Original Article

A Clinical Study on Comparative Evaluation of the Effectiveness of Carbamazepine and Combination of Carbamazepine with Baclofen or Capsaicin in the Management of Trigeminal Neuralgia

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Abstract

Background: Trigeminal neuralgia (TN) is characterized by recurrent attacks of lancinating pain in the trigeminal nerve distribution. Various medicinal and surgical procedures have been utilized for the treatment of TN. Over the time, several drugs other than carbamazepine have been used but none of them have shown satisfying results. **Objective:** The objective of the study is to evaluate the effectiveness of carbamazepine and combination of carbamazepine with baclofen or capsaicin in the management of TN. **Materials and Methods:** A total of 45 patients diagnosed with TN were randomly divided into three groups. The patients were prescribed carbamazepine in Group 1, carbamazepine and baclofen in Group 2, and carbamazepine and capsaicin in Group 3. All the patients were followed on the 7th day, 15th day, and 1-month period to evaluate the response to the drugs. Data were subjected to statistics. **Results:** The results are composed of a total of 45 patients (15 in each group). The mean visual analogue scale scores were calculated for each group at day 0, 7th day, 15th day, and 30 days, and it was found that there was statistically significant reduction of pain ($P < 0.001$) in all the three groups at different intervals. At day 7, comparative percentage reduction of pain in both groups was not statistically significant. At 15-days and 30 days, percentage change in pain reduction in Group 1 was 42.3% and 48.0% respectively and in Group 2 it was found to be 60.3% and 83.4%, respectively. The reduction in pain percentage was found to be statistically significant. Similarly, Group 1 was compared to Group 3, significant reduction of pain was found for carbamazepine-capsaicin combination at 30-day interval but the comparative reduction of pain at 7th day and 15th day was not statistically significant. **Conclusion:** Carbamazepine in combination with baclofen is more efficient and effective in reducing pain in TN patients, followed by carbamazepine-capsaicin combination compared to carbamazepine alone.

Keywords: *Baclofen, capsaicin, carbamazepine, therapeutic effectiveness, trigeminal neuralgia*

Introduction

Trigeminal neuralgia (TN) also known as "tic douloureux" is considered to be one of the most severe forms of pain in the human experience. It is a unilateral facial pain syndrome characterized by paroxysmal, brief electric shock-like pain attacks, which are abrupt in onset and located in the somatosensory distribution of the one or more divisions of the trigeminal nerve.[1,2]

According to the International Headache Society, TN can be classified as classical or idiopathic TN in

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which no cause of the symptoms is known except the neurovascular conflict and the symptomatic TN where identifiable underlying cause is responsible for the symptoms. Maxillary branch of trigeminal nerve is most frequently involved followed by the mandibular and ophthalmic branch.[1,3]

Growing neurosurgical data advocate a more specific new classification to differentiate TN into Type 1 defined by >50% episodic onset of TN pain and Type 2 defined by >50% constant pain.[4,5] It has also been theorized that TN type 1 can progress toward TN type 2.[6,7] The prevalence of TN in the general population is 0.015% approximately. Annual incidence is approximately 5/100,000, with a slight female preponderance, usually occurring typically after the fifth decade of life.[7,8]

As TN manifests with the severest possible pain, the proper management of the patients become a responsibility for the oral physician. According to 2008 guidelines of the American Academy of Neurology-European Federation of Neurological Societies, medical therapy must be started immediately after the TN is being diagnosed and surgical options are to be considered whenever there is failure to respond to the medicinal therapy.[9]

Various medicinal therapeutic agents have been known to be effective in controlling the symptoms in TN where carbamazepine and oxcarbazepine are recognized as the first-line therapy. The other pharmacotherapeutic agents used in the management of TN include baclofen, lamotrigine, gabapentin, pregabalin, topiramate, phenytoin levetiracetam, and botulinum toxin-A and capsaicin.

Since anticonvulsants have remained the mainstay of pharmacological treatment of TN this clinical study was undertaken to evaluate the effectiveness of established first-line drug carbamazepine alone and in combination with the alternative therapies such as baclofen and newer drug capsaicin.

Materials and Methods

This study was undertaken in the Department of Oral Medicine and Radiology in a Reputed Dental College, Hospital and Research Institute in Uttar Pradesh, India. A prospective randomized clinical trial was carried out with a total of 49 patients who met the inclusion criterion given below. Before undertaking the study, the ethical clearance was obtained from the ethical committee.

Inclusion criteria

A detailed clinical history and examination was done for all the patients. The diagnosis of idiopathic TN was made by a trained oral physician according to the diagnostic criteria of the International Headache Society guidelines [Table 1].

After diagnosis, all the individuals were explained about the study and a signed institutional approved informed consent was taken.

The patients were afterward randomly divided into three groups for the drug therapy irrespective of age, sex, caste, etiologic factors, division of trigeminal nerve involved, duration and intensity of pain, and side of the face affected. Patients who were already on drugs for the same pain (carbamazepine and anti-inflammatory drugs) were also included in the study.

1. Group 1: Carbamazepine in the dose range of 600–800 mg/day in divided doses
2. Group 2: Carbamazepine 600 mg/day plus baclofen 10–20 mg/day in divided doses
3. Group 3: Carbamazepine 600 mg/day plus capsaicin 0.25%.

Exclusion criteria

The patients with reported severe systemic illness, any odontogenic pain, and temporomandibular disorders were excluded from the study. Patients who were unable to come for periodic follow-up were also excluded from the study.

Methodology

The medications were prescribed to the patients according to the group they were assigned randomly. For the future

Table 1: International Headache Society diagnostic criteria for trigeminal neuralgia

Classical
Paroxysmal attacks of pain lasting from a fraction of a second to 2 min, affecting one or more divisions of the trigeminal nerve, and fulfilling Criteria B and C
Pain has at least one of the following characteristics
Intense, sharp, superficial, or stabbing
Precipitated from trigger zones or by trigger factors
Attacks are stereotyped in the individual patient
There is no clinically evident neurologic deficit
Not attributed to another disorder
Symptomatic
Paroxysmal attacks of pain lasting from a fraction of a second to 2 min, with or without persistence of aching between paroxysms, affecting one or more divisions of the trigeminal nerve, and fulfilling Criteria B and C
Pain has at least one of the following characteristics
Intense, sharp, superficial, or stabbing
Precipitated from trigger zones or by trigger factors
Attacks are stereotyped in the individual patient
A causative lesion, other than vascular compression, has been demonstrated by special investigations and/or posterior fossa exploration

reference, the pain was recorded on the day 0 of the treatment using the psychometric response scale, i.e., visual analog scale (VAS). A horizontal line, 100 mm in length with description stating no pain on the left hand end and very severe pain on the right hand end of the line was used. The patients marked the point on the line that they felt represented their current state of pain. The VAS score was determined by measuring in millimeters from the left hand end of the line to the point that the patient marks.[10]

The patients were recalled for posttreatment assessment of response to drugs after 7 days', 15 days', and 30 days' period. The review of response to the drugs was done by VAS in the subsequent visits by another physician who was blind about the patients as well as the drugs used.

The response of the patients to therapeutic effectiveness of the drug was decided based on percentage reduction of pain. The side effects were also recorded for all the patients. The data thus collected were subjected to statistical analysis where percentage reduction of pain was calculated, and Mann–Whitney test was applied to compare the effectiveness of drugs between different groups.

Results

A total of 49 patients were diagnosed and prescribed the drugs which included 16 patients in Group 1, 17 in Group 2, and 16 in Group 3. Of these patients, four patients did not report for follow-up, and thus the results are composed of a total of 45 patients (15 in each group). The minimum age of the patient in the study was observed to be 48 years, and the maximum age was 80 years. Out of the total sample size of 45, it was found that 27 (60%) patients were females and 17 (40%) were males [Table 2].

In Group 1, i.e., carbamazepine group, out of 15 patients, four patients were old patients who were already undergoing treatment for the pain and were on medications). In Group 2 and Group 3, the number of old patients were 5 and 3, respectively [Table 3]. The side effects were observed in 2 patients in Group 1 and 3 patients each in Group 2 and Group 3 [Table 3].

The mean VAS scores were calculated for each group at day 0, 7th day, 15th day, and 1 month, which signify that in all the three groups, the drugs prescribed effectively reduce pain in TN patients. NPAR Tests were applied, and it was found that there was statistically significant reduction of pain ($P < 0.001$) in all the three groups at different intervals [Table 4].

For comparative evaluation of drug responses in different groups, the Mann–Whitney test was applied, and the groups were compared to each other. When Group 1 was compared to Group 2, the mean of percentage change in pain at day 7 was 34.6% in carbamazepine group (Group 1) and 43.8% in carbamazepine plus baclofen group (Group 2). Comparative percentage reduction of pain in both groups was not statistically significant thus almost similar reduction of pain at day 7 was observed. At 15-day interval and 1 month, percentage change in pain in Group 1 was 42.3% and 48.0% and in Group 2 was 60.3% and 83.4%, respectively [Table 5]. Therefore, while comparing day 15 and 1 month, it was found that combination of carbamazepine and baclofen (Group 2) is more effective in reducing pain compared to carbamazepine (Group 1) and the results were statistically significant with $P < 0.001$.

Table 2: Distribution of individuals according to age and sex

Patients (*n*=45)	Group 1 (*n*=15)	Group 2 (*n*=15)	Group 3 (*n*=15)
Age range (years)	48-78	49-80	52-79
Mean (years)	63	64.5	65.5
Female/male	8/7	10/5	9/6

Table 3: Distribution of patients in different groups and side effects observed

Total patients (45)	Old cases	New cases	Side effects
Group 1 (15)	4	11	2
Group 2 (15)	5	10	3
Group 3 (15)	3	12	3

Table 4: Response of different drugs in pain reduction based on visual analogue scale

VAS mean	Baseline	7 days	15 days	1 month
Group 1 (15)	9.40	6.20	5.47	4.93
P value day 0 to next interval		0.001**	0.001**	0.001**
Group 2 (15)	9.27	5.20	3.67	1.53
P		0.001**	0.001**	0.001**
Group 3 (15)	9.40	5.93	4.27	2.87
P		<0.001**	0.001**	0.001**

**P< 0.001; VAS: Visual analogue scale

Table 5: Mean values of pain percentage reduction in all groups at different intervals

Group	Intervals	Mean of percentage change in pain	SD
Group 1	0-7 days	34.6667	15.75943
	0-15 days	42.3148	17.15671
	0-30 days	48.0185	18.42775
Group 2	0-7 days	43.8889	11.37969
	0-15 days	60.3519	13.00796
	0-30 days	83.4074	9.74683
Group 3	0-7 days	36.8519	11.06671
	0-15 days	54.8889	16.84848
	0-30 days	69.3704	12.54026

SD: Standard deviation

Table 6: Comparative evaluation of percentage reduction of pain in three groups

Time interval	Group 1 versus Group 2		Group 1 versus Group 3	
	Man-Whitney	*Z*-score	Man-Whitney	*Z*-score
0-7 days	75	−1.569	108	−0.189
P	0.117		0.850	
0-15 days	51	−2.566	68.5	1.837
P	0.001		0.066	
0-30 days	2.5	−4.574	36.5	−3.166
P	0.001		0.002	

Similarly, Group 1 was compared to Group 3, significant increased reduction of pain was found for carbamazepine-capsaicin combination (Group 3) at 1-month interval but the comparative reduction of pain at 7th day and 15th day was not statistically significant comparing both groups [Table 6].

Discussion

It has been recently shown that TN is the most frequent type of facial pain, among facial pain syndromes and shows overall increases in incidence with advancing age. The effectiveness of CBZ has already been demonstrated in several studies in the literature, and it is established as a first-line treatment for TN. Carbamazepine in a dose range of 200–1200 mg/day has been found to reduce both the frequency and intensity of painful paroxysms and was equally efficacious on spontaneous and trigger-evoked attacks.[11,12] On the contrary, there are reports of several cases in literature which are persistent and do not respond to carbamazepine. Hence, this study was undertaken to find the effectiveness of carbamazepine in combination with other drugs as an alternative treatment option.

Persistent or recurrent neuralgia have been found to respond to the GABA receptor agonist Baclofen, either alone or in combination with carbamazepine. Baclofen is initiated at 5–10 mg, two to three times daily and increased by10 mg/day every other day, maximum up to 60 mg/day. It has been shown in double-blind studies to be effective in 70% of patients at doses of 10–60 mg/day.[13]

Capsaicin (Zostrix) a highly selective, potent and high-affinity (in the low-nanomolar range) exogenous agonist for the transient receptor potential cation channel subfamily V member 1 receptors has been successful for treatment of TN pain. Capsaicin has been used in several studies as a treatment alternative for controlling neuropathic pain.[14] Less clinical trials have been done for evaluating its effectiveness when combined with carbamazepine.

In the present study, Group 1 included patients treated with carbamazepine in the divided dose range of 600–800 mg/day. Carbamazepine gave average response at day 7 and day 15 and good response at 1-month follow-up. It was found to be ineffective in 2 patients out of 15 in which there was no or minimum change of pain scores. The side effects such as sedation, dizziness, nausea, vomiting were observed in two patients. The results in the present study are in accordance with several studies in literature where carbamazepine was found to be effective in approximately 70%–80% of the patients.[11,15,16]

To date, baclofen has the strongest scientific evidence for efficacy in the treatment of TN next to carbamazepine. Thus, baclofen combined with carbamazepine was given to Group 2 patients, and it was found that this combination is most effective in treating TN as compared to medications in other groups. Parekh *et al*. reported a putative synergistic effect when baclofen is combined with 500 mg/day carbamazepine which is in accordance with the present study. Thus, in cases nonresponsive to carbamazepine alone baclofen can be combined for better management of pain.[17] Studies by Fromm *et al*., Parekh *et al*., and various other authors have also reported high effectiveness of baclofen alone or in combination with carbamazepine in the management of TN.

One patient out of 15 patients in Group 2 (carbamazepine plus baclofen) was nonresponsive to the therapy, thus some alternative medicinal therapy or surgical management was considered for that. Side effects such as nausea, drowsiness, weakness, and constipation were observed for three patients.

In Group 3, oral capsaicin 0.25% was used along with carbamazepine and the combination was found to be more effective in relieving pain than carbamazepine alone but less effective than carbamazepine–baclofen combination. Capsaicin was found to significantly reduce pain in TN in other studies reported in literature, similar to the present study.[14,18] According to a previous study, the capsaicin 8% patch provided non-inferior pain relief to an optimized dose of pregabalin in neuropathic pain, with a faster onset of action, fewer systemic side effects, and greater treatment satisfaction.[18] In our study, minor side effects were observed in two patients in this group which reduced with time, but one patient developed severe gastric toxicity, and the drug was discontinued.

The results completely signify that carbamazepine in combination with baclofen is more efficient and effective in reducing pain in TN patients followed by carbamazepine-capsaicin combination and then carbamazepine alone.

Conclusion

Carbamazepine combined with baclofen is most effective in alleviating pain in TN when compared with carbamazepine alone or carbamazepine-capsaicin combination. Thus, the study recommends that when first-line therapy with the carbamazepine fails, second-line treatment with the addition of baclofen or capsaicin can prove to be effective in the management of TN, but more controlled studies with long-term follow-up are required.

Side effects are also observed in many patients, thus while prescribing any of these medications, the complete blood count, serum sodium, and liver function tests within several weeks after starting therapy is advisable to detect any complications quickly.

Among many diagnostic and treatment options in the management of TN, only very few have proven their efficacy to modern evidence-based medicine standards. More controlled studies with a long-term follow-up are needed to compare different medicinal therapies.

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Conflicts of interest

There are no conflicts of interest.

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