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Comparison of carbamazepine alone and in combination with baclofen in trigeminal neuralgia

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Abstract--Introduction: Trigeminal neuralgia is a type of neuropathic facial pain that is characterized by unilateral paroxysmal pain that affects one or more trigeminal nerve divisions and is brought on by unimportant stimuli. People over the age of 40 are more likely to get it, and women are more frequently affected than males. Trigeminal neuralgia has been treated with a variety of drugs, including carbamazepine, oxcarbazepine, baclofen, lamotrigine, levetiracetam,

gabapentin, sodium valproate, botulinum toxin-A injection, and surgical. OBJECTIVES: The current study's objective was to assess the efficacy of carbamazepine in treating trigeminal neuralgia in individuals both on its own and in combination with baclofen. METHODS: A randomized control trial was conducted at Khyber College of Dentistry and Peshawar Dental College among the patients of trigeminal neuralgia presenting to OPD. Total 60 patients were randomly selected into two groups, each group had 30 patients. Carbamazepine was given to the Group A in the dose range of 300-600mg TDS whereas, Carbamazepine 300mg TDS along with Baclofen in the dose range of 10-20 mg B.D was given to Group B. The two groups were given the drugs for a period of thirty days. The data was collected through a self-structured questionnaire. The numerical rating scale was used to record the pain on the first day of the treatment. After the 7th, 15th, and 30th days, the patients were summoned back for evaluation in order to gauge how well the medications were working. Kruskal-Wallis test was used for statistical analysis. RESULTS: Complete relief from severe pain was observed in the both groups at the end of trial period. However, in the course of decline of severe pain, it was observed that Group B. CONCLUSION: Our study concludes that carbamazepine combined with baclofen is a better option in relieving pain associated with trigeminal neuralgia with showing least adverse drug reaction.

Keywords---Trigeminal, patients. Carbamazepine, Dentistry.

Introduction

People with Trigeminal Neuralgia (TN), also referred to as "Tic Douloureux," suffer from excruciating pain. The incidence of trigeminal neuralgia (TN) ranges from about 4-5/100,000/year and can go up to 20/100,000/year beyond age 60, with a prevalence of 0.1-0.2 per thousand. The ratio of women to men is roughly 3:2(1). The analysis of many case series reveals that the right side is more predominately affected by pain. Epidemiological research has revealed that glossopharyngeal neuralgia (GN), which has an incidence of 0.7/100,000 per year, is less severe than previously believed(2). The incidence of post-herpetic neuralgia and idiopathic TN are similar. Incidence of TN in the US population was 4.3 per 100,000, with a considerably greater(3). Stage estimates that the annual predictable incidence of TN increases from 4 to 12.5 per 100,000 people(4).

A variety of mechanisms, such as peripheral root pathology (compression or traction), dysfunction of the brainstem, basal ganglia, and cortical mechanisms of pain modulation, and dysfunction of peripheral root pathology are all potential contributors, neurovascular conflict is the most widely accepted theory (5). A characteristic of TN is recurrent attacks of lancinating pain in the region where the trigeminal nerve(3). The pain normally last a few seconds, but can happen repeatedly in a short period of time. 79 percent of pain is intermittent, only 21 percent of it is continuous(6).

There are numerous pharmacological treatments and surgical techniques available. Both approaches work well and are frequently used(6). Patients with TN are typically first treated with pharmacological agents. In around 80% of patients, pain can be easily controlled with medication(7, 8).

For their combined effects in reducing the symptoms of TN, several medications are occasionally administered with carbamazepine(9). The need to stop therapy may arise from the diminishing relief offered by carbamazepine or other medications with continued usage, as well as from undesirable side effects. Actually, it has been stated that about 50% of patients eventually need surgery to ease discomfort(10, 11).

Numerous medications used in the management and treatment of TN are linked to a number of adverse effects. However, the majority of the effects are tolerable, and when the average pain threshold is exceeded, the drug is stopped immediately(11).

Carbamazepine, is an anticonvulsant and analgesic medication used to treat trigeminal neuralgia pain and control seizures. The FDA initially authorized it in 1965. This medication is also used to manage bipolar disorder symptoms(12). Baclofen ($C_{10}H_{12}ClNO_2$) Gamma-aminobutyric acid (GABA) agonist and is used to relax skeletal muscles. It was initially launched in 1962 to treat epilepsy, however research has revealed that it is more beneficial in reducing spasticity in some people(13). In order to treat spasticity, baclofen was once again introduced in 1971, and the FDA later approved it in 1977(14).

In our community not only the rising resistance against Carbamazepine but also postsurgical complications of trigeminal neuralgia raise a dire need for the other treatment options. So this clinical study has been designed to evaluate the effectiveness of two Pharmacological drugs Carbamazepine, and Baclofen in patients with idiopathic Trigeminal neuralgia, the aim of this study is to find some robust synergistic combinations for better medical treatment of TN. The objective of study is to assess the efficiency of carbamazepine alone versus carbamazepine plus baclofen in treating trigeminal neuralgia-related pain.

Methodology

A randomized control trial was conducted at Khyber College of Dentistry and Peshawar Dental College among the patients of trigeminal neuralgia presenting to OPD. The inclusion criteria of study include all the patients diagnosed with Trigeminal Neuralgia reporting to OPDs of Oral Medicine Department of Khyber College of Dentistry and Peshawar Dental College, Patients between the ages of 45-65 years, Both male and female patients, Paroxysmal pain assaults that can last anywhere from a nanosecond to two minutes and impact one or more trigeminal nerve divisions., One or more of the following forms of pain (intense, sharp, superficial, or stabbing)., Induced by triggering stimuli or precipitated from trigger zones, Stereotyped attacks on the specific patient, With no clinically obvious neurological impairment, Pain not to be attributed to any other disorder and the exclusion criteria Pregnant women, Patients with severe systemic illness like congestive heart failure and liver disease, Odontogenic pain,

Temporomandibular disorders, Patients who are not able to attend scheduled follow-up appointments. After taking ethical approval from ethical review board of Peshawar Medical College and Khyber College of Dentistry, the patients fulfilling the inclusion criteria were enrolled in this study. The data was collected from the study subjects from October 2021 to July 2022. Two groups of patients were created at random. Total 90 patients were randomly selected into two groups, each group had 30 patients. The following drugs were recommended to the patients for a period of thirty days, per the group:

Group A: Using carbamazepine between 300 and 600 mg TDS.

Group B: Carbamazepine 300mg TDS plus Baclofen in the dose range of 10-20mgB.

The Randomization was carried out by third person through a lottery method. In this method, the different group names were written on different slips of paper. These slips were identical in shape, size and colour. The slips were folded up and placed in a container which later were mixed up. From the container, the number of slips equal to the desired size of the sample were chosen at random. In this method, there is no partiality or prejudice against the selection of any unit of the population(15).

The data was collected through structured questionnaire. It consisted of demographic variables and variables related to trigeminal neuralgia like pain, frequency, trigger zone. On day 0 of the treatment, the pain was reported using a numerical rating scale(16).

The description was a horizontal line (0–10) in length, with little discomfort on the left end and extremely intense pain on the right. The point on the line that best captured the patients' current level of discomfort was marked by the patients. The ordinal Numerical Rating Scale was used to calculate the score. All the patients were ensured about their medicine intake through a proper chart. After a period of seven days, fifteen days, and thirty days, the patients were called back for assessment of drug response. Another doctor who was unaware of the patients and the medications used in the subsequent appointments evaluated the patients' reaction to the medications using a numerical rating system(17).

Statistical Analysis:

The statistical package for social sciences was used to enter and analyse the data (SPSS version 21). Descriptive data was expressed as frequencies and percentages, as the data was skewed so Kruskal-Wallis test was applied to compare difference between the groups. Statistical significance was defined as a p-value of 0.05 or less.

Result

In the present study the total 90 patients were included, out of which 46.7% were male and 53.3% were females. There were 30 patients in each group. Group A

(Carbamazepine alone), Group B (Carbamazepine + Baclofen) and the mean age was 54.91 ± 6.44 .

At baseline, all 90 patients had pain frequency of more than four times a day as shown in **Table 1**.

In Group A, the number of patients with pain frequency of more than four times a day decreased to 30.0% at the first visit, 13.3% at the second visit, and 0.0% at the third visit.

In Group B, the number of patients with pain frequency of more than four times a day decreased to 30.0% at the first visit, and 0.0% at the second and third visits.

Table 1: Distribution of pain frequency in Group A, B and C at day 0, 7th, 15th and 30th

	Pain perception	GROUP A		GROUP B	
		n	%	N	%
Day 0	More than four times a day (7-10)	30	100.0	30	100
Day 7th (First Visit)	No pain (0)	0	0.0	0	0.0
	Two times a day (1-3)	0	0.0	0	0.0
	Three times a day (4-6)	21	70.0	21	70
	More than four times a day (7-10)	9	30.0	9	30.0
Day 15th (Second Visit)	No pain (0)	0	0.0	0	0.0
	Two times a day (1-3)	6	20.0	10	33.3
	Three times a day (4-6)	20	66.7	20	66.7
	More than four times a day (7-10)	4	13.3	0	0.0
Day 30th (Third Visit)	No pain (0)	1	3.3	1	3.3
	Two times a day (1-3)	8	26.7	23	76.7
	Three times a day (4-6)	21	70.0	6	20.0
	More than four times a day (7-10)	0	0.0	0	0.0

Distribution of pain severity among the experimental groups. When we observed the severity of pain by numerical rating scale (NRS) among Groups A, B and C and it was observed that at baseline all study subjects had severe pain (7-10).

At 1st follow-up 33.3% in Group A, 16.7% in Group B had severe pain. At 2nd follow up 26.7% of participants in Group A had severe pain whereas there was no severe pain in group B. At 3rd follow-up in two study groups there was no severe pain as shown in **Table 2**

Distribution of pain severity in Group A, B and C at day 0, 7th, 15th and 30th. When we observed the severity of pain by numerical rating scale (NRS) among Groups A, B and C and it was observed that at baseline all study subjects had severe pain (7-10).

At 1st follow-up 33.3% in Group A, 16.7% in Group B had severe pain. At 2nd follow up 26.7% of participants in Group A had severe pain whereas there was no severe pain in group B. At 3rd follow-up in all the three study groups there was no severe pain as shown in **table 2**.

Table 2: Distribution of pain severity in Group A, B and C at day 0, 7th, 15th and 30th

		GROUP A		GROUP B	
	Pain severity according to numerical rating scale (NRS)	n	%	N	%
Day 0	Severe (7-10)	30	100.0	30	100
Day 7th (First Visit)	No pain (0)	0	0.0	0	0.0
	Mild (1-3)	0	0.0	0	0.0
	Moderate (4-6)	20	66.7	25	83.3
	Severe (7-10)	10	33.3	5	16.7
Day 15th (Second Visit)	No pain (0)	0	0.0	0	0.0
	Mild (1-3)	2	6.7	10	33.3
	Moderate (4-6)	20	66.7	20	66.7
	Severe (7-10)	8	26.7	0	0.0
	No pain (0)	7	23.3	10	33.3
	Mild (1-3)	11	36.7	13	43.3

Day 30th (Third Visit)	Moderate (4-6)	12	40.0	7	23.3
	Severe (7-10)	0	0.0	0	0.0

When we compared the number of patients with complete pain relief among the groups, it was observed that Group B were significantly better than Group A.

Table 3

Groups	Number of patients with total pain relief at day 30th	Percentage of patients with total pain relief at day 30th	P—Value
Group A	7	23.33%	0.019*
Group B	10	33.33%	

Discussion

Trigeminal neuralgia has been found to be the most prevalent form of facial pain syndrome, with incidence rates generally rising with advancing age. Compared to other neuropathic pain syndromes, trigeminal neuralgia responds more favorably to medication treatment. The effectiveness of carbamazepine has previously been established in numerous studies, and it is frequently used as a first-line therapy for TN(18). This research was done to find out whether carbamazepine works well when combined with other medication as a different therapy option.

In the present study, a total of 90 patients with mean age of 54.91 ± 6.44 were included, 46.7% were male and 53.3% were female. There were 30 patients in each group. Group A was given carbamazepine alone, Group B carbamazepine plus baclofen.

We observed in our study that at baseline, all the patients had pain frequency of more than four times a day. In Group A (carbamazepine alone), the number of patients with pain frequency of more than four times a day decreased to 30.0% at the day 7, 13.3% at the day 15, and 0.0% at the end of the trial, In Group B (carbamazepine plus baclofen), the number of patients with pain frequency of more than four times a day decreased to 30.0% at the day 7, and 0.0% at day 15 and day 30. These findings are consistent with another study conducted by Nidhi P. et al., who examined the groups and discovered that the carbamazepine group's mean percentage change in pain frequency at day 7 was 34.6%, but the carbamazepine plus baclofen group's was 28.8%(1).

Another study done by KA Baker et al., also goes in favor of our study. They observed the comparative percentage reduction in pain frequency in two groups. There results were significantly better in carbamazepine plus baclofen group as compared to carbamazepine alone group. An almost identical reduction in pain was observed on day 7. Later on, however, the percentage change in pain in the

carbamazepine group was 42.3% and 48.0%, respectively, as opposed to 20.3% and 18.4% in the carbamazepine plus baclofen group at 15th and 30th day intervals(1, 19).

A systematic review by Nova, Zakrzewska et al., in 2020 summarized that pain frequency of trigeminal neuralgia can be reduced by using a definite treatment with antiepileptic or in combination with other drugs such as baclofen, botulinum toxin A injection and capsaicin(20).

The G H Fromm et al. also concluded that Baclofen reduced the number of painful paroxysms in patients with trigeminal neuralgia. The findings suggest that baclofen is an effective treatment for trigeminal neuralgia. Another previous study by Swaim et al. showed similar findings via a clinical trial on patients with trigeminal neuralgia. Out of 20 patients treated with baclofen drug, 45% had no pain attacks, while 20% had their pain intensity, and the number of attacks reduced by half as compared with baseline(21). Another investigation by Puri et al. showed that baclofen and carbamazepine 500 mg/day worked well together, which is what this study found as well (22).

In our study we compared the number of patients with complete pain relief in different groups. Group B showed statistically significant improvement as compared to Group A (p value- 0.019).

Steardo L conducted a clinical trial on rats in 1984 and reported that baclofen showed analgesic properties in trigeminal neuralgia induce rats. Baclofen has significantly exhibited an analgesic efficacy of 68.61%, like current study their results substantiate that baclofen is useful in the treatment of trigeminal neuralgia(23).

Conclusion

Our study concludes that a synergistic combination of carbamazepine with baclofen can be better alternatives in patients with trigeminal neuralgia, not responding to carbamazepine alone treatment.

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