provide a suitable reference for their clinical application.

METHODS

Clinical data collection

Ninety-seven Trigeminal neuralgia patients treated in the Pain Department of Wuhan Fourth Hospital from January 2018 to January 2021 were analyzed retrospectively. Among them, 45 patients treated with pulsed-radiofrequency therapy were divided into the control group (CG), and 52 who underwent carbamazepine combined therapy were enrolled in the study group (SG). This research was approved by the Medical Ethics Committee of the Wuhan Fourth Hospital (approval no. LL2021044). All study procedures were conducted in line with the principle of the Declaration of Helsinki [10].

Inclusion and exclusion criteria

Inclusion criteria

The symptoms of all patients were in line with the definition of TN by the International Headache Association (IHA). Patients were selected by the diagnosis of TN through clinical manifestations, imaging examination, diagnostic criteria. Patients that accepted denervation effect therapy. The clinical data of patients were complete.

Exclusion criteria

Patients with other complications such as tumors, Patients that were intolerant to this drug or procedure, with the course of disease less than 3 months, and Patients with other serious diseases, such as severe cardiovascular, liver, and kidney diseases were excluded from the study.

Treatment schemes

Patients in the CG were treated with pulsed-radiofrequency alone. The treatment was carried out in the computerized tomography (CT) room, and the conventional minimally invasive radiofrequency interventional operation kit and matching radiofrequency puncture needle were used for puncture before therapy. After the patients were routinely disinfected and toweled in the supine position, 0.5 % lidocaine (3 mL) was injected intradermally and subcutaneously at the needle entry point for subcutaneous local anesthesia.

A special needle with a core was used to pierce the skin vertically. The direction of the needle tip was observed on the front of the patients to align with the slightly medial side of the pupil, and to align with the midpoint of the zygomatic arch from the affected side.

Under the guidance of CT, when the needle was placed at a depth of 7 cm, the discharge sensation of the lower lip indicated that the depth was near the foramen ovale. The needle was placed at 1 cm to reach the semilunar ganglion of the ovary and then the core was pulled out. Without withdrawing cerebrospinal fluid and blood, gas was injected without resistance and connected to the radiofrequency instrument (resistance varied from 200 to 3000 Ω, current at 0.5 mA, frequency of 100 and 2 Hz, 60 s for one cycle, 3 cycles, once a day for 20 days).

All the patients received high-quality postoperative care. Based on the CG, patients in the SG were given carbamazepine (Sinopharm, Shanghai, China, SFDA Approval No. H31020798) 200 mg, twice a day. Then the dose was increased from 200 to 400 mg every other week, and the maximum dose was 800 mg a day. The drug was administered continuously for 20 days.

Evaluation of parameters/outcomes

Clinical efficacy/effectiveness

After 20 days of treatment, changes in the clinical efficacy of both groups were compared, and the efficacy was characterized as; markedly effective, effective, and ineffective. *Markedly effective:* The symptoms and signs had disappeared completely without recurrence. *Effective:* The symptoms and signs disappeared completely but patients occasionally relapsed, and the recurrent pain was less than that before treatment. *Ineffective:* The symptoms and signs did not decrease or increase. The total effective rate (TE) was calculated using Eq 1.

$$TE = \{(ME+EC)/TC\}100 \quad \ldots\ldots\ldots\ldots\ldots (1)$$

where ME = markedly effective cases, EC = effective cases, and TC = total cases

Enzyme-linked immunosorbent assay (ELISA)

This was carried out to determine changes in serum inflammatory factors (IL-6, IL-1 β, TNF- α) before and after treatment.

Secondary outcomes

The changes in VAS score before and after treatment were compared. There are 10 points in total, the higher the score, the more obvious the pain. The quality of life of patients before and after treatment was assessed via the European five-dimensional Health scale, with a total of 5 dimensions. It has 100 points in total, the lower the score, the worse the quality of life of patients. The occurrence of adverse reactions in the course of treatment was counted, and the incidence of adverse reactions in both groups was compared.

Statistical analysis

Data were analyzed using SPSS 21. Kolmogorov-Smirnov test was applied to assess data normality. Variables with normal distribution were presented as mean ± standard deviation (SD). Paired sample *t*-test was used to test intra-group differences, while an independent *t*-test was used to test inter-groups differences. Qualitative variables were expressed as frequencies and percentages, and the chi-square test was used for the comparisons. $p < 0.05$ was considered statistically significant. GraphPad was used for graphics rendering.

RESULTS

Clinical profile of patients

It was found that there are no significant differences in age, gender, body mass index (BMI), course of the disease, past medical history, and smoking history between both groups (Table 1; $p > 0.05$).

Clinical efficacy

The clinical efficacy and the total clinical effective rate of the CG were significantly lower than that of the SG (Table 2; $p < 0.05$).

Table 1: Comparison of baseline data

Parameter		Control group (n=45)	Study group (n=52)	*P*-value
Age (years)				
	≥60	28	24	0.113
	<60	17	28	
Gender				
	Male	13	12	0.514
	Female	32	40	
BMI (kg/m^2)				
	≥22	30	30	0.364
	<22	15	22	
Course of disease (years)				0.068
	≥3	22	16	
	<3	23	36	
Past medical history				
	Hypertension	22	20	0.301
	Diabetes	18	23	0.674
Smoking history				
	Yes	15	12	0.261
	No	30	40	

Table 2: Comparison of clinical efficacy/effectiveness

Group	Markedly effective	Effective	Ineffective	Total effectiveness
Control (n=45)	16	19	10	35 (77.78)
Study (n=52)	33	16	3	49 (94.23)
χ^2/Z		-3.016		5.627
P-value		0.003		0.017

Serum inflammatory factors

It was found that the serum levels of IL-6, IL-1β and TNF-α in the CG were higher than those in the SG ($p < 0\ 05$, Figure 1).

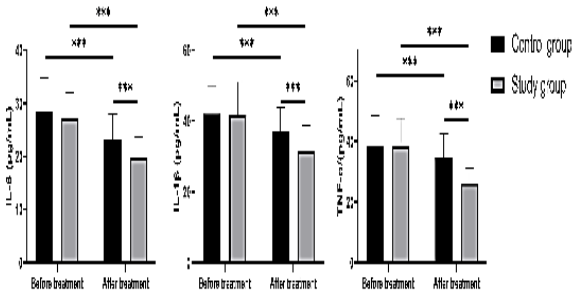

Figure 1: Changes in serum inflammatory factors in patients before and after treatment. (A) Changes in serum IL-6 levels in patients before and after treatment, (B) Changes in serum IL-1β levels in patients before and after treatment, (C) Changes of serum TNF-α in patients before and after treatment. ***$P < 0.001$ vs. CG

VAS scores

The results revealed that the VAS scores of CG patients were significantly higher than those of SG patients after treatment (Figure 2, $p < 0.05$).

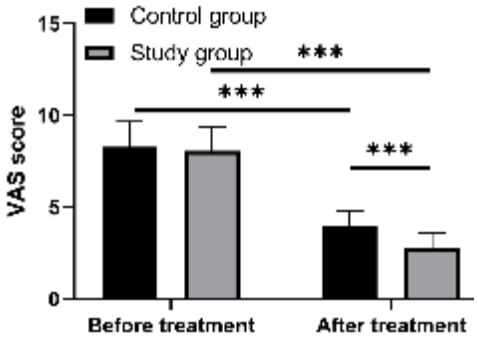

Figure 2: VAS scores of patients before and after treatment. ***$P < 0.001$ vs. CG

Quality of life

The quality of life score of patients in the CG after treatment was significantly lower than that in the SG (Figure 3, $p < 0.05$).

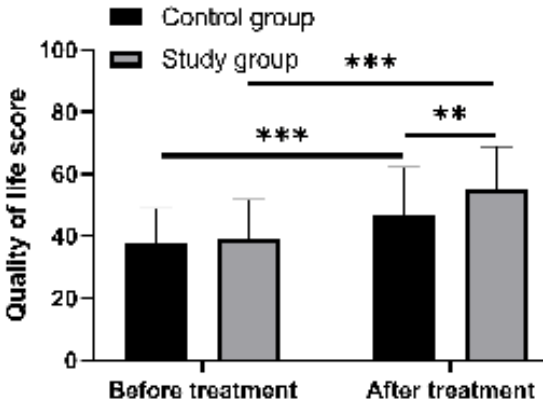

Figure 3: Quality of life scores of patients before and after treatment. **$P < 0.01$; ***$p < 0.001$ vs. CG

Incidence of adverse reactions

There was no significant difference in the incidence of adverse reactions between both groups ($p > 0.05$), as well as the total incidence of adverse reactions ($p > 0.05$, Table 3).

DISCUSSION

The pain associated with TN is severe and unbearable. Patients often suffer from severe complications such as tearing, hypertension, facial muscle spasms and sweating, and the pain becomes more severe with longer duration [11]. Currently, there is no clinical consensus on the etiology of TN. Existing clinical studies have shown that it may be related to external mechanical stimulation. Various factors lead to local demyelination of the trigeminal nerve and superimposition of ectopic impulses, resulting in TN [12].

The clinical treatment for TN is pharmacological, consisting mainly of antiepileptic drugs and other non-antiepileptic drugs. Carbamazepine is a broad-spectrum antiepileptic drug which is effective in the treatment of major seizures, psychomotor epilepsy and localized epilepsy [13]. It relieves pain mainly by inhibiting the pathological multiple nerve reflex of trigeminal nerve and reducing the excitability of cell membrane. Nevertheless, long-term use of carbamazepine has side effects [14].

Table 3: Comparison of incidence of adverse reactions

Group	Nausea and vomiting	Leucopenia	Vertigo	Blurred vision	Gastrointestinal discomfort	Total incidence
Control (n=45)	3	2	2	4	3	14 (31.11)
Study (n=52)	2	1	2	2	1	8 (15.38)
χ^2/Z	0.393	0.511	0.022	1.057	1.373	3.402
P-value	0.531	0.474	0.883	0.304	0.241	0.065

Therefore, the clinical treatment is combined with other schemes at the same time. In addition to oral medication, local medication and surgical treatment such as microvascular non-invasive decompression can be given. Pulsed-radiofrequency technology has been successfully used to treat a variety of neuropathic pains [15]. It is conducted through adjusting the nerve rather than destroying it, so that the surrounding tissue will not be adversely affected. Previous studies have found that pulsed-radiofrequency is effective in TN [16]. However, the efficacy of combining carbamazepine with pulsed-radiofrequency is controversial.

In this research, the efficacy of carbamazepine and pulsed-radiofrequency therapy in TN patients was compared. It was found that the clinical efficacy of the SG was better than that of the CG after treatment, and the total clinical efficiency of the former was also higher, indicating that the combination therapy can effectively improve the treatment. Moreover, the changes of serum inflammatory factors in patients before and after treatment were further compared. There is a vital relationship between inflammatory factors and TN occurrence. When TN occurs, the destruction of nerve macrophages, mast cells and vascular endothelial cells leads to inflammation, which increases the expression of inflammatory factors [17]. The IL-6 promotes the differentiation and growth of bone marrow-derived cells and enhance the function of natural killer cells.

The TNF-α directly kills tumor cells but has no obvious toxicity to normal cells [18]. It was discovered that the levels of serum IL-1, IL-1β and TNF-α in both groups after treatment were lower than those before treatment. After treatment, the levels of serum IL-1, IL-1β and TNF-α in the SG were lower than those in the CG, which indicated that the combined therapy could further reduce the occurrence of inflammation in patients. Besides, it was confirmed that after treatment, the VAS score of patients in the SG was lower than that in the CG, while that of quality of life was higher. This shows that the combination of carbamazepine and pulsed-radiofrequency reduced inflammation, relieve the damage of nerve cells, reduce the excitability of nerve cells and pain, and improve the quality of life of patients. Afterwards, the occurrence of adverse reactions in the course of treatment was counted, and found that there was no difference between both groups, which indicated that the combination therapy does not increase morbidity due to carbamazepine [19].

Limitations of this study

The study population was relatively small. As this was a retrospective study, a large sample collection was not conducted and could only be accessed through electronic archives. On the other hand, patients were not followed up for a long period and it was ambiguous whether these two treatments affected the patients' recurrence. Thus, prospective research needs to be done in the future.

CONCLUSION

The combination therapy of carbamazepine and pulsed-radiofrequency is effective in short-term treatment of TN, relieving pain, reducing inflammation, and improving the quality of life of patients. It does not increase the incidence of adverse effects.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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