Current Medical Science
DOI https://doi.org/10.1007/s11596-019-2085-4
39(4):638-644,2019

Triple Puncture for Primary Trigeminal Neuralgia: A Randomized Clinical Trial*

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Summary: To evaluate the effect of triple puncture on primary trigeminal neuralgia (pTN), 64 patients with pTN were randomly assigned to two groups: treatment group and control group. The participants in the treatment group received triple puncture treatment of 6 times per week for 4 weeks, and those in control group were given carbamazepine (300–600 mg per day) for at least 1 month. Before and after treatment, the primary outcomes including the total efficiency rate and the VAS pain scores, and the secondary outcomes including the frequency of pain attack and adverse events were observed. Sixty-two participants finished the study (33 in treatment group and 29 in control group individually). After treatment, the symptoms (mainly pain) of the two groups were alleviated. The total efficiency rate in the treatment group and control group was 90.9% and 75.9% respectively. The VAS pain scores and frequency of pain attack were significantly reduced in the treatment group as compared with the control group (P<0.05). The incidence of adverse events in the treatment group and control group was 9.1% and 24.1% respectively. It can be inferred that triple puncture can effectively improve the quality of life of patients with pTN and has less side effects.
Key words: triple puncture; primary trigeminal neuralgia; randomized clinical trial

Trigeminal neuralgia (TN), one of the most common clinical diseases in trigeminal nerve, i.e., cranial nerve V (CN V), is characterized by sudden onset, unilateral, transient and recurrent electric shock-like pain[1], with part of the function of trigeminal nerve impaired. Patients with TN have a sudden onset of pain and are subjected to severe pain like cutting pain, burning pain and lightning pain. It happens unexpectedly and stops suddenly, and the periodicity of acute episodes is obvious. In severe cases, patients will have a reflexive twitching of the facial muscles. It is unbearable and difficult to cure. Talking, chewing, coughing, shaving, brushing teeth and cold can all cause seizures. Multiple attacks often lead to depression, anxiety, fear and even despair.

Usually, pain outbreaks on one side of the face with one or several branches of the trigeminal nerve. Generally speaking, pain episodes of the second and third divisions are more frequent[1]. Epidemiological researches also show that the right side is reported most often in those with TN and it is common in elderly patients, especially in women[2, 3]. The incidence is 4.3–28.9 per 100 000 people annually in worldwide[4].

The risk of recurrence is high, which has a serious impact on daily life and social interaction. How to effectively alleviate the degree of pain in patients with TN, reduce the frequency of acute attack and improve the quality of life has been paid more and more attention.

The pathogenesis of TN is still not very clear. Neurovascular compression (NVC) of the CN V at the root entry zone (REZ) is the most common cause of TN[5]. According to the cause, TN can be divided into primary and secondary types. In secondary TN, organic pathological changes can be found through clinical examination. While primary type can not find the cause.

At present, there is no special treatment for primary TN (pTN) in western medicine. Minimally invasive techniques such as microvascular decompression[6], balloon compression[7], continuous radiofrequency thermocoagulation[8], gamma kniferadiosurgery[9], and medicine were used to treat TN. Some of them have achieved good curative effects, but there are different

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*This work was supported by Wuhan Young and Middle-aged Medical Talents Foundation Project of Hubei Province, China (No. 2018116).

degrees of recurrence and various side effects. It is easy to produce corresponding complications and is not suitable for long-term use. Medicines mainly including many antiepileptic drugs and analgesic drugs such as carbamazepine[10], oxcarbazepine[11], or baclofen[12] are used to intervene the disease in order to alleviate the symptoms of patients for long periods. Although they may alleviate pain to different extents, many may have sensory side effects[13]. Particularly, carbamazepine is one of the most effective drugs for the treatment of TN. It does reduce the symptoms of pain in 60% of patients, but it is not effective for the control of the frequency of acute attack. As time goes, the treatment effect will cut down. Long term taking will do great harm to the function of liver and kidney. In addition, adverse reactions such as hyponatremia or difficulty with balance will occur[14].

Acupuncture is generally used as alternative therapeutic method for diverse conditions, including chronic diseases and pain control[15]. There is evidence that acupuncture is favorable in treating neuropathic pain, including neuralgias[16], however there are few reports with good methodology in literature[17].

In recent years, it has also been reported that acupuncture has a good effect on the treatment of pTN[18] and is relatively safe. Triple puncture is one kind of acupuncture, which punctures with one needle directly in a point and two by side. It is also one of the traditional needling method, which was used to treat pTN and achieved good results[19]. The main reason is that the multi-needle can enhance the sense of needle and achieve a more remarkable effect than the single needle method. It is widely used in clinical practice. It can improve the patients' quality of life by reducing pain, whereas, very little is known about the effectiveness and safety of this remedy. The application of triple puncture for the treatment of TN is limited by inadequate scientific and safety evidence. Therefore, we designed such a research to clarify the effect of triple puncture on pTN.

1 MATERIALS AND METHODS

1.1 Characteristics of Patients

Eighty-six subjects were assessed for eligibility, of whom 22 were excluded and 64 were randomly allocated to the treatment or control group: 34 in the treatment group (12 males and 22 females, average age of 47.3 years old), 30 in the control group (11 males and 19 females, average age of 45.8 years old). Two cases dropped out (1 in the treatment group due to fear of acupuncture and 1 in the control group due to loss of patience). Sixty-two subjects completed the study. The research flow chart is shown in fig. 1. Brain MRI

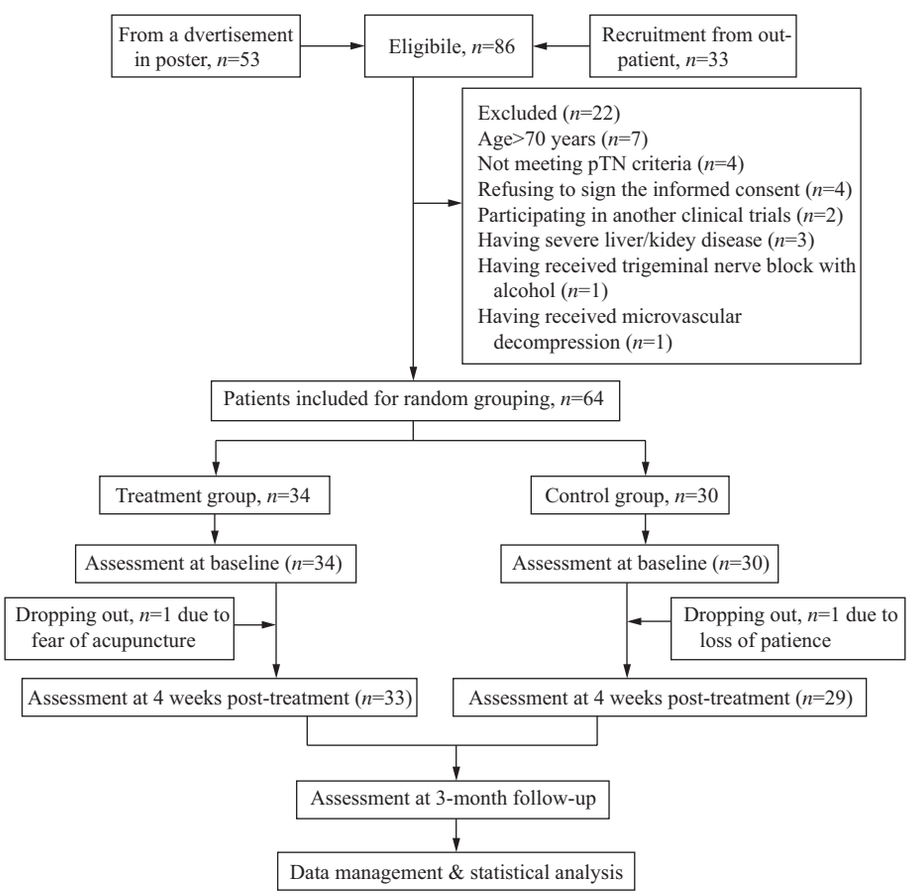

Fig. 1 Flow chart for patients screening in this study

Table 1 Clinical characteristics of the study patients

Characteristics	Treatment group (*n*=34)	Control group (*n*=30)	Total (*n*=64)	*P* value
Age (years)	47.3±5.7	45.8±9.2	46.2±6.4	0.64
Sex (Male/Female)	12/22	11/19	23/41	0.52
Course of disease (years)	4.37±4.1	4.60±3.7	4.50±3.8	0.61
Branches, *n* (%)				
First	4 (11.8)	3 (10)	7 (10.9)	0.82
Second	16 (47.1)	15 (50)	31 (48.4)	0.76
Third	14 (41.1)	12 (40)	26 (40.7)	0.58
Side, *n* (%)				
Left	14 (41.2)	12 (40)	26 (40.6)	0.48
Right	20 (58.8)	18 (60)	38 (59.4)	0.39
VAS	5.12±1.12	4.98±1.21	5.01±1.17	0.46

VAS: visual analogue scale

was carried out in all study patients to exclude the possibilities of a tumor or multiple sclerosis or other factors.

The patients' characteristics are presented in table 1. There were no significant differences in demographic and clinical features between the randomly allocated participants (*n*=64) (*P*>0.05 for all). The mean age of the subjects was 46.2 years and the average course of disease was 4.5 years. Forty-one participants (64%) were women.

1.2 Clinical Data

We designed a single-center, randomized controlled trial to compare the effect of triple puncture with carbamazepine on pTN.

All the 64 patients with pTN were chosen as observation objects who were treated at Department of Physical Medicine and Rehabilitation, Hubei Provincial Hospital of Integrated Chinese and Western Medicine from January 2016 to July 2018.

Patients with pTN aged from 18–70 years according to the following criteria were included. The diagnostic criteria for pTN were based on the principle of International Classification of Headache Disorders (IHS)-III (2013)[1]. It was detailed as follows: paroxysmal attacks of facial or frontal pain lasting a few seconds to less than 2 min; pain distributed along one or more divisions of the trigeminal nerve; sudden intense, sharp, superficial, stabbing, or burning in pain; severe intensity; the precipitation of pain from trigger areas or by certain daily activities (e.g., chewing, coughing, shaving, talking, facial washing, or brushing teeth); no symptoms between paroxysms; and no clinically obvious neurologic defect[20].

Diagnoses were made after a careful inquiry of history including the evaluation of characteristics of the pain and observation of non-verbal behaviors such as, speech interruption or abomination to anyone or anything touching the face during an attack of pain during an interview.

Exclusion criteria were as follows: secondary TN caused by tumors, intracranial lesions, multiple sclerosis, or herpes zoster (excluded through clinical evaluation and imaging exams–CT and/or MRI); severe organ disease; coagulation disorder; mental disorders; pregnancy or breast feeding mothers or unwilling to sign the informed consent.

Eligible patients would be randomly assigned to treatment group treated by triple puncture and control group given oral carbamazepine by an independent administrator by a random number table.

The study-hypothesis is that triple puncture is more effective and safer than carbamazepine in relieving pain from pTN.

This study was approved by the local Ethics Committee of Hubei Provincial Hospital of Integrated Chinese and Western Medicine (China) (2015113), and all patients provided informed consent before participation.

1.3 Acupuncture Treatment

Acupoints taken in the treatment group were based on expert's opinion. The main acupoints were: Quanliao (SI 18), Yanglingquan (GB 34), Fenglong (ST 40). Matching acupoints were selected according to the branch of the trigeminal nerve.

For neuralgia of the 1st branch, Yuyao (EX-HN4) was selected. Needle was inserted into the point 0.5 cm deep to reach the bone surface of the orbital margin and induce a sensation of electric transmission.

For neuralgia of the 2nd branch, Sibai (ST 2) was selected. Needle was inserted into the point via the infraorbital foramen of an angle of 40°–50° posterolaterally upwards to a depth limited within 1 cm, followed by appearance of the electric shock sensation radiating to the upper lip and the upper teeth.

For neuralgia of the 3rd branch, Xiaguan (ST 7) was selected. Needle was inserted into the point posteriorly towards the medial side for about 4 cm (never deeper than 5 cm). A sensation like a electric shock radiating to the mandibula appeared.

Quanliao as the main acupoint was pierced vertically by a disposable sterilized filiform needles, 0.25 mm in diameter and 40 mm in length (HUANQIU,

China) after the routine disinfection, then the needles were lifted and twisted to make the patient feel swelling at electric shock which could be tolerated. Next two needles were pierced obliquely for 2–4 cm from the point of about 1.5 cm on the left and right sides, with a 45 degree. The mild reinforcing-reducing method was adopted after "De Qi", an acupuncture specific sensation, which can be described as a feeling of soreness, numbness, swelling or heaviness. The needles were left in the acupoint for 40 min, manually stimulated every 10 min by twirling to strengthen the sense with the frequency of 80–100 times per min for 2 min. Yanglingquan and Fenglong acupoints were pierced vertically for 3–4 cm, using reducing method with lifting and twisting after "De Qi". When needling Yanglingquan and Fenglong acupoints, the patients would have the sensor of Qi passing through.

All acupuncture treatment conforms to the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) revised in 2010[21].

Subjects received the treatment 6 times per week for 4 consecutive weeks. All acupuncture treatments were performed in an independent quiet treatment room by the same acupuncturist, who had at least 3 years of clinical experience of providing acupuncture treatment.

1.4 Carbamazepine Treatment

The patients in control group received treatment of oral carbamazepine (Tegretol, Beijing Novartis Pharma Ltd, H11022279, China) for at least 1 month (300–600 mg per day).

1.5 Study Procedure

All participants in this study were given a pain diary containing a daily categorical verbal pain intensity scale (VPIS). A pain intensity scale with items severe/moderate/slight/no pain was used[22, 23]. Visual analogue scale (VAS) pain scores 0–10 (where 0 means no pain and 10 means the worst possible pain) were used. Each patient was asked to record his/her average 24 h pain intensity using this scale in the evening. In addition, the number of bursts of pain and their strength were noted using an 11-point numeric rating scale.

1.6 Follow-up

All patients were followed up for a period of three months after the end of the treatment of the study. They were asked to note treatments sought for pTN during this period and to judge treatment outcome using the above described categorical pain relief scale. Long-term efficacy of acupuncture treatment was studied.

During the follow-up period, carbamazepine was given orally if the patient suffered from unbearable pain. The dose and time taken were recorded.

1.7 Outcome Measurement

1.7.1 Primary Outcome The primary outcomes of this study included the total efficiency rate and VAS pain scores.

The degree of pain relief was evaluated in accordance with the World Health Organization's evaluation criteria for pain relief. It includes four levels: complete remission (CR), indicating complete resolution of pain; partial remission (PR), indicating significant resolution of pain (50%–75%); mild remission (MR), indicating partial resolution of pain (<50%); and no response (NR), indicating no resolution of pain. The total efficiency rate (%) is equivalent to $[(CR + PR + MR)/n] \times 100\%$.

The VAS value was 0–10, in which 0 represented no pain, 1–3 represented mild pain, 4–6 represented moderate pain, 7–9 represented severe pain, and 10 represented unbearable pain.

1.7.2 Secondary Outcome Secondary outcome measures contain the frequency of pain attack (The number of pain attacks per day was recorded and the average value was calculated) and adverse events.

The evaluation of subjects was performed at the baseline, the end of the 4-week treatment period (post-treatment assessment) and 3 months following the end of treatment (follow-up). The duration of the clinical trial was 4 months.

Adverse effects were also reported. Doses of carbamazepine were collected at each assessment time and divided by the number of days of the period to determine daily requirements.

After treatment, an independent investigator who was blinded to the group allocation would conduct the analysis of the score of VAS, write diaries which recorded frequency of pain attack, adverse events and statistical analysis.

1.8 Adverse Events

Acupuncture was well tolerated in the treatment group. Only one felt fatigue, one developed dizziness and one drowsiness. In control group, two subjects developed fatigue, one dizziness, two drowsiness and two gastrointestinal reaction (nausea or vomiting). All adverse events were mild in severity. The ratio of adverse events was calculated.

1.9 Sample Size Calculation

A sample size calculation was performed based on the log-rank test. We found 80% power could detect a hazard value of 3.3 or greater and it was acceptable, and we assumed a 20% dropout in both groups. We found that 30 subjects needed to be enrolled in each treatment arm. An intention to treat analysis was agreed to assign dropouts at the study end.

1.10 Statistical Analysis

SPSS software 20.0 version (SPSS Inc., US) was used for statistical analysis. Descriptive data were expressed as $\bar{x} \pm s$. Total effective rate, the score of VAS, frequency of pain attack and adverse events were analyzed using independent sample *t*-tests at baseline to determine equality of the two groups. For qualitative data, for example, sex differences, a Chi-squared

test was used. An efficacy analysis was done using both per-protocol and intention-to-treat analyses. The factors are periods of treatment (3 levels: pre-, 4-week post-treatment and 3-month follow-up) and groups (2 levels: treatment and control) and their interaction. The significance level was set at $P<0.05$.

2 RESULTS

2.1 Subjective Measure

2.1.1 Total Efficiency Rate Table 2 presents the total efficiency rate of treatment and control groups. After treatment, the patients were followed up for 3 months. The total efficiency rate of the two groups was 90.9% (treatment group) and 75.9% (control group) respectively, and there were significant between-group differences in the total effective rate ($P=0.038<0.05$).

2.1.2 VAS Score Table 3 presents the VAS scores for treatment and control groups. After treatment, the scores of VAS in the two groups were significantly reduced as compared with those before treatment (all paired *t*-test, $P<0.01$). The one-way analysis of covariance (ANCOVA) showed that patients in treatment group had significantly greater reduction in the score of VAS than that in control group at 4th week post-treatment and 3rd month during the follow-up period (ANCOVA, $P<0.05$).

2.2 Secondary Outcome

2.2.1 Frequency of Pain Attack Table 4 presents the frequency of pain attack for treatment and control groups. The frequency of pain attack was significantly lower in both groups after treatment ($P<0.01$), and that in the treatment group was significantly lower than that in control group ($P<0.05$).

2.2.2 Adverse Events Adverse events contained fatigue (1 in the treatment group and 2 in the control group), dizziness (1 in the treatment group and 1 in the control group), drowsiness (1 in the treatment group and 2 in the control group) and gastrointestinal reaction (nausea or vomiting) (0 in the treatment group and 2 in the control group). The ratio of adverse events in the treatment and control groups was 9.1% and 24.1% separately. There was significant difference between the two groups ($P=0.009<0.01$).

3 DISCUSSION

There is great benefit in the study of alternatives for treatment of pTN because patients who suffer from pTN require effective and safe alternative therapy because of pharmacological refractoriness or intolerance of surgery.

This research is a single-centre randomized controlled clinical trial with an appropriate sample size on the effect of triple puncture for treating patients with pTN. The hypotheses of the study were that there would be a significant difference in the total efficiency rate, the score of VAS, the frequency of pain attack and adverse events between the two groups.

Acupuncture is a highly safe procedure with few

Table 2 Comparison of therapeutic effects (*n*)

Groups	Cured	Markedly effective	Effective	Invalid	Total efficiency rate (%)
Treatment (n=33)	8	17	5	3	90.9$^{\triangle}$
Control (n=29)	4	8	10	7	75.9

$^{\triangle}P<0.05$ *vs.* control group

Table 3 The VAS scores across study time points

VAS scores	Treatment group (n=33)			Control group (n=29)			ANCOVA ^{a}P value
	$\bar{x}\pm s$	Within-group effect size	Paired *t*-test ^{b}P value	$\bar{x}\pm s$	Within-group effect size	Paired *t*-test ^{b}P value	
Baseline	5.12±1.12			4.98±1.21			0.46
4th week post-treatment	1.12±0.12	1.38	<0.001	2.01±0.59	1.47	<0.001	0.03
3rd month during follow-up	1.41±0.47	1.46	<0.01	2.58±0.94	1.53	<0.01	0.018

VAS: visual analogue scale; ^{a}P value: treatment group *vs.* control group; ^{b}P value: 4th week post-treatment *vs.* baseline, 3rd month during follow-up period *vs.* baseline

Table 4 The frequency of pain attack across study time points

Frequency	Treatment group (n=33)			Control group (n=29)			ANCOVA ^{a}P value
	$\bar{x}\pm s$	Within-group effect size	Paired *t*-test ^{b}P value	$\bar{x}\pm s$	Within-group effect size	Paired *t*-test ^{b}P value	
Baseline	9.64±2.81			9.56±2.94			0.38
4th week post-treatment	3.89±1.24	0.12	<0.001	5.51±3.09	0.10	<0.001	0.04
3rd month during follow-up	4.41±1.07	0.09	<0.01	6.22±2.56	0.07	<0.01	0.02

^{a}P value: treatment group *vs.* control group; ^{b}P-value: 4th week post-treatment *vs.* baseline, 3rd month during follow-up period *vs.* baseline

complications reported. Currently, the drug choice for treatment of pTN is carbamazepine, which is considered the gold standard in treatment for symptoms of pTN. The second is oxcarbamazepine, according to the criteria of European Federation of Neurological Societies (EFNS) 2010[24]. Carbamazepine has been shown to increase pain relief compared with placebo, but also increases adverse effects, such as drowsiness, dizziness, constipation, and ataxia.

Both protocols were effective in relieving pain to variable degrees. All patients had good alleviation of pain in comparison to pre-enrollment values. Although VAS was comparable between groups during the follow-up period, the benefit of acupuncture is better than carbamazepine from the assessment values.

The present study examined the safety and effectiveness of using triple puncture for pTN. Our results showed that triple puncture was associated with a lower pTN recurrence rate in 3 months after 4-week treatment than carbamazepine. In addition, the long-term complication rates were comparable between triple puncture and oral carbamazepine.

These results are supported by a previous uncontrolled study that indicated acupuncture is an effective and safe option for patients with idiopathic trigeminal neuralgia (ITN), especially when neurosurgery was not allowed due to clinical conditions[17]. In another uncontrolled study, electroacupuncture has been shown as a good option even in the beginning of the treatment of ITN[25].

Traditional Chinese medicine considers that facial pain (PTN) is caused by invasion of the facial collaterals by exopathic wind-cold or wind-heat, leading to a stagnated flow of qi and blood, hence the occurrence of pain. According to Miraculous Pivot, the pain is considered as excess in nature. The application of acupuncture can make qi reach the diseased area and enhance the intensity of stimulation, so as to promote the flow of qi and blood to check the pain.

Triple puncture is one of the acupuncture methods used to treat local pain with multiple needles. It not only strengthens the stimulation of the needled acupoints and the effect of relieving pain, but also enlarges the area of the acupuncture point and the scope of treatment.

We have obtained satisfactory curative effect in the treatment of pTN. Good therapeutic effects can be expected only when the needling sensation is made to radiate to the painful area. This therapy has been proved highly effective for pTN.

Past studies have suggested that the analgesic effect of acupuncture is through increased activation of the serotonin and endorphin neurotransmitters in the thalamus and brain stem, which leads to decreased release of substance P in the trigeminal nucleus[26, 27]. These mechanisms are associated with the descendant suppression pain system[28]. They include cortical and hypothalamic pathways that are activated from the spinal cord after peripheral stimulation[29].

Another proposed mechanism is that the acupuncture needle, acting as an electrode, might activate changes in the ionic milieu of the interstitial fluid, leading to a rapid increase in the conductance of the electrolyte medium along the fascial lamellar.

From the data obtained, the two groups both showed an outstanding recovery in improving symptoms during the research period. We have found statistically remarkable improvements on the score of VAS when testing for differences within the groups compared with baseline values.

However, our study has several limitations. First, the treatment course and follow-up time are limited. Our treatment period and follow-up time should be longer, thus the effect of treatment can be further objective. Second, we did not evaluate hypesthesia. However, a certain degree of hypoesthesia after the study procedures is expected to occur, and many patients were elderly and could not clearly explain the extent of sensation loss. Third, we did not compare quality of life before and after the study procedures. In fact, few studies have described changes in the quality of life resulting from acupuncture in pTN. Usually, the major factors that impact the quality of life of pTN patients are incomplete pain relief and intolerable complications.

In spite of these limitations, we strongly believe that our present data support the notion that triple puncture should be reconsidered as a useful treatment option for pTN, because it offers a high rate of complete pain relief and has a long lasting effect without serious complications.

Conflict of Interest Statement

The authors declare that there is no conflict of interests.

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(Received Dec. 24, 2018; revised May 21, 2019)