Treatment Failures in Trigeminal Neuralgia Patients: An Institutional Audit.

***Abah AA, **Emeka OM, **Agbelusi GA**
*Oral Medicine Unit, Department of Pathology/Oral Medicine, College of Medicine, Lagos State University, Lagos.
**Oral Medicine Unit, Department of Preventive Dentistry,College of Medicine, University of Lagos, Lagos.

Correspondence: Abah AA
Email: debowun@gmail.com

Abstract

Background: Trigeminal Neuralgia (TN) is a frequent cause of paroxysmal facial pain and headaches in adults. It frequently presents in the fourth and fifth decade of life and affects the 5th cranial nerve. It is usually unilateral and does not disturb sleep.

The gold standard drug is Carbamazepine (CBZ) and treatment failure to CBZ could be attributed to intake of drugs or food containing B group vitamins, patients' tolerance to the medication and the use of fake medication. The effectiveness of this drug has been reported but, there is dearth of literature that demonstrates causes of failure of CBZ in the treatment of trigeminal neuralgia.

Objective: To determine the causes of treatment failure in Trigeminal neuralgia patients attending the Oral Medicine Clinic of Lagos University Teaching Hospital, Lagos, Nigeria.

Materials and Methods: This was a retrospective study of cases of Trigeminal Neuralgia who presented at the Oral Medicine Clinic of the study institution between April 2009 and April 2012. Data were collated from patients' case notes and clinical records. The recorded parameters included patients' bio data, response to treatment and treatment failure.

The results were analyzed using Statistical Package for Social Sciences for Windows(version 16).

Results: A total number of 32 patients were diagnosed with Trigeminal neuralgia during this period. There were 22 (68.87%) females and 10 (31.2%) males; with female to male ratio of 2.2:1. Age range was 9 to 82years (mean 53.4±13.86). Carbamazepine was the principal drug prescribed. There was treatment failure associated with it due to the use of B group vitamins in 10 patients (31.5%); 5 (15.63%) from tolerance to the drug and 2(6.10%) from fake drugs. Twenty-seven (84.4%) patients went into remission when all the factors leading to failure were addressed; therefore the response rate was good.

Conclusion: Carbamazepine was used as the primary drug in the treatment of trigeminal neuralgia and treatment failure was largely due to taking drinks and drugs containing B group vitamins.

Key words: Trigeminal neuralgia, Carbamazepine, B group Vitamins, treatment failure.

Introduction

Trigeminal Neuralgia (TN), otherwise known as Tic douloureux or Fothergill's disease, is a neuropathic disorder characterized by sudden, sharp, extreme, stabbing, lancinating or electric shock-like pain which affects one or more branches of the 5th cranial nerve

(trigeminal nerve). The maxillary branch is mostly affected while the ophthalmic branch is the least affected[1,2]. It is typically unilateral, brief, with recurrent episodes of pain and usually with a trigger zone or trigger factor/s[3]. It has been described as one of the most painful conditions known to mankind[4]. The intensity of the pain can be physically and mentally incapacitating and has a great effect on the quality of life[5].

International classification of Headache Disorders-2nd edition (ICHD-2) by International Headache Society (HIS), classified TN as Classic TN and Symptomatic TN6b. Classical TN includes patients in which no identifiable cause can be found other than a vascular compression of the trigeminal nerve. Symptomatic TN describes those patients, in which an identifiable cause can be found, such as a tumour, arteriovenous malformation or multiple sclerosis (MS) other than a vascular compression. Not every patient with TN will fulfill the IHS diagnostic criteria; therefore the diagnoses of 'atypical' or 'type II' Trigeminal Neuralgia can be applied[6].

Type 1(typical) or classical TN is characterized by intense, sharp, stabbing pain that lasts from a fraction of a second to two minutes per episode. Type 2 (atypical) is characterized by constant aching, burning, stabbing pain of lower intensity than Type 1[7].

The revised international classification of Headache Disorders-3(ICHD-3), suggested three variants: (1) classical trigeminal neuralgia often caused by microvascular compression of the trigeminal root entry to the brain stem; (2) Trigeminal neuralgia with concomitant persistent facial pain and (3) Symptomatic trigeminal neuralgia caused by a structural lesion other than vascular compression.

TN diagnosis is based principally on the patient's history but a physical and neurological examination must be carried out[5]. Other conditions that cause facial pain must also be ruled out.

In the treatment of TN, medical therapy is usually considered, especially in a resource limited setting, nevertheless, for refractory TN or vascular compression related TN, surgical option(such as Gasserian ganglion percutaneous techniques, gamma knife surgery, microvascular decompression) should be tabled before the patient.

The main treatment is primarily with anticonvulsants with recently published international guidelines suggesting Carbamazepine and oxcarbazepine as the first-line drugs. Other anticonvulsants that are employed are Phenytoin (Dilantin) and gabapentine (Trileptal)[9,10]. Muscle relaxants (baclofen) and antidepressants (amytriptyline) have also been found effective in combination with the anticonvulsants[11,12,13].

Carbamazepine (CBZ) with the chemical formula 5-carbamyl-5H-dibenzapine, is an iminostilbene, structurally and chemically related to tricyclic antidepressant, impramine hydrochloride. Its main pharmacological action is that of an anticonvulsant.

Patients are usually placed on 100mg-200mg twice daily on commencement of the drug and may be gradually increased until the pain is completely alleviated. Good relief of pain may be achieved at low doses (600mg/day). CBZ induces its own metabolism by means of auto induction, usually within 3–5 weeks of first dosage[14]. Thus, patients do not often respond to therapeutic doses of CBZ and achieve relief only at higher doses and this increases the side and toxic effects (nausea, vomiting, dizziness, ataxia and neurological defects).The higher doses may also be required during severe attacks of pain. The usual effective dose ranges from 600 to 1200mg/day.

Carbamazepine sometimes does not give a lasting solution as tolerance to the drug occurs. It also exhibits a drug-drug reaction reducing its efficacy. Yadav et al reported failure of medical treatment with the use of carbamazepine and in combination with other first line and second line drugs[15] and Bennetto et al reported drug intolerance and adverse drug reactions[16]. Since medical treatment is employed in this institution and no case of surgical treatment yet, there is the need to evaluate this drug and find the causes of treatment failure experienced in this centre; if there is really a need to switch over to another anticonvulsant as the 1st line drug (example pregabalin) or the option of surgery as the case warrants. Also, there is dearth of literature that demonstrates causes of failure of CBZ for treating trigeminal neuralgia, so the compelling factor also for this study.

Therefore, the aim of this study is to determine the causes of treatment failure in patients using anticonvulsants in the treatment of Trigeminal Neuralgia at LUTH.

Materials and Methods

This was a retrospective study of cases of Trigeminal Neuralgia who presented at the Oral Medicine Clinic of the study institution between April 2009- April 2012. Data were collated from patients' case notes and clinical records. The recorded parameters

included patients' bio data, response to treatment and treatment failure.

The diagnosis of trigeminal neuralgia was based on history and clinical features after other causes of pain have been ruled out. In the case notes, emphasis was made to avoid intake of multivitamin supplements containing B groups and drinks fortified with B vitamins. On every visit, it was mandatory each patient presented a notebook containing all the food, drinks and medications they took in the course of their treatment. Treatment response and failure were adjudged as decrease or no change in pain character assessed by Visual Analogue Scale (with no pain designated as 0 and 10 designated as worst possible pain).

Additionally treatment failure was also evaluated based on drug efficacy. The evaluation was based on National Agency for Food and Drug Administration and Control (NAFDAC) registration number. A questionable/fake drug was concluded if the number was not seen on the drug pack and pain remained status quo.

Data analysis was performed using Statistical Package for Social Sciences (SPSS) for windows (version 16.0), SPSS Inc., Chicago, IL.

Results

A total number of 32 patients were diagnosed with Trigeminal neuralgia during this period. There were 22 (68.8%) females and 10 (31.2%) males with F: M ratio of 2.2: 1. Age range was 9-82years (mean 53.4±13.86); age range of 51-60years (34.4%) had the highest prevalence **(Figure 1)**.

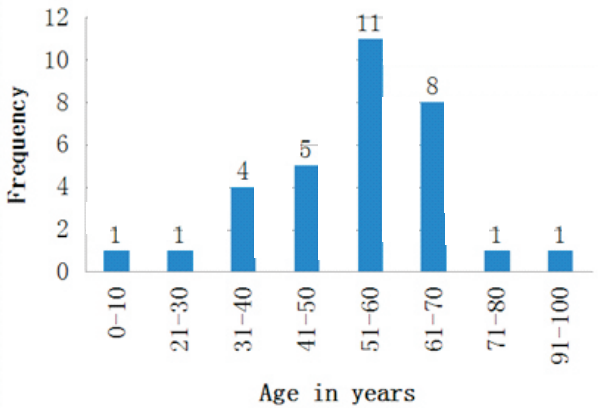

Figure 1: Age Distribution

Carbamazepine was the main drug used initially by the 32 patients along with folic acids, but at the end of the three years, only 23(71.9%) still maintained this regime. Multidrug therapy was employed when the patients noticed no further reduction or there was an increase in the intensity of the pain. One (3.1%) used CBZ + folic acid + phenytoin; 2(6.2%) used CBZ + folic acid + Amitriptyline; 5(15.6%) used CBZ + folicacid + phenytoin + Amytriptyline; and 1(3.1%) used CBZ + folic acid + baclofen.

Ten (31.25%) had treatment failure when B group of vitamins was used alongside CBZ and folic acid; Five (15.63%)of the patients on CBZ + folic acids developed tolerance while 2(6.10%) had failed treatment due to the use of fake carbamazepine **(Figure 3)**. Twenty seven (84.4%) patients went into remission for 3-6months within the three years course of their treatment when all the factors leading to failure were also addressed. Therefore the response rate was good.

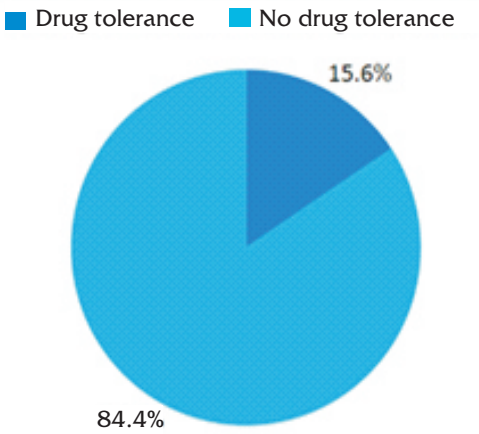

Figure 2: Drug tolerance

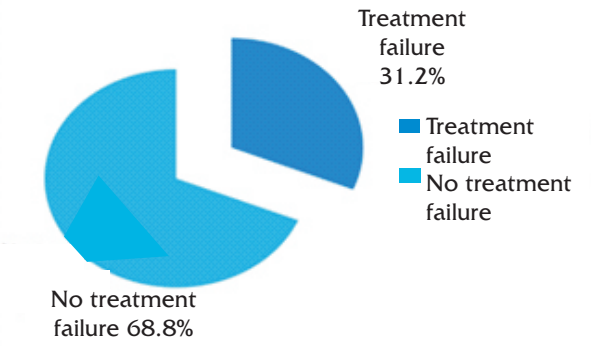

Figure 3: Treatment failure due to B group vitamins

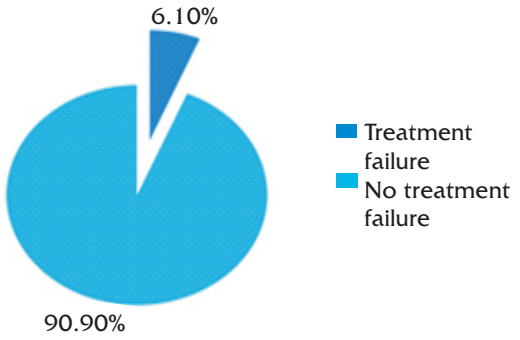

Figure 4: Treatment failure from the use of fake carbamazepine

Discussion

Trigeminal neuralgia (TN) has been described as one of the most painful conditions known to mankind and often referred to as the 'suicide disease[17]; its characteristic pain is spontaneous, lancinating, throbbing and electric shock-like which usually last few seconds or minutes in the typical type but may last for hours in the atypical type.

The prevalence was higher in the age group 51-60 years, which is in agreement with reports in the literature where TN has been seen in patients above 50years[15,18]. It is predominant in females, an occurrence consistent with the literature[19].

Carbamazepine is the gold standard drug for the treatment of TN[16,20,21,22]. This drug is a Na + channel blockers and relieves trigeminal neuralgia pain by suppressing membrane resonance and stimulation of injured afferents. Patients find immediate relief with carbamazepine similar to previous study carried out by Agbelusi et al [23]. Pain relief may be incomplete and there may be a need to increase the dose or add another agent/s like phenytoin, Amitriptyline or baclofen or even switch drugs[16]. Prolonged use of carbamazepine may result in depletion of folic acid in the body[24, 25]; therefore patients are advised to be on daily folic acid to prevent anaemia.

The long term effect of carbamazepine has been evaluated in few studies showing either loss of effect or tolerability in one half of the patients over a 10 year period. In all the patients seen in that study, carbamazepine was found to be effective in controlling pain initially, though multi-drug therapy was administered at the end in majority of them [20].

In this study group, 10 (31.25%) patients had treatment failure when B group vitamins were administered in form of multivitamin syrups and capsules. This was detected from their notebooks. Other drugs like antihypertensive were ruled out. Vitamin B group are neurotrophic drugs potentiating the action of nerves and regeneration of damaged nerves[26]. The patients' medications were never supplemented with it and also advised to avoid the vitamin. When vitamin B complex is used with CBZ, there is a drug-drug interaction which invariably affects the availability of CBZ to reduce pain. There is resultant vitamin B depletion in the body. This was observed in a study where low serum vitamin B12 was seen in 23 patients with trigeminal neuralgia on Carbamazepine [27].

Therefore, patients being managed for TN should avoid the use of any vitamin B containing drugs or drinks. Pain is usually abated when B group vitamins are stopped. This is also consistent with studies cited in the literature[26].

After one year use of Carbamazepine with folic acid, it was observed that 5 (15.6%) of the patients developed tolerance to the drug after using the maximum dose and this could not control the pain anymore. For the 5 patients, phenytoin and amytriptyline were introduced to achieve proper pain control.

All the patients suffered from one side effect or the other (dizziness, drowsiness, ataxia, nausea) on commencement of Carbamazepine. This is consistent with other studies[28]. Although after a while, almost all the patients adapted to the side effects, but about 6(18.8%) of the patients could not bear the side effects and therefore stopped the medications within two weeks of use. This was due to the discomfort and its effect on the quality of life and their jobs. The pain therefore recurred in such cases and these patients were placed back on their medications after re-counselling.

Use of fake drugs is a common feature in our society and resulted in treatment failure in 2(6.1%) of the patients. These patients may purchase and use their medications judiciously, despite this, the pain is not abated. Clinicians will need to always investigate the efficacy of the drugs their patients are using.

Spontaneous remission is one of the characteristics of TN. In our study, no patient had spontaneous remission, but total remission from the use of medications was experienced in 27(84.4%) of the patients for a period of 3-6months with the 3year period of intervention.

Conclusion

Carbamazepine was used as the major drug in the treatment of trigeminal neuralgia with good response. Treatment failure was mainly due to the use of vitamin B and tolerance. Patients' medications must always be monitored.

None of the patients had surgical intervention as an alternative to medical treatment. This may be beneficial to those that have not gone into remission. This is an option to look into. The side effects of some of the surgical intervention must also be explained to them. These patients are usually financially constrained so governmental and non- governmental agencies may be called upon for assistance.

Conflicts of interest

The authors declare there are no conflicts of interest.

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