EVALUATION OF THE EFFICACY OF CARBAMAZEPINE AND GABAPENTIN IN THE MANAGEMENT OF TRIGEMINAL NEURALGIA: A CLINICAL STUDY

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ABSTRACT
Background: Trigeminal neuralgia (TN) is a syndrome of unilateral, paroxysmal, stabbing facial pain, originating from the trigeminal nerve. Carbamazepine still remains as the gold standard drug in terms of efficacy in TN. Over the time, several other drugs are also used as alternatives for TN such as oxcarbazepine, baclofen, lamotrigine, levetiracetam, gabapentin, valproate, botulinum toxin A injection. Objective: To Evaluate the efficacy of Carbamazepine and Gabapentin in the management of Trigeminal Neuralgia. Materials and Methods: A total of 42 patients with a mean age of 52.78 years included in the study were randomly divided into two groups A and B and were given the tablets of carbamazepine in the dose range of 400mg to 1200 mg and gabapentin in the dose range of 600mg to 1800mg and recalled after 3rd day, 15th day, 1 month and 3 month period to evaluate the response to the drugs. The collected data was subjected to statistical analysis. Results: The therapeutic effectiveness of carbamazepine recorded as good response in 52.38% of patients of group A after 72 hours of recall while 42.8% patients had an average response. The therapeutic effectiveness of gabapentin recorded as good response in 52.38% of group B patients after 72 hours of recall while 42.8% patients had an average response at the dose of 600mg of gabapentin. Conclusion: The study suggests that gabapentin can be effective as first or second line treatment of trigeminal neuralgia, even in cases resistant to traditional treatment modalities.

KEYWORDS: Carbamazepine, gabapentin, therapeutic efficacy, trigeminal neuralgia.

INTRODUCTION
The trigeminal neuralgia (TN) is defined as a “unilateral disorder characterized by brief electric shock-like pains, abrupt in onset and termination, and limited to the distribution of one or more divisions of the trigeminal nerve.”[1] According to the International Headache Society, TN can be classified as classical or idiopathic TN and the symptomatic TN.

The criteria for diagnosis of TN are:[1]  
1. Paroxysmal attacks of pain lasting from a fraction of a second to two minutes that affect one or more divisions of the trigeminal nerve  
2. Pain has at least one of the following characteristics: Intense, sharp, superficial, or stabbing which can be precipitated from trigger areas or by trigger factors.  
3. Attacks are similar in individual patients.  
4. No neurological deficit is clinically evident.  
5. Not attributed to another disorder.

Various studies have revealed the global incidence and prevalence of TN, approximately ranging from 4 to 28.9%; usually it occurs in fourth to th decade of life and affects females more commonly than males.[2-5] When severity and frequency of attacks increases with time, chronic preventive treatment is required. According to the 2008 guidelines of American Academy of Neurology-European Federation of Neurological Societies, medical therapy must be started immediately after the diagnoses of TN, and surgical options should be considered whenever there is failure to respond to the medicinal therapy.[6] Pharmacotherapy had little success in the treatment of TN until Bergouignan’s discovery in 1942 that phenytoin was effective in preventing pain paroxysms. Following the introduction of carbamazepine for treatment of epilepsy, controlled trials were published showing its superiority over placebo in TN. Since then, anticonvulsants have remained the mainstay of pharmacological treatment of TN.
Carbamazepine is established as an effective drug for controlling pain in classic or idiopathic TN. Other drugs such as oxcarbazepine, gabapentin, baclofen, phenytoin, lamotrigine, pregabalin, and topiramate can also be used for the treatment of idiopathic TN. This clinical study was undertaken to evaluate the effectiveness of two pharmacological drugs, carbamazepine and gabapentin, in patients with idiopathic TN.

**MATERIALS AND METHODS**

This study was undertaken in the Department of Oral Medicine and Radiology and oral pathology departement. Before undertaking of the study, ethical clearance was obtained.

**Inclusion criteria**

Detailed clinical history and examination was done according to the International Society of Headache guidelines, and diagnosis of idiopathic TN was made. After that every patient’s consent was taken. Previous drug history for the same pain was also taken into consideration.

The physician randomly divided the diagnosed patients into two groups: marked as A and B and numbered them from 1 to 42 for monotherapy drug trial, irrespective of age, sex, caste, etiologic factors, division of trigeminal nerve involved, duration and intensity of pain, and side of face affected.

The carbamazepine 200 mg and gabapentin 300 mg tablets were removed from the strips and stored in packets labeled as X and Y. Another physician giving the tablets and even the patients of both groups were blind about the packets. All the patients were given 6 tablets and each patient was given a dose of 400 mg of carbamazepine and 600 mg of gabapentin initially and was recalled after third day. The dose of the carbamazepine was increased to 800 mg and gabapentin was increased to 900 mg on third day and the patients were recalled after 15th day. The dose of the carbamazepine was increased to 1200 mg and gabapentin to 1800 mg on 15th day, and the patients were recalled after 1 month and 3 months period for review of response to the drugs. Another physician who was blind about the patients as well as the drugs did the review of response. The response of the patients to therapeutic effectiveness of drug was decided based on the frequency of attacks, i.e., good response: no attacks of pain; average response: two to three attacks of pain per day; and nonresponsive with no decrease in the frequency of attacks of pain. The data thus collected by the third physician were handed over to the first physician who had diagnosed and numbered the patients. The collected data were subjected to statistical analysis.

**RESULTS**

A total of 42 patients in the age group 40–68 years, with a mean age of 52.78 years were included in the study. Out of 42 patients, 27 were females and 15 were males. Moreover, 19 patients were already under treatment for TN, taking a dose of carbamazepine ranging from 200 to 800 mg/day. Most of these patients were not taking the medicine regularly [Table 1]. The therapeutic effectiveness of carbamazepine recorded a good response in 52.38% of patients of Group A after 72 h of recall, whereas 28.57% patients had an average response and 19% patients did not get relieve from pain attacks at the dose of 400 mg of carbamazepine. With subsequent increase in the dose of carbamazepine to 800 mg for the nonresponsive patients, average response was observed in 38% of patients and good response in 61.19% of patients after 15 days of follow-up, while 14.28% of patients had the adverse effects such as drowsiness, vertigo, nausea, and vomiting. For further increase in dose from 800 to 1200 mg, 66.66% of patients had good response and 33.33% patients had an average response after 1 month and 3 months of follow-up. But with time, adverse effects have increased from 19 to 28.57% of patients [Table 2].

**Table 1: Distribution of patients in Group A and B**

<table>
<thead>
<tr>
<th>Group</th>
<th>New cases</th>
<th>Old cases</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A carbamazepine (21)</td>
<td>11</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Group B gabapentin (21)</td>
<td>11</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 2: Therapeutic response to the carbamazepine.**

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose</th>
<th>Good response (%)</th>
<th>Average response (%)</th>
<th>Not responsive (%)</th>
<th>Side effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third day</td>
<td>400 mg</td>
<td>11 (52.38)</td>
<td>6 (28.57)</td>
<td>4 (19.04)</td>
<td>-</td>
</tr>
<tr>
<td>15 days</td>
<td>800 mg</td>
<td>13 (61.9)</td>
<td>8 (38.09)</td>
<td>-</td>
<td>3 (14.28)</td>
</tr>
<tr>
<td>First month</td>
<td>1200 mg</td>
<td>14 (66.6)</td>
<td>7 (33.3)</td>
<td>-</td>
<td>4 (19.04)</td>
</tr>
<tr>
<td>Third month</td>
<td>1200 mg</td>
<td>14 (66.6)</td>
<td>7 (33.3)</td>
<td>-</td>
<td>6 (28.57)</td>
</tr>
</tbody>
</table>

**Table 3: Therapeutic response to the gabapentin.**

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose</th>
<th>Good response (%)</th>
<th>Average response (%)</th>
<th>Not responsive</th>
<th>Side effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third day</td>
<td>600 mg</td>
<td>11 (52.38)</td>
<td>9 (42.8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15 days</td>
<td>900 mg</td>
<td>15 (71.4)</td>
<td>6 (28.5)</td>
<td>-</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>First month</td>
<td>1200 mg</td>
<td>18 (85.7)</td>
<td>3 (14.2)</td>
<td>-</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Third month</td>
<td>1800 mg</td>
<td>21 (100)</td>
<td>-</td>
<td>-</td>
<td>2 (9.5)</td>
</tr>
</tbody>
</table>
Gabapentin, a GABA receptor agonist, acts primarily on presynaptic calcium channels of neurons to inhibit the release of excitatory neurotransmitters. Gabapentin has been used in randomized control trials of neuropathic pain and was proven effective. Its use and effectiveness were also reported in several TN studies. Treatment can be started at a dose of 300 mg/day and may be gradually increased by 300 mg every 2-3 days as tolerated. For maximum efficacy, the dose can be increased to 1800 mg/day. Gabapentin has many advantages, including faster titration, no known drug interactions, no known idiosyncratic skin reactions, and a favorable side effect profile, with mild somnolence, dizziness, headache, confusion, nausea, and ankle edema.

In our study, 66.66% of patients had good response to the carbamazepine therapy when dose was increased up to 1200 mg per day in divided doses; on the other side, 100% patients reported with the good response when dose was increased up to 1800 mg per day in divided doses. The adverse effects were observed in 28.57% of patients having 1200 mg of carbamazepine per day, but on the contrary only 9.5% of patients having 1800 mg of gabapentin per day experienced adverse reactions.

A study conducted by Campbell et al. (1966) reveals that the efficacy of carbamazepine is approximately 80% initially and with time higher doses may be needed to maintain efficacy, which declines to approximately 50% of patients due to auto induction of carbamazepine as happened in our study.

A retrospective study conducted by Cheshire WP Jr in 2002 observed effective range of stable daily dose of gabapentin varied from 100 to 2400 mg in three daily divided dosages, with a mean of 930 mg. The pain relief was even sustained in two-thirds of patients during a mean follow-up of 8 months.

A study conducted by Lemos et al. (2008) found that gabapentin showed adequate efficacy alone and in combination with local injections of ropivacaine used to block trigger points in TN patients, which is in accordance with our study. The therapeutic effectiveness of gabapentin was found in the range of 70–100% of patients with increase in dose from 300 to 1800 mg, which was in accordance with other study.

CONCLUSION
The common causes of failure of previous anticonvulsant drug are the development of drug resistance and intolerance. The fact that gabapentin was well-tolerated and without serious side effects is an important advantage when prescribing for elderly patients. Regarding side effects gabapentin is more tolerable than carbamazepine.

Therefore, the present study suggests that gabapentin can be effective as first- or second-line treatment for TN, even in cases of resistant to traditional treatment modalities.

DISCUSSION
TN is one of the most common causes of facial pain seen in dental and neurologic practices. Carbamazepine is usually the first-line therapy for TN, although gabapentin also has shown to be effective in the treatment of this disease. Carbamazepine acts by inhibiting voltage-gated sodium channels and reduces the excitability of neural membranes. It also potentiates gamma amino butyric acid (GABA) receptors made up of α-1, β-2, and γ-2 subunits. In the newly diagnosed cases of TN, the usual starting dose is 100–200 mg twice daily. The daily dose should be increased by 100 mg every other day until relief from pain is attained or until intolerable side effects that prevent further upward titration. The typical total maintenance dose is 300–800 mg/day, which should be given in two to three divided doses. A maximum total dose of 1200 mg/day could be given. The common side effects include sedation, dizziness, nausea, vomiting, ataxia, increase in the level of hepatic enzymes, and hyponatremia, which may contraindicate in elderly patients. The uncommon but serious side effects include leukopenia, aplastic anemia, allergic rash, systemic lupus erythematosus, hepatotoxicity, and Stevens-Johnson syndrome. Therefore, the complete blood count, serum sodium, and liver function tests within several weeks after starting therapy are advisable to detect any complications quickly.

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REFERENCES


