

Evaluation of transcutaneous electrical nerve stimulation as an adjunct therapy in trigeminal neuralgia - a randomized double-blind placebo-controlled clinical study

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Background: Trigeminal neuralgia (TN) is a severe form of pain that affects the daily activities of a patient. Transcutaneous electrical nerve stimulation (TENS) therapy is an emerging option for the treatment of acute and chronic pain. The aim of this study was to evaluate the effect of TENS therapy as an adjunct to drug therapy for the treatment of TN.

Methods: A total of 52 patients diagnosed with TN according to the International Classification of Headache Disorders (version 3) were included. Each patient was randomized to either the TENS or placebo TENS groups. Intervention was given in continuous mode and 100-Hz frequency for 20 mins biweekly for 6 weeks. Parameters were measured at baseline, TENS completion and 3 months, 6 months, and 1 year of follow up. The parameters observed were mean carbamazepine dose, mean visual analog scale (VAS) score, mean present pain intensity (PPI) score, and functional outcome. Non-parametric analyses, one-way ANOVA and the Kruskal-Wallis test were applied for intragroup comparisons, while the Mann-Whitney U test and independent t-test were used for intergroup comparisons of variables. The chi-square test was applied to analyze categorical data.

Results: Compared to the placebo TENS group, the mean dose of carbamazepine in the TENS group was significantly reduced at TENS completion, as well as at 6 months and 1 year follow up. Changes in mean VAS score, mean PPI score, and functional outcome did not show significant differences between the groups (P>0.05).

Conclusion: TENS therapy does not lead to any changes in pain levels but it may reduce the mean dose of carbamazepine when used as an adjunct treatment in patients with TN.

Keywords: Carbamazepine; Present Pain Intensity; Transcutaneous Electrical Nerve Stimulation; Trigeminal Neuralgia; Visual Analog Scale.



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INTRODUCTION

Trigeminal neuralgia (TN) is defined by the International Headache Society, 2013 as "a disorder characterized by recurrent unilateral brief electric

shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli. It may develop without apparent cause or be a result of another diagnosed disorder. There may or may not be, additionally, persistent background facial pain of

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moderate intensity" [1]. The classical symptom of TN is a sudden, excruciating paroxysmal pain in the distribution of the trigeminal nerve triggered by innocuous mechanical stimuli and separated by pain-free refractory periods.

The latest International Classification of Headache Disorders (version 3) (ICHD-3) categorizes TN into classical, secondary, or idiopathic. Idiopathic TN includes all cases without an established etiology, while classical TN includes those without apparent cause other than neurovascular compression. Secondary TN is caused by an underlying disease, such as multiple sclerosis (MS) plaques, tumors, and abnormalities of the skull base [1]. Generally, drug therapy is initiated with carbamazepine (200 - 1200 mg/day), with a titrated dose of 100 mg every other day. Second-line treatment is based on very little evidence, including gabapentin, lamotrigine, baclofen, phenytoin, clonazepam, valproic acid, and topiramate. However, long-term use of medication may lead to decreased drug efficacy, increased incidence of side effects, and recurrent ongoing costs of buying drugs [2].

Transcutaneous electrical nerve stimulation (TENS) therapy is an emerging and promising option for the treatment of acute and chronic pain, in which an electric current is transmitted across the intact skin surface to activate underlying nerves with the aim of relieving pain. Very few studies have been conducted on TENS therapy for the management of pain in TN [3,4,5]. Such studies had an inadequate study design, a lack of control groups, and no clear information regarding the type of drug therapy being simultaneously used. The daily use of TENS therapy in a clinical setting, as done in previous studies, may lead to non-compliance and an increased number of dropouts. In addition, it is difficult to achieve pain control initially with TENS therapy alone, and it is unethical to let patients suffer from pain until the therapeutic goal is achieved through TENS.

Therefore, the aim of this study was to evaluate the role of TENS and placebo TENS therapy as an adjunct to drug therapy in the management of TN patients.

METHODS

A randomized double-blind placebo-controlled clinical study involving patients with classical or idiopathic TN (as per ICHD-3), selected from the outpatient department from January to December 2018, was conducted. Ethical clearance was obtained from the Institutional Ethical Committee (IEC/17/21), and written informed consent was obtained from all patients. Patients were randomly allocated to the study group (carbamazepine + TENS therapy) or control group (carbamazepine + placebo TENS therapy).

Inclusion criteria

- 1. Patients clinically diagnosed with classical or idiopathic TN (ICHD version 3).
- 2. Patients who had not previously undergone treatment.
- 3. Patients who had stopped TN treatment for the past 6 months.

Exclusion criteria

- 1. Patients who were medically compromised.
- 2. Patients who had undergone any surgical treatment in relation to the areas supplied by trigeminal nerve.
- 3. Pregnant females.
- 4. Hypertensive patients.
- 5. Patients with a pacemaker.
- Patients with trigeminal neuropathy related to other diseases (post-herpetic neuralgia, multiple sclerosis, and abnormalities of the skull base and tumors).

1. Procedure

After obtaining sufficient history and clinical examination, a diagnostic block was administered to localize the affected branch of the trigeminal nerve. All patients underwent MRI to rule out secondary TN, while T2-weighted fluid attenuated inversion recovery MRI sequence was used to identify any mass or lesion in the head and face region. Diffusion-weighted imaging was used to visualize inflammatory changes in the trigeminal nerve. The 3D-FIESTA sequence was used to rule out

a central cause, while a 3D constructive interference in steady state sequence demonstrated thinning of the root entry zone and allowed exact identification of the vascular loop. The required imaging modality was used to rule out odontogenic pain. Patients who fulfilled the inclusion criteria were included in the study. All patients were evaluated for the following parameters at baseline:

- Pain intensity reported on visual analog scale VAS score (0 - 10) - patients were asked to mark their level of pain from 0 (no pain) to 10 (worst pain) on the case recording sheet.
- Present pain intensity on the PPI scale (0 5) patients were asked to score their pain from 0 (no pain) to 5 (excruciating pain).
- Short-form McGill Pain Ouestionnaire 2 (SF-MPQ2) score (0 - 10) - assesses the quality or type of pain that the patient was suffering from, which was scored from (0) no pain to (10) worst pain.
- Functional outcome score (0 10) patients were asked about how their daily activities are affected by their pain. It was recorded at subsequent sittings to determine whether treatment was resulting in any pain relief while performing daily activities.

Twenty-six patients were randomly assigned to each group. Baseline parameters were evaluated by an independent observer who was not involved in the treatment of the patient and who was unaware of the group allocation. Patients in the study group were given TENS therapy at 100 Hz in continuous mode and intensity according to the patients' tolerance for 20 mins biweekly for 6 weeks. Carbamazepine was prescribed along with TENS at an initial dose of 100 mg BD (200 mg), which was titrated with additional 100 mg every 48 h until the patient achieved complete relief or reached the maximum tolerable dose. In the control group, all parameters were the same except for the intensity of the TENS therapy, which was kept at zero.

After the maximum or maximum tolerated dose of carbamazepine was reached, a second line drug,

gabapentin, was added to achieve pain relief wherever required. All parameters were recorded at baseline, re-evaluated at TENS completion and at 3 months, 6 months, and 1 year follow up by the same observer, who was blinded to the allocation of the patients (Figure 1).

2. Statistical analysis

A sample size of 26 patients in each group was calculated at an alpha level of 0.05, 80% power. The normality of the data distribution was determined using the Shapiro-Wilk test. Data on the mean carbamazepine dose, mean VAS score, mean PPI score, and proportion of functional outcomes were found to be non-normally distributed in both groups. Non-parametric analyses were applied to the respective variables. One-way ANOVA and Kruskal-Wallis tests were applied for intragroup comparison of variables, while intergroup comparisons were performed using the Mann-Whitney U test and independent t-test between the two groups. The chi-square test was used to analyze categorical data.

RESULTS

A total of 52 patients, with ages ranging 28 - 95 years (mean age, 56 years) were included in the study. Mean age, sex distribution, trigeminal nerve division involvement, side involvement, and mean number of trigger zones between both groups were not significantly different (Table 1).

1. Parameter evaluation in intragroup follow up visits

Intragroup change in the mean dose of carbamazepine, mean VAS score, and mean PPI score

There was a statistically significant decrease in VAS score from baseline to 1 year follow up in both groups. A non-significant decrease in the mean dose of carbamazepine and PPI score from TENS completion to 1 year follow up was also observed.

Further, there was a decrease in the percentage of patients with pain during functional activities from

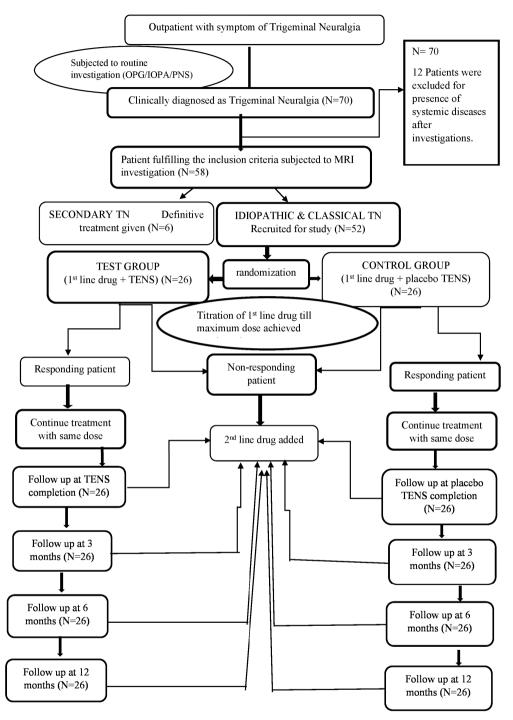


Fig. 1. Flowchart representation of recruitment and treatment plan of trigeminal neuralgia patients

baseline to 1 year follow up, which was found to be statistically significant in both groups (P < 0.001).

2. Parameter evaluation in study group versus control group (intergroup) on follow up visits

Study group versus control group comparison of mean

dose of carbamazepine at different visits

The difference in the decrease of mean carbamazepine dose on intergroup comparison was statistically significant at TENS therapy completion (P < 0.006), 6 months follow up (P < 0.012), and 1 year follow up (P < 0.009), but non-significant at 3 months follow up (P < 0.009)

Table 1. Demographic representation of the data

		Study Group	Control Group	P VALUE	
Sample (n)		26	26		
Age (Yr)		54.3	56.7	0.527#	
Gender	М	10	15	0.165#	
	F	16	11	0.103#	
	V1,V2,V3	0	1		
Division involved	V2	17	10	.136#	
Division involved	V2,V3	0	2	.130#	
	V3	9	13		
Side involved	Right	22	16	0.061#	
Side ilivoived	Left	4	10	0.001#	
Number of trigger zones (mean ± SD)		5.27 ± 2.308	4.88 ± 2.197	0.541#	

[#] Statistically non-significant

Table 2. Intergroup comparison of mean carbamazepine dose at different visits

Means dose of carbamazepine	Study group (Mean \pm SD)	Control group (Mean ± SD)	P value
Baseline	$200.00 \pm .000$	$200.00 \pm .000$	1.00#
TENS completion	430.77 ± 197.523	586.54 ± 174.102	.006*
3 months follow up	469.23 ± 193.431	540.38 ± 173.216	.157#
6 months follow up	384.62 ± 182.630	509.62 ± 166.144	.012*
1 year follow up	376.92 ± 179.572	501.92 ± 156.512	0.009*

^{*}Statistically significant, #Statistically non-significant

Table 3. Intergroup comparison of mean VAS scores at different visits

Means VAS score	Study group (Mean ± SD)	Control group (Mean ± SD)	P value
Baseline	8.69 ± 1.123	8.88 ± .711	.673#
TENS completion	1.23 ± 1.632	2.12 ± 2.917	.458#
3 months follow up	1.46 ± 2.626	1.00 ± 2.059	.655#
6 months follow up	0.23 ± 0.652	0.50 ± 1.175	.421#
1 year follow up	0.54 ± 1.749	0.35 ± 1.231	.655#

[#] Statistically non-significant

> 0.05) (Table 2).

- Study group versus control group comparison of mean VAS scores at different visits

The difference in mean VAS scores between both groups was not statistically significant at all time intervals. (Table 3).

- Study group versus control group comparison of mean PPI scores at different visits

Similarly, the difference in the mean PPI score between both groups was not statistically significant at all time intervals. (Table 4)

- Study group versus control group comparison of functional outcome percentage at different visits

Functional outcomes were also not statistically significant between the two groups (Table 5).

DISCUSSION

TN is an uncommon disease with a prevalence of 100 - 200 cases per 100,000 people. The reported annual incidence of TN has varied among studies, ranging from

SD, Standard deviation; V1, Ophthalmic branch of the trigeminal nerve; V2, Maxillary division of the trigeminal nerve; V3, Mandibular division of the trigeminal nerve.

SD, Standard deviation; TENS, Transcutaneous electrical nerve stimulation.

SD, Standard deviation; TENS, Transcutaneous electrical nerve stimulation; VAS, Visual analog scale.

Table 4. Intergroup comparison of mean PPI scores at different visits

Means PPI score	Study group (Mean ± SD)	Control group (Mean ± SD)	P value
Baseline	$3.58 \pm .857$	$3.69 \pm .679$.390#
TENS completion	0.42 ± .857	0.92 ± 1.354	.171#
3 months follow up	0.73 ± 1.343	0.62 ± 1.203	.736#
6 months follow up	0.08 ± .392	0.42 ± .902	.083#
1 year follow up	$0.23 \pm .863$	0.15 ± 0.543	0.968#

[#] Statistically non-significant

Table 5. Intergroup comparison of functional outcome percentage at different visits in the study and control group

		Baseline	TENS completion	3 months	6 months	1 year follow up	P value
Eating & Drinking —	Study	26	12	9	7	2	0.0001*
	Control	25	14	7	5	2	
Brushing/Rinsing —	Study	23	10	7	1	0	0.0001*
	Control	24	10	6	4	2	
Washing face —	Study	22	9	6	2	2	0.0001*
	Control	22	10	5	4	3	
Sleeping	Study	9	2	1	0	0	0.0001*
	Control	15	5	3	2	0	
Speaking —	Study	24	9	8	2	1	0.0001*
	Control	20	11	4	4	2	
Shaving	Study	13	5	4	2	1	0.0001*
	Control	8	6	2	1	0	
Air blast —	Study	19	6	5	2	2	0.0001*
	Control	17	10	6	3	1	

^{*}Statistically significant

TENS, Transcutaneous electrical nerve stimulation.

4.3 to 27 new cases per 100,000 people per year [6]. In most previous studies, TN has been more frequently reported in female patients [6-10]. Of the 52 patients in this study, 27 were male (51.9%) and 25 were female (48.1%). Only one recent study concurs with our finding of male predominance (55% male and 45% female) [11].

In the current study, the average age of the patients was 56 years (range, 28 – 95 years), with a mean patient age of 54.3 in the study group and 56.7 in the control group. This supports the evidence from previous studies that TN is more common in the older population [7.9-11].

We also found that the right side of the face was more frequently involved than the left in both groups, which is consistent with the findings of other studies [6,7,9,10,12]. Neto et al. hypothesized that the propensity of TN to be present on the right side of the face may be caused by entrapment of the second and third divisions

of the trigeminal nerves when crossing the foramen ovale, which is narrower on the right side of the human skull [13].

The maxillary (V2) (51.9%) division was more frequently involved than the mandibular (V3) (42.3%) division, both V2 and V3 (3.8%), and all three branches (1.9%). Some of the previous studies also favor the preponderance of V2 involvement [6,11,14], while others found that V3 was the most frequently involved branch [7,8,10,15]. However, all studies concluded that the combination of two or three divisions was less prevalent, as seen in this study. Kerr proposed a mild, permanent pulsatile contact of the carotid artery with the ventral surface of the V2 and V3 divisions of the trigeminal nerve [16]. This could explain the involvement of the V2 and V3 branches. In this study, we did not encounter any patient with ophthalmic division, which could perhaps be

PPI, Present pain intensity; SD, Standard deviation; TENS, Transcutaneous electrical nerve stimulation.

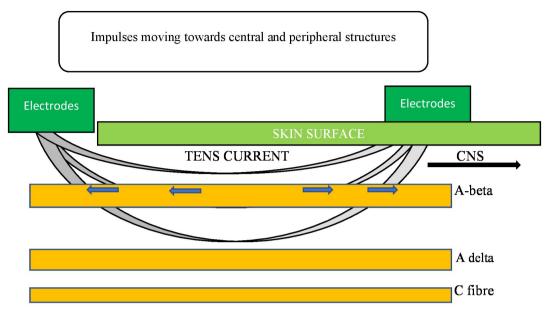


Fig. 2. Mechanism of conventional transcutaneous electrical nerve stimulation

explained by the fact that such patients are more likely to visit medical departments other than the orofacial pain clinic.

The etiopathogenesis of TN is not yet established. However, neurovascular compression of the central axons of the TN at or near the dorsal root entry zone of the nerve and a few secondary diseases associated with traumatic compression result in focal [17] and nerve demyelination leading to ephaptic transmission of impulses has been proposed to be the underlying cause of pain [18].

MRI of the brain and face is useful for differentiating between classical, idiopathic, and secondary TN by ruling out MS, tumors, cysts, or other causes of secondary TN. Therefore, all patients underwent MRI prior to recruitment in order to rule out secondary TN. Hence, only classical and idiopathic TN cases were included in this study.

The characteristic or quality of pain was analyzed using the SF-MPQ2, which showed that all patients experienced electric shock-like, sharp, and shooting pain, while few felt a burning type of pain.

The analgesic effect of TENS is based on two main theories:

1. Gate control theory

TENS-achieved pain control occurs as a result of an increase in large fiber input and a decrease in small fiber input, thus closing the pain gate [19] (Fig. 2).

2. Endogenous opioid theory

TENS stimulates the release of endogenous opioids in the spinal cord, which could result from the activation of local circuits within the spinal cord or from the activation of descending pain-inhibitory pathways [20]. Very few studies are available regarding the use of TENS therapy for TN [3,4,5]. Moreover, these studies lacked clarity in the study design, and did not have a control group. Further, none of the above mentioned studies ruled out secondary TN, and inclusion criteria were variable. Instead, they included patients who were either refractory, had partial relief with medication, or had intolerance to the drug. In addition, there was ambiguity regarding the medicines prescribed simultaneously during TENS therapy. Finally, unlike in previous studies, and for ethical reasons, our study used TENS therapy as an adjuvant rather than first line treatment.

In this study, patients were recruited into two groups: the study group received TENS + medicine (carbamazepine as first line drug) and the control group received placebo TENS + medicine (carbamazepine as first line drug). TENS was administered biweekly in continuous mode for 6 weeks according to previous studies, while considering patient compliance [4,21].

The mean decrease in VAS score was statistically significant on intragroup comparison and non-significant on intergroup comparison from baseline to 1 year follow up, which was in accordance with the findings of Singla et al. and Yameen et al. [3,4]. At 3 months follow up, the VAS score was found to be increased as some patients had stopped taking the medications on their own due to having achieved pain relief. The mean PPI score was not statistically significant in intragroup or intergroup comparisons.

The percentage decrease in pain-related functional outcome was statistically significant (P < .001) from baseline to 1 year follow up on intragroup comparison but non-significant on intergroup comparison. Patients were able to perform their routine activities comfortably with less or no pain. The results concurred with those reported by Singla et al. [3].

An initial symptomatic relief of pain was observed during the titration phase only. The decrease in the mean dose of carbamazepine was not statistically significant from baseline to 1 year follow up within the groups. However, intergroup comparison showed a statistically significant decrease in the dose at TENS completion and at 6 months and 1 year follow up in the study group compared to the control group. At 3 months follow up, the results were not statistically significant due to the cessation of medications by patients who had achieved pain relief after TENS completion.

This study was the first randomized double-blind controlled study to compare TENS with placebo TENS therapy for the management of TN patients diagnosed using the ICHD (2018) criteria; patients underwent an MRI to rule out secondary TN. This study was also the first to evaluate PPI score, which is more reliable. Functional outcomes were also evaluated, as TN affects the routine activities of patients. However, this study has some

limitations. This study had a small sample size, and the follow period was 1 year, which is considered a short-term follow up for chronic and long-lasting disorders such as TN. Further, several clinical trials have concluded that TENS has initial benefits that decrease with time, and TN may also undergo spontaneous regression episodes over the said period. Therefore, longer follow up periods are required. Moreover, daily, rather than biweekly administration of TENS can lead to better results, but daily visits to the clinic were not possible for most of the patients. Another limitation of this study is that the intensity of TENS could not be standardized, as it depended on the patient's ability to bear the electric sensations. In this study, five patients in the study group stopped taking the medicine carbamazepine when pain relief was achieved, which may have led to inconsistent results at the 3 months follow up. However, this factor was not controlled. Finally, the electrodes used in this study were not specifically designed for the facial skeleton; hence, inaccurate placement of electrodes may occur in some cases, which may have affected the outcome.

In conclusion, within the limitations of the study, it may be concluded that TENS is a safe, cheap, non-invasive, and convenient technique that can be used to reduce the mean dose of carbamazepine when used as an adjunct therapy to medication. However, TENS cannot be proposed as a first line management for TN.

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