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Clinical Efficacy of Oxcarbazepine compared with Carbamazepine in terms of Pain Relief in the Management of Trigeminal Neuralgia

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ABSTRACT

Background: Despite various pharmacological drugs used for the treatment of Trigeminal Neuralgia (TN), the clinical efficacy of carbamazepine with oxcarbazepine in terms of pain relief particularly in Pakistani population is poorly studied. This study aimed to compare the efficacy of carbamazepine with oxcarbazepine for treating Trigeminal Neuralgia. **Objective:** To compare oxcarbazepine with carbamazepine in the management of trigeminal neuralgia in terms of mean pain. **Study Design:** Quasi-Experimental study. **Settings:** Fauji Foundation Hospital, Rawalpindi Pakistan. **Duration:** Six months i.e. 30th Apr 2018 to 30th Oct 2018. **Methods:** This single-centre, prospective clinical study was conducted on 70 patients diagnosed with TN. Patients were divided into two groups; Group A: Control group (n = 35), in which patients were given Carbamazepine 200mg twice a day upto1800mg and Group B: an Experimental group (n = 35), in which the patients receive Oxcarbazepine (300mg BD daily up-to 1800mg). The clinical parameters were evaluated by a self-reported questionnaire. Pain level was assessed at 1st and 2nd month follow-up using a Visual Analog Scale. **Results:** The mean postoperative pain was measured for both groups. Although the mean pain score at 1st follow-up month was similar for Group A (5.2±1.0) and B (4.9±1.1), p=0.328, higher clinical efficacy was observed in 2nd follow-up month for Group B– Oxcarbazepine (3.1±0.8) when compared with Group A– Carbamazepine (5.14±0.8) in terms of mean pain score that was statistically significant p<0.001. **Conclusion:** This study concludes that in term of pain relief, Oxcarbazepine appears to be a more effective as compared to Carbamazepine in the treatment of TN.

Keywords: *Trigeminal neuralgia, Oxcarbazepine, Carbamazepine.*

INTRODUCTION

Trigeminal neuralgia (TN) is a severe, incapacitating neuropathic condition characterized as recurrent, unilateral and paroxysmal electric shock-like pain, evoked by innocuous sensory stimuli.[1] Based on the International Classification of Headache Disorders (ICHD-3) it is classified as idiopathic, classic, or secondary trigeminal neuralgia[2]. Over a lifetime, the incidence of TN is estimated to be 0.16%–0.3%. Women being more affected than men, (F: M ratio 3:2)[2]. The average age of onset among the elderly is in the range of 24-93 years.[3]

Regardless of equivocalness about the etiology and pathophysiology, there are several therapies available for trigeminal neuralgia, perhaps not a single curative treatment modality is available. With growing evidence based on information, it seems that anticonvulsants are and will be progressively significant in the administration of neuropathic torments.[4]

Benzodiazepines and older anticonvulsants like phenytoin, carbamazepine, valproate and phenobarbital have been used to treat epilepsy for a long time. Since the beginning of the 1990s, numerous newer antiepileptic medications, such as felbamate, gabapentin, lamotrigine,

oxcarbazepine, topiramate, tiagabine, vigabatrin, zonisamide, pregabalin, and levetiracetam, have been developed. These new medications have advanced pharmacokinetics in comparison to the conventional antiepileptic medications in terms of longer half-lives, allowing twice-daily dosing, reduced drug interactions and a general lack of hepatic enzyme induction, making poly-therapy and other aspects of treatment easier.[5,6]

Carbamazepine is the current drug of choice for trigeminal neuralgia, results in the stabilization of hyper-excited neuronal membranes and the inhibition of repetitive firing. The typical starting dose is 100 to 200 mg twice daily. The daily dose should be increased by 100 mg on alternate days until sufficient pain relief is attained. The typical maintenance dose is 300-800 mg/day, given in 2-3 divided doses. The maximum suggested total dose is 1200mg/day. Due to rigorous blood monitoring and multiple side effects such as hypernatremia, thrombocytopenia, confusion, hypersensitivity reactions, drowsiness, blood dyscarias, and so on, the drug must be discontinued or alternative drugs must be used.[7]

Oxcarbazepine, a novel anticonvulsant, is a keto derivative of carbamazepine that does not pass through the liver cytochrome system, resulting in a better patient safety profile and fewer drug interactions than carbamazepine. Start with 150 mg twice daily of oxcarbazepine. The dose can be increased in 300 mg increments every third day until pain relief is achieved. The maintenance doses are 300-600 mg twice daily. The maximum recommended daily dose is 1800 mg.[8]

According to The American Academy of Neurology and the European Federation of Neurological Societies 2008 evidence-based treatment guidelines, carbamazepine has been shown to be effective (level A) and oxcarbazepine is probably effective (level B) at controlling pain in classic Trigeminal Neuralgia.[9] Oxcarbazepine should be avoided if a carbamazepine allergy is present due to the approximately 25% risk of allergic cross reactivity between the two medications. In the treatment of trigeminal neuralgia, oxcarbazepine has precedence over carbamazepine due to its improved tolerability, twice daily dosing, no routine blood testing is necessary and lower risk of side effects.

Despite the various pharmacological treatments for Trigeminal Neuralgia the clinical efficacy of carbamazepine with oxcarbazepine in terms of pain relief, particularly in the Pakistani population, has received little attention. Also, very few studies have compared these two medications as a single drug therapy for TN. Nonetheless, the impacts of these medications have been documented in literature when contrasted with different medications or when utilized in a triple therapy combination. Taking both drugs as monotherapy for TN can help us to determine which one is more effective as monotherapy, allowing us to develop combination therapies based on their effectiveness in the future. The current study aimed to compare the efficacy of carbamazepine with oxcarbazepine for treating Trigeminal Neuralgia among Pakistani population.

METHODS

This prospective clinical study was conducted on patients reporting to the Oral and Maxillofacial Surgery Out-Patient Department at of a Tertiary Care Hospital in Rawalpindi over a period of 6 months. The study used non-probability consecutive sampling due to practical considerations of our clinical setting and efficiently recruited eligible participants over a specified timeframe. All the patients reporting to the dental OPD with acute intense shooting pain on one side will be chosen following a history, clinical examination, and radiographic evaluation, as well as diagnostic nerve blocks on the affected, for therapeutic purposes. The inclusion criteria comprised of age 31-70 years, either gender, non-smoker, non-alcoholic, with sharp shooting paroxysmal pain attacks that is unilateral involving any division of trigeminal nerve, whereas people who are already receiving any type of medicine for neuralgia hypersensitivity to carbamazepine or oxcarbazepine or having acute or chronic liver failure and pregnant females/lactating mothers and those who lost to followup were excluded from the study. Written informed consent was obtained from all the study participants before data collection.

Patients were divided into two different study groups utilizing the lottery method (Group A and Group B), in a single-blinded way. Group I was treated with Carbamazepine 100mg twice daily initial dose & which was increased up to 1200mg. whereas Group II was treated with Oxcarbazepine 150mg twice daily dosage and was increased up to 1800 mg if the pain was not relieved.

Estimation of an effective therapeutic dose of both drugs was based on the evaluation of pain response that is categorized as excellent (free from all symptoms), good/moderate (decreased intensity in the number of attacks), and no response at all. The dose of the drug increased in a stepladder pattern till an excellent response was obtained. Patients were instructed to reduce the drug dosage during remission phases and to adjust the dosage according to their burden of pain. Between scheduled visits, patients were allowed to call the hospital staff with questions concerning dose adjustment. The pain level was measured using a Visual Analogue Scale (VAS) that is a horizontally drawn line 10 cm long with verbal signals on both ends and a number provided after every centimeter, for a total of 10 numbers. Number

one was no pain at all, and number ten was the most terrible pain. Followup periods were noted in 4th week and 8 weeks.

Evaluation of pain response was made at successive follow-up visits by recording the subjective description of pain made by the patient. All information will be collected on a specially designed Performa.

The minimum required sample size (n=70, 35 in each group) was calculated with the help of the WHO sample size calculator, considering a 95% level of confidence, 5% alpha error, 80% study power, pooled standard deviation of 0.94, 3.42[1] as test value of the population mean, 4.21 anticipated population mean and 10% precision.

The data was entered and analyzed using IBM SPSS software (version 22.0). The descriptive statistics of quantitative variables were reported as mean and standard deviation, while for categorical variables percentages and frequencies were reported. The independent sample t-test was used to compare mean pain between the two groups. The chi-square test was used to compare categorical data. A p-value of 0.05 was deemed significant.

RESULTS

There was a total of 70 participants included in this study. Overall, there were 54 (77.1%) females and 16 males (22.9%) in the study group, with mean age of 57.9±10.0 years, and age range of 31 to 80 years. In majority of the participants, 50 (71.4%) the right side of the face was involved, while remaining 20 (28.6%) had left side involvement. Mandibular nerve involvement was found to be more common as compared to maxillary / infraorbital nerve involvement i.e. 68.6% vs 31.4% respectively. There were 35 participants each in two study groups, the participants in Group A received Carbamazepine drug, while Group B participants received Oxcarbazepine drug. Table 1 gives a summary of baseline characteristics of study group.

Table 1: Baseline characteristics for participants in two study groups

Characteristics		Overall (n=70) (mean ± SD)	Group A Carbamazepine (n=35) (mean ± SD)	Group B Oxcarbazepine (n=35) (mean ± SD)	*p*-value
Mean age in years		57.9±10.0	57.9±9.9	57.9±10.2	0.968*
Age Groups	30-45 years	8 (11.4%)	4 (11.4%)	4 (11.4%)	0.875**
	46-60 years	33 (47.1%)	16 (45.7%)	17 (48.6%)	
	61-85 years	29 (41.4%)	15 (42.9%)	14 (40.0%)	
Age range		31-70	31-69	41-70	-
Gender	Male	16 (22.9%)	9 (25.7%)	7 (20.0%)	0.569**
	Female	54 (77.1%)	26 (74.3%)	28 (80.0%)	
Site	Right	50 (71.4%)	26 (74.3%)	24 (68.6%)	0.597
	Left	20 (28.6%)	9 (25.7%)	11 (31.4%)	
Branch	Maxillary / infraorbital nerve	22 (31.4%)	11 (31.4%)	11 (31.4%)	1.0
	Mandibular nerve	48 (68.6%)	24 (68.6%)	24 (68.6%)	
	Mental nerve	25/48 (52.1%)	14/24 (58.3%)	11/24 (45.8%)	
	Inferior alveolar nerve	23/48 (47.9%)	10/24 (41.7%)	13/24 (54.2%)	

**Independent samples t-test, **Chi-square test*

In group A, the mean dose for participants belonging to group A was calculated to be 680±248.2 mg while 548.5±312.8 mg, with no significant difference as given in the table 2.

Table 2: Mean dose estimation of carbamazepine and oxcarbazepine in two study groups

	Group A Carbamazepine Drug Dose	Group B Oxcarbazepine Drug Dose	p-value
Mean dose (mg)	680.0 ± 248.2	548.5 ± 312.8	0.056
Minimum dose (mg)	200	300	
Maximum dose (mg)	1200	1800	

The baseline pain score before starting the procedure was measured by VAS analog for both the groups. A slightly higher score was recorded for patients belonging to group B (7.7±1.0) as compared to participants of group A (7.1±1.2), with a significant difference (p=0.029). At first follow up, 1-month after the initiation of therapy, the mean pain score in both the groups decreased where in group A the pain score decreased to 5.2±1.0, while in group B it decreased to 4.9±1.1 from baseline score. Similarly, at the second follow-up, the mean pain score in group B further reduced to 3.1±0.8, while in group A the mean pain score remained almost the same 5.14±0.8, with

slight decrease in mean value. The repeated measures comparison for group A and B is given in the table 3.

The baseline pain score before starting the procedure was measured by using VAS log for both the groups. When the pain scores at 1-month follow-up were compared for both the groups, no significant difference was found. The mean pain score at 1-month follow up was almost same for group A and group B (5.2±1.0 vs. 4.9±1.1 respectively, p=0.328). Higher clinical efficacy was observed in 2nd follow-up month for Group B – Oxcarbazepine (3.1±0.8) when compared with Group A – Carbamazepine (5.14±0.8) in terms of mean pain score that was statistically significant p<0.001 as shown in the table 3.

Table 3: Comparison of pain score at 1 and 2 months follow up with baseline pain score in two study groups

	Overall (n=70)	Group A Carbamazepine (n=35)	P*	Group B oxcarbazepine (n=35)	P*	P**
Baseline pain score	7.39 ± 1.1	7.1 ± 1.2	<0.001	7.7 ± 1.0	<0.001	0.029
Pain score at 4th week follow up	5.10 ± 1.1	5.2 ± 1.0		4.9 ± 1.1		0.328
Pain score at 8th week follow up	4.12 ± 1.3	5.14 ± 0.8		3.1 ± 0.8		<0.001

**Within group comparison via Repeated measures ANOVA*
***Inter-group comparison via independent samples T-Test*

DISCUSSION

The extent and severity of the pain have a significant impact on patients' quality of life. There is growing evidence that TN can cause psychological distress, which often leads to suicidal ideation. Delays in diagnosis, fear of sudden recurrence of pain, drug side effects, and a lack of psychological support were all observed to cause distress in TN patients. According to recent clinical trials, the frequency of depression and anxiety in TN patients is nearly three times that of matched controls, and it is positively associated with pain scores and disease duration.[10]

Trigeminal neuralgia can be treated in a variety of ways; however, it is usually recommended to provide medical treatments first and if failed to respond, then resort to surgery. Carbamazepine and Oxcarbazepine, two anti-epileptic medicines (AEDs), account for the majority of medical treatment.

In the current study, the mean age of these patients was 57.9±10.0 years with an age group of 31- 80 years with female preponderance. Ayele et al [11] showed mean age of 50.7±14.2 years with an age range of 21-78 years. Whereas Shah et al[12] reported mean age of participants was 56.5 ± 8 years with an age range of 36-71 years. Previous studied reported that the optimum onset age range is between the 5th and 8th decades. In the current research, similar demographic pattern was observed, with the highest age found between the 5th to 7th decades.

Neurologists, based on the clinical data pertaining to numerous case histories of trigeminal neuralgia have come to the conclusion, that there is no one specific pain location. Although the disease typically affects only one side of the face, there are some patients who experience bilateral pain. Trigeminal neuralgia affects the right side of the face more frequently than the left, by a 3:2 ratio, when it comes to general pain location. Pain lateralization in TN has been hypothesized to be caused by a narrower foramen rotundum and foramen ovale on the right side, but this hypothesis has not yet been proven correctly.[9,12]

In this study, the right side was involved in 50 cases (71.4%), while the left side was involved in 20 cases (28.5%). In comparison to our study, Shah et al[12] discovered that the right side of the face was involved in 32 patients (64%) and the left side in 18 patients (36%). Similarly, Shafiq et al[1] discovered that the right side of the face was involved in 127 cases forming (62.85%), while the left side was involved in 75 cases making (37.15%) of all patients.

Mandibular division is involved in 48 (68.6%) of the cases, while maxillary division is involved in 22 (31.4%) of the cases. In comparison to our study, Shah et al[12] reported mandibular division involvement in 30 cases (60%) and maxillary division involvement in 17 cases (34%). Among the mandibular division, the mental nerve was involved in 25 cases (52.1%), while the inferior alveolar nerve was affected in 23 cases (47.9%) in our study.

In this study, the pain scores obtained using a visual analog scale on the first follow-up after 1 month were (5.2±1.0) for the carbamazepine group and (4.9±1.1) for the oxcarbazepine group. In contrast, on the second follow up visit after 2nd month, the oxcarbazepine group (3.1±0.8) shows improved results in terms of mean pain score and demonstrates higher patient comfort when compared to the carbamazepine group (5.14±0.8).

According to Shafiq and colleagues[1], oxcarbazepine is more effective as opposed to carbamazepine for pain relief in patients with trigeminal neuralgia (3.42±0.82 vs.4.21±0.98). This finding supports the results of this study that Oxcarbazepine has a higher efficacy for pain control than carbamazepine. According to recently

published research, the mean pain score was significantly better with oxcarbazepine (2.82±0.77) when compared to carbamazepine (4.36±0.86), i.e. p-value0.001, and the safety profile was also better for oxcarbazepine.[13]

In the current study, the therapeutic dose of oxcarbazepine that resulted in the best response in the majority of cases of trigeminal neuralgia was between 300-900 mg/day, whereas carbamazepine shows excellent response in the dose range of 800-1200mg/day, which is similar to the results shown by Debta et al[14] that oxcarbazepine exhibits therapeutic effectiveness among the greater majority of the patients in the dosage of (300-900mg) per day.

In contrast to the results reported by this study, the following two studies found carbamazepine to be more effective than Oxcarbazepine. Stefano et al[15] found that Carbamazepine (600 mg dose, Dose range: 200-1220 mg) and Oxcarbazepine (1200 mg dose, Dose range: 600-1800 mg) had 98% and 94% response rates, respectively. Besi et al[16] reported a response rate of 80% with carbamazepine at a dosage of (200-300 mg) and 68% with oxcarbazepine at a dose range of 300-600 mg in a randomized, controlled study. The latest research from India found that with carbamazepine, 73.07% of patients responded successfully to an increased dose of 1200 mg every day.[17]

CONCLUSION

The current study concludes that oxcarbazepine is more effective than carbamazepine in the course of medical therapy of trigeminal neuralgia with regards to mean pain relief. Oxcarbazepine has potent anti-neuralgic properties, no routine monitoring is required, thus seems to be an appropriate replacement for carbamazepine in patients who does not tolerate the drug or who experience substantial adverse reactions.

LIMITATIONS

Our study has several practical limitations, due to the use of pain as the primary outcome, which is a subjective measurement, and smaller sample size, the results may exhibit bias in reading and interpreting the VAS. There was a lack of double blinding, and the results should be evaluated over a longer period of time with proper extended follow-ups, as well as evaluating potential adverse effects within each drug group that leads to withdrawal of medical therapy.

SUGGESTIONS / RECOMMENDATIONS

The purpose of this study was to present the available data and serve as a starting point for future research, with the hope that in the long run, large, international, well-conducted, randomized controlled trials will precisely compare the efficacy of oxcarbazepine as monotherapy as well as triple treatment in combination with additional medications to treat trigeminal neuralgia more effectively in patients with a favorable prognosis**.**

CONFLICT OF INTEREST / DISCLOSURE

There was no conflict of interest.

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Nil.

ETHICAL STATEMENT

Ethical approval was provided by the Ethical Review Committee at Foundation University Medical College, Foundation University, Islamabad (Ref. No: FF/FUMC/215-137/Phy/21).

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