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Original Article

Dentistry Section

Evaluating the Therapeutic Efficacy of Carbamazepine and Oxcarbazepine in Trigeminal Neuralgia: A Randomised Clinical Trial

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ABSTRACT

Introduction: Trigeminal Neuralgia (TN) is neuropathic pain disorder manifesting as intense, episodic, shock-like facial pain that severely affects quality of life. Although carbamazepine is the first drug of choice for the treatment of TN, it causes adverse effects like drowsiness, ataxia, myelosuppression and other serious side-effects. Oxcarbazepine (OXC), a keto-analogue of carbamazepine, may serve as superior substitute as it has lesser side-effects and improved safety profile.

Aim: To compare the effectiveness and safety of carbamazepine and OXC in patients with classical TN.

Materials and Methods: This study was a randomised clinical trial was conducted in the Department of Oral Medicine and Radiology, Dayananda Sagar College of Dental Sciences, Bengaluru, Karnataka, India. Patient recruitment was carried out over a period of eight months, from February 2025 to September 2025. In this randomised clinical trial, 60 patients with TN were allocated to receive either carbamazepine (100 mg twice daily, titrated up to 1200 mg/day) or OXC (150 mg twice daily, titrated up to 1800 mg/day). Pain intensity was assessed using a 0-10 Visual Analogue Scale (VAS) at baseline, two, four, and eight weeks. Adverse effects were recorded throughout the 8 months of study period. Within-group comparisons of VAS scores over multiple follow-up points were performed using repeated measures Analysis of Variance (ANOVA). Between-group comparisons at each follow-up point were conducted using an Independent sample's t-tests

Results: The mean age of participants in group A and B was 53.8±6.2 and 52.4±5.9 respectively. Intragroup comparison using ANOVA showed both medications significantly reduced pain scores over time (p-value <0.01). Independent samples t-test showed OXC produced a greater reduction in VAS scores at four weeks (2.5±0.9 vs 4.1±1.1; p-value=0.01) and eight weeks (1.9±0.8 vs 3.1±1.0; p-value=0.01) compared to carbamazepine. Adverse effects were reported in 53.3% of patients receiving carbamazepine and 23.3% of those receiving OXC.

Conclusion: OXC was more efficient in reducing pain compared to carbamazepine at the end of four and eight weeks and had fewer side-effects. Hence, OXC can be recommended as a safer and better substitute in the long-term management of TN. However, larger studies with longer follow-up are warranted to confirm these results.

Keywords: Adverse drug reactions, Anticonvulsant therapy, Neuropathic facial pain, Visual analogue scale

INTRODUCTION

The TN is a chronic neuropathic pain disorder characterised by sudden onset of severe and recurrent facial pain along one or more branches of the trigeminal nerve. It is one of the most excruciating pain syndromes that may be accompanied by facial spasm or tic [1]. It occurs commonly due to vascular compression of TN by the blood vessels as the nerve enters the brain stem leading to demyelination of the nerve [2]. It is classified into classical TN, idiopathic TN and secondary TN. It typically presents with intense, sharp, brief, stabbing, lancinating or shock-like pain, initiated by physical stimuli such as talking, touching, or mastication [3]. The diagnosis of TN is mainly established by a thorough clinical history and comprehensive examination aimed at excluding other potential causes of facial pain.

Management options for TN include pharmacotherapy, nerve blocks and surgical treatment. Carbamazepine has been the drug of choice for treating TN for decades. However, it is associated with various side-effects like dizziness, ataxia, hyponatremia, and increased levels of hepatic enzyme and long-term use can lead to leukopenia, aplastic anaemia [4].

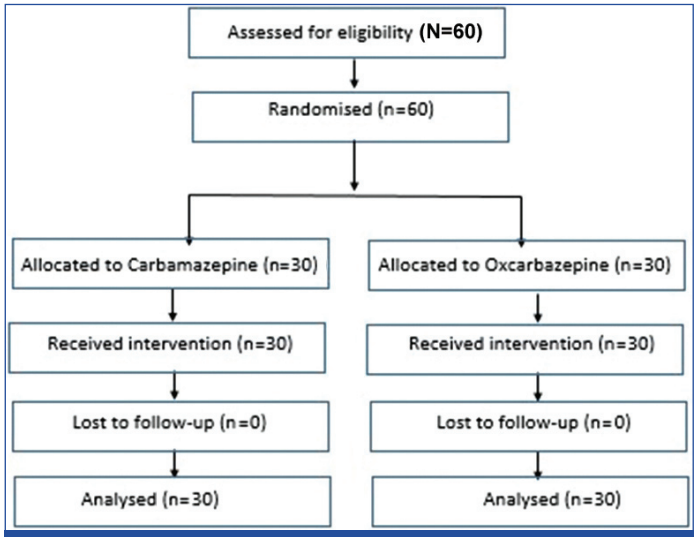
The OXC, a keto-analogue of carbamazepine, is a better alternative drug with similar or superior efficacy with limited side-effects, fewer drug interactions and better tolerability [5].

While multiple studies, systematic reviews, and meta-analyses have evaluated carbamazepine and OXC in TN [6,7], substantial heterogeneity exists across individual studies with respect to study design, dosing and titration strategies, duration of follow-up, and reporting of adverse drug reactions. Given the differences in genetic background, drug tolerability, and healthcare access that may influence treatment outcomes, region-specific clinical data are essential. Therefore, the present study was designed to provide region-specific evidence by directly comparing the efficacy and safety of carbamazepine and OXC in the study population, using standardised dosing, systematic titration, and consistent follow-up, with detailed monitoring of adverse effects. More specifically the objectives were to compare the reduction in pain intensity using VAS among patients treated with carbamazepine and OXC and to identify and compare adverse drug reactions in both groups.

MATERIALS AND METHODS

This study was a randomised clinical trial was conducted in the Department of Oral Medicine and Radiology, Dayananda Sagar College of Dental Sciences, Bengaluru, Karnataka, India. Patient recruitment was carried out over a period of eight months, from February 2025 to September 2025. Permission and Ethical clearance was taken from the Institutional Review Board of Dayananda Sagar College of Dental Sciences, Bengaluru (approval number- 324-IRB-2025). A Consolidated Standards of Reporting Trials (CONSORT)

flow diagram depicting the progress of participants through the trial is shown in [Table/Fig-1].



[Table/Fig-1]: CONSORT flow diagram of participant enrollment, allocation, follow-up, and analysis.

Inclusion criteria: Adults aged 18-75 years diagnosed with classical TN, patients willing to provide informed consent and patients not currently on other anticonvulsants or neuropathic pain medications were included.

Exclusion criteria: Patients with known hypersensitivity to carbamazepine or OXC, pregnant or lactating women, severe hepatic, renal, or cardiac impairment and patients with psychiatric illness interfering with pain assessment.

Sample size calculation: The sample size was calculated based on differences in treatment response reported in a previous comparative study by Iqbal S et al., [8].

$$n = (Z\alpha/2+Z\beta)^2 \times \{p1(1-p1)+p2(1-p2)\}$$

$$(p1-p2)$$

p1=0.43 (carbamazepine group)- Proportion of patients showing complete pain relief / satisfactory treatment response in the carbamazepine group, reported as 42.9% (approximately 0.43) 0.2451.

p2=0.68 (OXC group)- Proportion of patients showing complete pain relief/satisfactory treatment response in the OXC group, reported as 67.9% (approximately 0.68)

$Z\alpha/2=1.96$ for a two-sided significance level of 5%.

$Z\beta=0.84$ for 80% power

A minimum of 14 participants was required in each group; this was increased to 30 participants per group to increase the power and precision of the study, resulting in a total sample size of 60.

Participants were allocated using a computer-generated random sequence with allocation concealment ensured through sequentially numbered opaque sealed envelopes. Group assignment was concealed through the use of sequentially numbered, sealed, opaque envelopes that were opened only at the time of treatment initiation. Due to differences in dosing schedules and titration requirements between carbamazepine and OXC, blinding of participants and investigators was not feasible.

Intervention protocol:

- Group A: 30 patients treated with carbamazepine 100 mg twice daily, titrated gradually up to 1200 mg/day based on response and tolerance.
- Group B: 30 patients treated with OXC 150 mg twice daily, titrated up to 1800 mg/day based on response and tolerance.

Study Procedure

Demographic data was recorded, and detailed pain history a was obtained followed by a thorough examination. Informed consent was taken from all the patients. The severity of pain was measured using 0-10 VAS (where 0 indicated no pain and 10 indicated the worst imaginable pain) and was recorded at baseline, two weeks, four weeks and eight weeks and presence or absence of adverse effects was also noted [Table /Fig-1].

Rationale for dose selection and titration: The initial doses and titration schedules for carbamazepine and OXC were selected based on standard clinical practice guidelines and published literature. Dose escalation in both groups was individualised based on clinical response and tolerability, with predefined maximum daily doses of 1200 mg for carbamazepine and 1800 mg for OXC [9].

Outcome measures:

- The primary outcome measure was pain intensity assessed using the VAS. VAS scores were recorded at baseline, two weeks, four weeks, and eight weeks.
- Secondary outcome measures included the incidence and nature of adverse drug reactions, which were recorded at each follow-up visit through patient self-reporting and clinical evaluation.

STATISTICAL ANALYSIS

Data were analysed using Statistical Package Social Sciences (SPSS) software version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables, including VAS scores, were expressed as Mean±Standard Deviation (SD), while categorical variables were presented as frequencies and percentages.

Prior to statistical testing, normality of continuous variables was assessed using the Shapiro-Wilk test. Based on these results, parametric tests were applied for normally distributed variables. Within-group comparisons of VAS scores over multiple follow-up points were performed using repeated measures ANOVA. Between-group comparisons at each follow-up point were conducted using an Independent samples t-tests. In addition to p-values, 95% Confidence Intervals (CIs) and effect sizes (Cohen's d) were calculated for between-group comparisons to provide a measure of clinical relevance. A p-value <0.05 was considered statistically significant.

RESULTS

The present study was conducted to compare the reduction in pain intensity and frequency among patients of TN treated with carbamazepine (group A) and OXC (group B). The demographic data of the patients are summarised in [Table/Fig-2].

Parameters	Group A (n=30)	Group B (n=30)	p-value
Mean age (in years)	53.8±6.2	52.4±5.9	0.61
Gender (M/F)	12/18	14/16	0.062
Duration of symptoms (in months)	26.5±9.4	29.8±10.1	0.77

[Table/Fig-2]: Demographic data of the patients.

The baseline VAS score in group A was 8.6±0.7 and group B was 8.4±0.8. After two weeks, the VAS score for group A was 5.2±1.2 and for group B was 3.9±1.0 both of which were statistically significant compared to baseline values of their respective groups. After four weeks, VAS score for group A was 4.1±1.1 and for group B was 2.5±0.9 both of which were significant compared to baseline values of their respective groups. After eight weeks, the VAS score for group A was 3.1±1.0 and for group B was 1.9±0.8 both of which were significant compared to baseline values. The results of intra group comparison of VAS are summarised in [Table/Fig-3] (group A) and [Table/Fig-4] (group B).

Parameters	Group A (n=30)	p-value
Baseline VAS score	8.6±0.7	<0.01
2 weeks	5.2±1.2	
4 weeks	4.1±1.1	
8 weeks	3.1±1.0	

[Table/Fig-3]: Intragroup comparison of VAS score in group A.
VAS: Visual analogue scale; 0=no pain, 10=worst pain imaginable

Parameters	Group B (n=30)	p-value
Baseline VAS score	8.4±0.8	<0.01
2 weeks	3.9±1.0	
4 weeks	2.5±0.9	
8 weeks	1.9±0.8	

[Table/Fig-4]: Intragroup comparison of VAS score in group B.
VAS: Visual analogue scale; 0=no pain, 10=worst pain imaginable

The VAS score between group A and group B at the baseline did not show any statistical significant difference (8.6±0.7 vs 8.4±0.8, p-value=0.58). The VAS score between group A and group B after two weeks follow-up did not show any statistical significant difference (5.2±1.2 vs 3.9±1.0, p-value=0.38). However, statistically significant difference in VAS score were seen between the groups at the end of four weeks (4.1±1.1 vs 2.5±0.9, p-value=0.01) and eight weeks (3.1±1.0 vs 1.9±0.8, p-value=0.01) implying that OXC showed greater efficacy in reducing pain compared to carbamazepine [Table/Fig-5].

Parameters	Group A (n=30)	Group B (n=30)	Mean difference (95% CI)	Cohen's d	p-value
Baseline VAS score	8.6±0.7	8.4±0.8	0.2 (-0.2 to 0.6)	0.26	0.58
End of 2 weeks	5.2±1.2	3.9±1.0	1.3 (-0.7 to 3.3)	1.13	0.38
End of 4 weeks	4.1±1.1	2.5±0.9	1.6 (0.7 to 2.5)	1.57	0.01
End of 8 weeks	3.1±1.0	1.9±0.8	1.2 (0.4 to 2.0)	1.33	0.01

[Table/Fig-5]: Comparison of VAS score between group A and group B (N=60).

Adverse effects like dizziness, drowsiness, nausea and vomiting were seen in 16 patients in group A (53.3%) and 7 (23.3%) patients in group B indicating that OXC showed fewer side-effects and better safety.

DISCUSSION

The present study was conducted to compare the efficacy and safety of carbamazepine and OXC in patients with classical TN. The VAS score between group A and group B at the baseline did not show any statistical significant difference (8.6±0.7 vs 8.4±0.8, p-value=0.58). The VAS score between group A and group B after two weeks follow-up did not show any statistical significant difference (5.2±1.2 vs 3.9±1.0, p-value=0.38). However, statistically significant difference in VAS score were seen between the groups at the end of four weeks (4.1±1.1 vs 2.5±0.9, p-value=0.01) and eight weeks (3.1±1.0 vs 1.9±0.8, p-value=0.01) indicating that OXC showed greater efficacy in reducing pain. Both drugs exert their therapeutic effect primarily by blocking voltage-gated sodium channels, thereby stabilising hyperexcitable neuronal membranes and suppressing ectopic discharges in demyelinated trigeminal nerve fibers. However, OXC, a keto-analogue of carbamazepine is rapidly converted to its active metabolite, the 10-Monohydroxy Derivative (MHD), which exhibits more predictable pharmacokinetics and stable plasma concentrations. OXC does not undergo metabolism to a reactive epoxide intermediate, which is responsible for many dose-related and idiosyncratic adverse effects associated with carbamazepine, including dizziness, ataxia, and haematological toxicity. The absence of this toxic epoxide metabolite results in improved tolerability and a lower incidence of systemic side-effects [10] Additionally, OXC induces hepatic cytochrome P450 enzymes to a much lesser extent than carbamazepine, leading to fewer drug–drug interactions and reduced metabolic variability [11].

Iqbal S et al., conducted a randomised trial to evaluate efficacy of carbamazepine versus OXC in treating TN among 56 patients. Results revealed that OXC showed a higher complete response rate than carbamazepine (67.9% vs. 42.9%; p-value=0.017), and the mean pain score was lower with OXC (2.82±0.77) compared with carbamazepine (4.36±0.86; p-value <0.001). Additionally, adverse effects were more frequent with carbamazepine (35.7%) than with OXC (14.3%) [8].

In the study by Paiker S et al., patients treated with carbamazepine and OXC had similar mean pain scores at one month (5.2±1.0 vs. 4.9±1.1; p-value=0.328), but at two months follow-up the OXC group showed significantly lower mean VAS scores than the carbamazepine group (3.1±0.8 vs. 5.14±0.8; p-value <0.001), indicating superior pain relief with OXC [12]. Similar findings were observed in the present study, where OXC did not demonstrate a significant reduction in pain at two weeks but showed significant pain reduction at four and eight weeks.

Ahmad RM et al., in their study included 122 patients of TN aged 25-80 year and randomly divided them to two groups, one receiving carbamazepine and other receiving OXC. He found that OXC provided significantly greater pain relief than those taking carbamazepine, as reflected by a lower mean VAS score (2.6±1.2 vs. 3.7±1.89, p-value=0.001) and concluded that OXC as a preferable first-line treatment option [13]. In Shafiq H et al., comparative study of 202 patients with TN, pain relief was achieved in 84.2% of patients treated with OXC, compared with 25.7% of those treated with carbamazepine (p-value=0.00005), indicating significantly greater effectiveness with OXC [14]. In a prospective open-label study of 35 patients with idiopathic TN unresponsive to carbamazepine, OXC monotherapy (mean maintenance dose -773.7 mg/day) provided significant pain improvement over 12 weeks. After treatment, 37.1% of patients experienced pain relief, and 67.5% had a ≥50% reduction in pain frequency compared with baseline (p-value <0.05) [15].

In the present study, statistically significant difference in VAS score were seen between OXC and carbamazepine group at the end of four weeks (4.1±1.1 vs 2.5±0.9) and eight weeks (3.1±1.0 vs 1.9±0.8) suggesting that OXC showed greater efficacy in reducing pain compared to carbamazepine which is in accordance to the above studies. However, in a systematic review and meta-analysis by Mendieta CD et al., which included 838 patients from three observational studies and two randomised trials, OXC and carbamazepine showed comparable efficacy in the treatment of TN (OR=0.52; 95% CI: 0.13-2.04; p-value=0.35) [6].

In the present study, adverse effects occurred in 53.3% of patients receiving carbamazepine, whereas only 23.3% of those on OXC experienced side-effects. Ahmad RM et al., reported fewer treatment interruptions and adverse events in the OXC group [13]. Mendieta CD et al., meta-analysis confirmed this trend, reporting a significantly higher-risk of adverse events with carbamazepine (OR=2.35; 95% CI: 1.51-3.67; p-value=0.0002) [6]. Iqbal S et al., found that adverse effects were more frequent with carbamazepine (35.7%) than with OXC (14.3%) [8]. Overall, OXC was better tolerated than carbamazepine, with fewer and less adverse effects reported across studies that could be due to reduced induction of liver enzymes, more stable plasma concentrations and lack of toxic epoxide metabolite compared to carbamazepine.

Limitation(s)

Although the study provides valuable comparative data on carbamazepine and OXC, the follow-up was limited to eight weeks due to which long-term outcomes could not be assessed. Although

the calculated sample size was achieved, the modest sample size and single-centre nature of the study may limit generalisability. Therefore, larger multicentre studies with extended follow-up are recommended to validate the findings.

CONCLUSION(S)

In the present study, both carbamazepine and OXC significantly reduced pain intensity (p-value <0.001) in neuralgia patients. However, OXC was more efficient in reducing pain compared to carbamazepine at the end of four and eight weeks and had fewer side-effects compared to carbamazepine implying that OXC can be recommended as a safer and more effective alternative to carbamazepine in the long-term management of TN. Further studies with larger sample sizes and longer follow-up are warranted to confirm these findings and to assess the sustained efficacy and safety of both medications over time.

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