Original Article

The Efficiency of Oxcarbazepine and Carbamazepine in the Management of Trigeminal Neuralgia: First Comparative Study in Bangladesh

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Abstract

Background: Trigeminal neuralgia (TNg) is considered as one of the most severe painful disorders in the orofacial region. Anticonvulsants are most commonly used for such pain management. Carbamazepine is considered as first line of drug for the pain management of TNg. But, a new medicine namely, oxcarbazepine, that is a keto derivative of Carbamazepine, recently caught attention for its promising effect as an anti-convulsant drugs. However, little is known about its effect and safety in TNg management in aspects of Bangladeshi patients. Here, in this study we aim to compare the effectiveness and tolerability of carbamazepine versus oxcarbazepine in the pain management of TNg.

Methods: People Patient with TNg were identified while visiting Bangabandhu Sheikh Mujib Medical University for treatment purpose. Thirty patients with TNg were selected irrespective of age, gender, religion or socioeconomic status of the patients, and selection criteria. Patients were administrated with oxcarbazepine (group A) and carbamazepine (group B) for certain time, and data were collected during indicated follow up.

Results: In this study, 53.3 % patients were found within 51-60 years age group, followed by (46.7%) were in the age group of 40-50. It was reported that 43.3% were male and 56.7% patients were female. In present study, pain was significantly reduced in group A compared to group B ($p < 0.001$). The mean pain score in group B was 4.11+0.91, but promisingly in group A was 1.41+ 0.78. Although, after one month of treatment, we found adverse effects in 4 (26.7%) patients in group A and 9 (60.0%) patients in group B. However, after 6 months of treatment no side effect was observed in group A, but 11 (73.3%) patients had side effect in group B. Side effects were significantly decreased in group A after 3 and 6 months compared to group B ($p<0.05$).

Conclusion: The significant analgesic effects of oxcarbazepine and its generally improved safety and tolerability profile compared to carbamazepine, suggest that oxcarbazepine will be an important addition to TNg pain management.

Keywords: Trigeminal neuralgia, Facial pain, carbamazepine, oxcarbazepine, Anti-convulsant.

Journal of Dentistry and Allied Science, Vol. 7 No 1
Article Received: 14 Oct 2023, Accepted: 07 Dec 2023

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1. Introduction

The trigeminal nerve (TN) is the 5th number (V) and the largest of all cranial nerves. It is responsible for detecting sensory stimuli that arise around the craniofacial area [1]. This nerve is sub-divided into three branches: ophthalmic (V1), maxillary (V2), and mandibular (V3). Trigeminal neuralgia (TNg) is a very painful neurological condition that associated with sudden, severe, short-lasting stabbing pain in face, which arise after attack in one or more of the TN branches [2]. The momentary bursts of pain usually begin from the same spot on the face each time. The pain can be triggered by touching the area, washing, shaving, eating, drinking, or even talking. Even a cool breeze across the face can set on this TNg attack. Pain is more severe at the ends of the affected nerve, especially over the lip, chin, nostrils, or teeth [3]. This neuropathic pain condition affects basic human psychological, physical, and social needs and activities, leading to a severe reduction in the quality of life of affected patients [4].A previous epidemiological study suggested that increased anxiety, depression, and poor sleep in patients with TNg, highlighting the condition's effect on mental health [5]. This condition is unusual in those underaged 50 and more often occurs after 70. Women are three times more likely to have the condition than are men. When trigeminal neuralgia does occur in younger people, it is often associated with multiple sclerosis [6,7].

Globally TNg is clinically managed by dentist, precisely oral and maxillofacial surgeons [8]. Initially, if the patient's past history, clinical examination and diagnostic imaging indicate no evidence of posterior fossa tumor. It can be diagnosed and confirmed as idiopathic trigeminal neuralgia. The medical therapy is the first line of treatment of choice in this circumstance [9,10,11]. In preliminary stage, TNg treatment is pharmacological in the form of monotherapy, however, combined therapy with different drugs may be used when the efficacy of monotherapy is low [12,13]. Patients not responsive to pharmacological treatment or those who present with severe side effects are candidates for more invasive strategies such as nerve block or surgery [14].

Anti-convulsant are most commonly used for pain management as medical therapy 15. Carbamazepine is considered as first line of drug for the pain management of trigeminal neuralgia with an onset of action within 24 hours [16]. It is officious in only 70-80% of patients, and can be associated with adverse effects such as toxicity manifested by drowsiness, confusion, nausea, ataxia, nystagmus and hypersensitivity necessitating discontinuation of medication. Twenty per cent of patients responding initially to treatment may subsequently become refractory to carbamazepine because of its greater side effects compared to other drugs [17, 18, 19].

Oxcarbazepine (10, 11-dihydro- 10-oxo-5H-dibenz (b,f) azepine 5 carboxamide), a keto derivative of carbamazepine, has been shown to have equal efficacy to carbamazepine in the management of epilepsy. Also, it has greater tolerance and less side effects compared to other medicines. Oxcarbazepine is rapidly absorbed after oral ingestion and is metabolized to two major metabolites 10, 11- dihydro-10-hydroxycarbamazepine (10-OH-carbazepine) and trans- 10, 1 1-dihydro- 10, 11-dihydroxy- carbamazepine. 10-OH-carbazepine is the primary metabolite and is active pharmacologically as an anticonvulsant drug [19,20,21]. Additionally, oxcarbazepine has been found useful in the management of affective

convulsion disorders and spasticity. Recently, in a study it is reported that, oxcarbazepine has antineuralgic properties in the absence of significant side effects in patients with trigeminal neuralgia [22].

Recently, number of patients with TNg has increased in prospect of Bangladesh and anti-convulsant drugs such as carbamazepine has become a drug of choice among the doctors in Bangladesh. In contrast, oxcarbazepine is one of the most overrated drugs in psychiatry, and has been started to use in convulsant disorders treatment. It is used frequently, even though it has little to no scientific basis for being used at all. Despite their widespread use of anti-convulsant medicine among Bangladeshi patients having TNg, a scientific register of patients with comparison of different anticonvulsant medicine is currently lacking. To the best of our knowledge, no scientific study has been conducted to compare and assess, the efficacy and tolerability of oxcarbazepine and carbazepine in the management of TNg in Bangladesh. Therefore, in this study we aim to compare and identify the best possible medicine for TNg among carbazepine and oxcarbazepine in Bangladeshi patients.

2. Materials and methods

2.1 Sample selection

Thirty patients diagnosed with TNg were selected who visited Bangabandhu Sheikh Mujib Medical University for their treatment. Patients were selected based on history, clinical examination and diagnostic methodology considering the inclusion and exclusion criteria (Table 1). Diagnosis was carried out by giving local anesthesia.

Table 1: Eligibility criteria of patient to be enrolled in this study.

Inclusion criteria	Exclusion criteria
a. Diagnosed case of TNg b. Patient with refractory cases	a. Case of TNg received surgical intervention. b. Medically compromised patient. c. Patient with other types of neuralgic pain. d. Psychotic & uncooperative patient.

2.2 Informed consent:

A signed informed consent form was mandatory to enroll the samples in this study. After eligibility screening, informed consent was taken from the patient or legal guardians after duly informing about the procedure of treatment and possible advantages, disadvantages and complications considering all ethical issues. They were then enrolled in this study by an examiner blinded to the allocation.

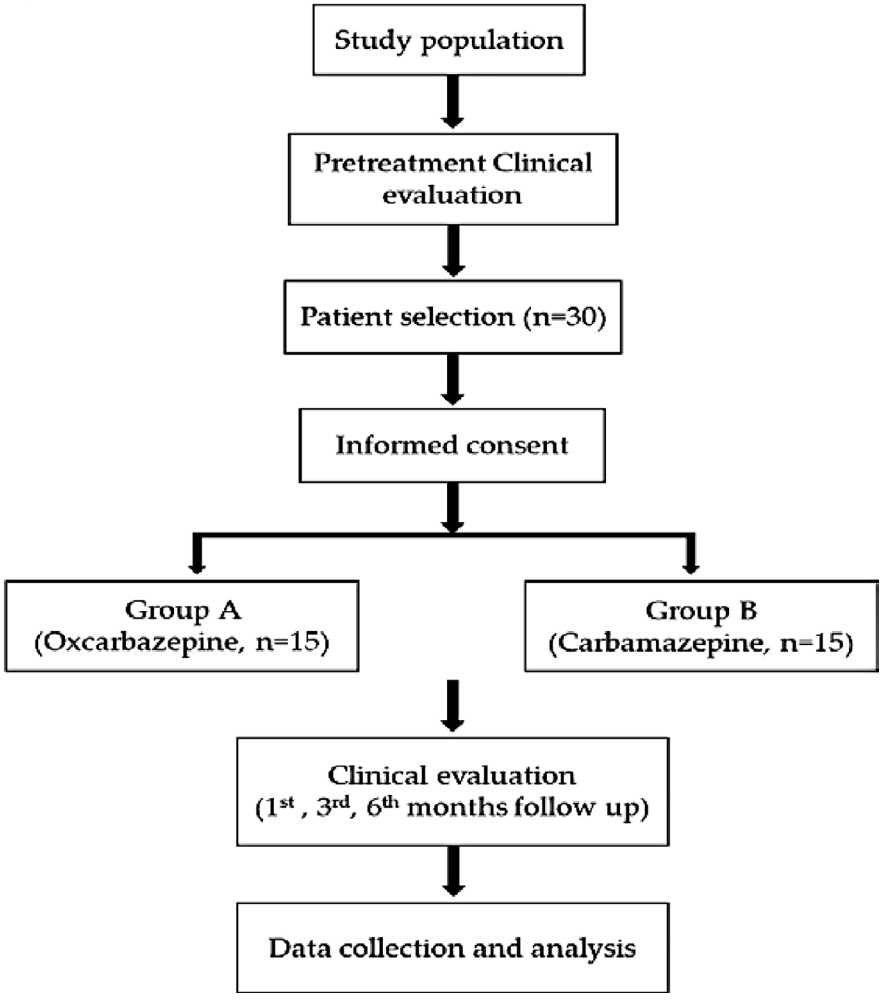
2.3 Treatment protocol:

After TNg diagnosis patients were randomly allocated into two equal groups. Group- A was treated with oxcarbazepine; from 300 mg up to 1200 mg BD dose daily. Group-B was treated with carbamazepine; from 200 mg up to 1200 mg BD dose daily. Initially this drug is given for six months (at three intervals follow up- 1st months, 3rd months and 6th months). Above dose regimen is standard dose but we can reduce the minimum dose level or increases the maximum dose level if necessary.

2.4 Scoring parameters:

Effectiveness of indicated drugs were measured by pain intensity. Pain intensity included three parameters; Severity (no, mild, moderate) of pain, Duration and Number of attacks. Patients were asked to use visual analogue scale to score the pain and note the score in diary. We also intended to observe tolerability and degree of side effects (Dizziness, Drowsiness Headache, Vomiting, Ataxia etc.) for these drugs among the patients. Effectiveness and tolerability of those drugs were observed in three intervals (1st month, 3rd month and 6th month) follow up. Some anticonvulsants have effect on liver, especially carbamazepine, therefore, we also did liver function test before and after administration of drugs at every month's interval.

Figure 1: A schematic design of the study.



2.5 Data Collection Procedure:

A face-to-face interview and clinical examination were performed to collect data by using semi structured questionnaire. A schematic model of this study is presented in flow chart (Fig 1).

2.6 Procedure of data Analysis and interpretation:

All data were processed and analyzed using SPSS (Statistical Package for Social Sciences). Statistical significance was assessed using students- test, chi square (X2) as appropriate. All results will be considered significant if P<0.05 (CL 95%). The summarized data then presented in the form of tables and graphs.

3. Results

3.1 Oxcarbazepine plays promising role in suppressing TNg pain, than carbamazepine

In this study, we found that after 1 month of medication, 8 (53.3%) patients had mild pain and 2 (13.3%) patients had moderate pain, in group A. But, in group B, 7 (46.7%) cases had mild pain and 6 (40.0%) had moderate pain. After 3 months, 4 (26.7%) patients had mild pain only in group A, where in group B, 8 (53.3%) cases had mild pain and 5 (33.3%) had moderate. Interestingly, after 6 months medication, only 2 (13.3%) patients had mild pain and 13 (86.7%) patients had no pain in group A. In contrast, 9 (60.0 %) subjects had mild pain and 4 (26.7%) had moderate pain in group B. Pain is significantly decreased in group A compared to group B after 3 months and 6 months (p<0.05) (Table 2). The mean pain score in group A was 1.41±0.78 and in group B was 4.11±0.91. Pain significantly reduced in Oxcarbazepine to Carbamazepine group (<0.001). Pain measurement by VAS scale (Table 3). These data suggesting that anti-pain efficiency of oxcarbazepine is greater than carbamazepine, and work efficacy is faster in oxcarbazepine.

Table 2: The severity of pain after 1st, 3rd, 6th months of medication.

Pain	Oxcarbazepine (n=15) No. (%)	Carbamazepine (n=15) No. (%)	P value
A. After 1 month			
No pain	5 (33.3%)	2(13.3%)	0.187^{ns}
Mild pain	8 (53.3%)	7(46.7%)	
Moderate pain	2 (13.3%)	6(40.0%)	
B. After 3 months			
No pain (0)	11 (73%)	2 (13.3 %)	
Mild pain (3-4)	4 (26.6%)	8 (53.3%)	0.002*
Moderate pain (5-6)	0 (0.0%)	5 (33.3%)	
C. After 6 months			
No pain (0)	13 (86.7%)	2(13.3%)	<0.001*
Mild pain (3-4)	2 (13.3%)	9(60.0%)	
Moderate pain (5-6)	0 (0.0%)	4(26.7%)	

Statistical analysis was done by Chi-square, ns= bot significant, *= significant.

3.2 Number of Attack and duration of pain decreased in oxcarbazepine group

Furthermore, we analyzed the role of medicines precisely in controlling the number of attacks and in regulating pain duration, during TNg. The mean duration of pain (seconds) in group A was 54.35±6.12, and 63.45±8.89 was in group B. Duration of pain is significantly reduced in group A compared to group B after 1 month ($p < 0.002$) and after 3 months ($p<0.001$) of medication. However, surprisingly, after 6 months there is no pain in Oxcarbazepine group. Mean number of attacks in Oxcarbazepine group was 21.36±4.34 and 4.84±1.21 after 1 and 3 months respectively. Mean number of attacks significantly decreased in oxcarbazepine group compare to carbamazepine group after 1month ($p=0.004$) and 3 months ($p=0.001$) (Table 4), indicating the promising potential role of oxcarbazepine in managing pain than compared to carbamazepine.

3.3 Oxcarbazepine has higher tolerability and lower adverse effect

Next, we were interested in detecting adverse effects resulted from these drugs. Our data showing that dizziness was present in 3 (20.0%) patients and drowsiness in 2 (13.3%) patients, in group A, while, 6 (40.0%) patients had dizziness and 4 (26.7%) had drowsiness, in the group B, after 1 month treatment. After 3 months medication, in group A, dizziness was found in 2 (13.3%) patients and drowsiness in 1 (6.7%) patient, on the other hand, in group B, 7 (46.7%) patients with dizziness and 5 (33.3%) with drowsiness were found. Later, after 6 months of medications, dizziness in 7 (60.0%) and drowsiness in 4 (26.7%) cases were found in group B. But no adverse effects were observed in patient taken oxcarbazepine (group A) after 6 months. Surprisingly, Side effects were significantly decreased in oxcarbazepine group after 6 months ($p <0.05$) (Table 5).

Table 3: Difference in pain score between oxcarbazepine and carbamazepine.

Pain score	Oxcarbazepine (n=15)	carbamazepine (n=15)	P value
(mean± SD)	1.41 ± 0.78	4.11 ± 0.91	<0.001*

Statistical analysis was done by Unpaired students' t-test, *significant.

Moreover, we compared the significance of adverse effects between the groups during treatment follow-up. It has shown that, adverse effects presented in 4 (26.7%) patients in oxcarbazepine group and 9 (60.0%) patients in carbamazepine group, after 1 month treatment. Then, after 3 months of treatment patients with adverse effects were decreased to 2 (13.3%) in Oxcarbazepine group, while, patients were increased to 10 (66.7%) in carbamazepine group.

However, after 6 months no side effects were observed in oxcarbazepine group, unlike, 11(73.3%) patients had side effect in carbamazepine group. Side effects were significantly decreased in oxcarbazepine group after 3 and 6 months compared to carbamazepine group ($p < 0.05$) (Table 6), suggesting that oxcarbazepine has greater tolerability and less or no side effect than compared to carbamazepine when treatment duration were prolonged.

3. Discussion

TNg has chronic pain syndrome and high frequency that responds to anticonvulsant medications, particularly carbamazepine [23]. However, present dogma is suggesting that carbamazepine has several adverse effects, and patient are losing interest in taking it after first experience [24]. As of current conditions, it is highly desired to identify a substitute drug of carbamazepine for TNg treatment [25]. Oxcarbazepine, a keto derivative of carbamazepine, which is already known for its safe anti-convulsant activity. Thus, in present study we confirmed the higher effectiveness and tolerability of oxcarbazepine, over carbamazepine.

Table 4: Comparison of duration of pain and number of attacks between two groups.

	Duration	Oxcarbazepine (n=15) Mean ± SD	carbamazepine (n=15) Mean ± SD	P value
Duration of pain (seconds)	After 1 month	54.35±6.12	63.45± 8.89	0.002*
	After 3 month	26.51± 1.91	33.14± 2.72	0.001*
	After 6 month	0.0	4.71± 0.22	-
Number of Attacks	After 1 month	21.36 ± 4.34	26.23±4.17	0.004*
	After 3 month	4.84± 1.21	7.21± 2.12	0.001*
	After 6 month	0.0	3.42± 0.19	-

Statistical analysis was done by Unpaired students' t-test, *significant.

In previous study it is reported that females are more prone to attack of TNg than male [26]. In this study our data also suggesting similar impression where 43.3% were male and 56.7% patients were female. 53.3% patients were found to be with the age group of 51- 60 years, followed by 46.7% were in the age group of 40-50 years.

Table 5: Association of different adverse effects in two groups.

Follow-up	Adverse effect	Oxcarbazepine (n=15) No. (%)	carbamazepine (n=15) No. (%)	P value
After 1 month	a. Dizziness	3 (20 %)	6 (40%)	0.192^{ns}
	b. Drowsiness	2 (13.3 %)	4 (26.7%)	0.361^{ns}
	c. Headache	0 (0.0 %)	0 (0.0 %)	
	d. Vomiting	0 (0.0 %)	0 (0.0 %)	
	e. Ataxia	0 (0.0 %)	0 (0.0 %)	
After 3 months	a. Dizziness	2 (13.3%)	7 (46.7%)	0.108^{ns}
	b. Drowsiness	1 (6.7%)	5 (33.3%)	0.329^{ns}
	c. Headache	0 (0.0 %)	0 (0.0 %)	
	d. Vomiting	0 (0.0 %)	0 (0.0 %)	
	e. Ataxia	0 (0.0 %)	0 (0.0 %)	
After 6 months	a. Dizziness	0 (0.0 %)	7 (46.7%)	<0.001*
	b. Drowsiness	0 (0.0 %)	4 (26.7%)	0.031*
	c. Headache	0 (0.0 %)	0 (0.0 %)	
	d. Vomiting	0 (0.0 %)	0 (0.0 %)	
	e. Ataxia	0 (0.0 %)	0 (0.0 %)	

Statistical analysis was done by Unpaired students' t-test, *significant.

In previous study it is reported that females are more prone to attack of TNg than male [26]. In this study our data also suggesting similar impression where 43.3% were male and 56.7% patients were female. 53.3% patients were found to be with the age group of 51- 60 years, followed by 46.7% were in the age group of 40-50 years. The mean age of these patients was 56.6±6.28, which is consistent with previous findings [27]. These data indicating that females are in higher risk to be affected by TNg after 40 years in Bangladesh. But, there are no concrete evident to confirm that people having TNg in young age.

In present study we found 13 patients had pain (7 mild, 6 moderate) in carbamazepine group, and 10 patients had pain (8 mild, 2 moderate) in oxcarbazepine group after 1 month of treatment. But, after 6-month treatment, though 13 patients found with pain (9 mild, 3 moderate) in carbamazepine group, interestingly only 2 patients had found with mild pain in oxcarbazepine group. The mean pain score in oxcarbazepine group was 1.41± 0.78 and in carbamazepine group was 4.11±0.91. Statistical analysis showed that pain was significantly reduced in oxcarbazepine group compare to carbamazepine group. Also, we found that number of TNg attack and pain duration decreased in tapering manner with prolonged treatment time in oxcarbazepine group. Oxcarbazepine was effective from the first month of treatment. There was a significant reduction in pain frequency, leading to patient's increasing satisfaction. In contrast not much changes were observed in carbamazepine group. In this study our data clearly suggesting that pharmacological efficiency of oxcarbazepine is far effective than carbamazepine in managing TNg disorders.

Table 6: Comparison of adverse effects between two groups.

Follow-up	Adverse effect	Oxcarbazepine (n=15) No. (%)	carbamazepine (n=15) No. (%)	P value
After 1 month	a. Present b. Absent	4 (26.7%) 11(73.3%)	9 (60.0%) 6(40.0%)	0.065^{ns}
After 3 months	a. Present b. Absent	2 (13.3%) 13 (86.7%)	10 (66.7%) 5 (33.3%)	0.003*
After 6 months	a. Present b. Absent	0 (0.0%) 15 (100%)	11(73.3%) 4 (26.7%)	<0.001*

Statistical analysis was done by Unpaired students' t-test, *significant.

Already it is reported that carbamazepine has many adverse effects, tolerability score is poor. Another aim in this study was to identify and compare side effects of both drugs. We detected only 4 patients suffered from adverse effects in oxcarbazepine group and 9 in Carbamazepine group after 1 month. Surprisingly, after 6 months there is no side effect in oxcarbazepine group, conversely, 11 patients had side effect in carbamazepine group. Side effects were significantly decreased in oxcarbazepine group after 3 and 6 months ($p<0.05$). These results confirming that oxcarbazepine is more tolerable than Carbamazepine both in, dose related side effects and allergy related cases. When treating chronic neuralgiform conditions affecting the face, clinicians frequently have to go recommended maximum prescription doses of both carbamazepine and oxcarbazepine in order to reach therapeutic benefit. This comes at the cost of frequent development of side effects, leaving clinicians without any clear evidence-based guidance. Recent reviews of both general and analgesic drug trials have shown the lack of systematic reporting of adverse effects [28,29].

Taking together all data, our study clearly demonstrating that oxcarbazepine has more efficacious property than compared to carbamazepine, as an emerging drug in the treatment of TNg in both new and intractable case. In addition, this study confirming well- tolerated profile and very minimum adverse effect in oxcarbazepine only during initial stage of treatment. It is still necessary to conduct similar study, nationwide to clarify the outcome and benefits of these drugs using big sample size with long term follow-up. Future studies will improve appropriate strategies in dealing neurogenic disorders and give direction to the pharmacological research in developing new therapies in the management of TNg with no side effect at affordable rate.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and was approved by the Institutional Review Board (or Ethics Committee) of Bangabandhu Sheikh Mujib Medical University.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflict of interest: The authors declare no conflict of interest.

Disclaimer: This paper has not been published nor submitted in full or in part elsewhere.

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