ORIGINAL ARTICLE POJ 2018:10(1) 51-55

'Triple drug therapy' for the management of carbamezapine refractory trigeminal neuralgia

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Abstract

Introduction: Trigeminal Neuralgia is encountered in practices of dentists and specialists quite often. Many therapeutic regimes are used for its treatment. Hence the purpose of the present research was to evaluate the efficacy of combination therapy using Oxcarbazepine, Gabapentin and Amitriptyline among patients presenting with Trigeminal Neuralgia refractory to Carbamazepine therapy.

Material and Methods: A self-administered questionnaire consisting of questions on the intensity of pain and the impact of patient's pain on their quality of life was distributed among patients presenting with Trigeminal Neuralgia refractory to Carbamazepine therapy. The collected data was analyzed using SPSS software. The study was conducted at the Department of Oral & Maxillofacial Surgery, de'Montmorency College of Dentistry / Punjab Dental Hospital, Lahore, from January, 2017 to August, 2017.

Results: A total of 32 patients participated in the study out of which 6 were lost during follow-up. Of the remaining 26, 21 (80.76%) patients had pain relief while 5 (19.23%) reported no improvement in symptoms. Of the 21 patients with improvement in pain symptoms, 12 (57.14%) reported their pain as moderate after 3 months and 9 (42.85%) reported their pain level as mild. Furthermore, the mean score for quality of life in these patients also improved from a mean of (8797) to (7768) in a period of 3 months.

Conclusions: It was concluded from the present study that combination therapy using Oxcarbazepine, Gabapentin and Amitriptyline for intractable Trigeminal Neuralgia leads to significant reduction in pain levels as well as improvement in quality of life and should be explored further.

Keywords: Orofacial pain; gabapentin; amitriptyline; refractory pain

Introduction

Trigeminal neuralgia (TN) is a characteristic severe pain disorder that affects 4 in 100,000 people and produces intense, sharp, shooting or stabbing pain in the area of distribution of the fifth cranial nerve.[1] Typically, diagnosis is based on the history of paroxysmal pain lasting from a few seconds to several minutes and refractory to stimulation between attacks, the frequency of which can be greater than a hundred in a day.[2] The pain of TN has a profound effect on the quality of life as the pain can be triggered by daily activities like eating, speaking, washing the face and brushing the teeth.[3] The etiology is thought to be compression of the trigeminal nerve root in 80-90% of cases due to a blood vessel in which case it is labeled as classical or idiopathic TN. The remaining 10% fall under the category of symptomatic TN with a demonstrable benign tumor or multiple sclerosis.[4] Another classification based on symptoms categorizes TN into typical and atypical forms.[5]

Medical therapy with anticonvulsants is considered the first line of treatment, with surgical treatments being reserved for medically unresponsive TN or in patients in whom significant side effects of the medical therapy appear.[6] The surgical treatments

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include microvascular decompression in which the posterior fossa is explored and the compressing vessel addressed or an ablative treatment that addresses the trigeminal nerve in different ways and includes percutaneous balloon compression, glycerol rhizotomy, radiofrequency thermocoagulation and gamma knife radiosurgery.[7]

Carbamazepine is considered to be the drug of choice for managing TN but is only effective in 70-80% of patients and may lead to the development of considerable side effects.[8] Furthermore, 20% of those initially responding to therapy may become refractory to the drug. In such intractable cases, 2nd line agents can be added or switched to and these include but are not limited to Oxcarbazepine, Gabapentin, Lamotrigine, Baclofen, Clonazepam and Topiramate.[9]

Our proposed treatment regimen for intractable TN is combination therapy with Oxcarbazepine, Gabapentin and Amitriptyline, the latter two of which have proven efficacy for the treatment of neuropathic pain but are lacking in data specifically for TN. The rationale is that combination therapy with these drugs utilizes different mechanisms for improving both the pain and quality of life patients with TN.

Material and Methods

This descriptive case series was conducted on patients presenting to the Department of Oral & Maxillofacial Surgery at de'Montmorency College of Dentistry Lahore / Punjab Dental Hospital Lahore from January 2017 to August 2017. Patients included in the study were those with established Trigeminal Neuralgia that had become unresponsive to carbamazepine therapy. Patients with history of any surgical treatments were excluded from the study.

A total of 32 patients were followed in this study. We used a self-administered questionnaire (Fig 1) to measure the levels of pain and the quality of life at the time of presentation which was serially followed at the interval of 1 and 3 months. The questionnaire measured current pain due to trigeminal neuralgia and categorized it into the following five levels: no pain, mild pain, moderate pain, severe pain and extremely severe / unbearable pain. Similarly, the quality of life was measured by evaluating the effect of pain on the patient's job, household work, mood, diet and their ability to maintain their orofacial hygiene. The measures for quality of life was also assessed on a five-point scale from no effect, mild effect, moderate effect, severe effect to unbearable effect. Results obtained from the questionnaires were analyzed by using SPSS version 22.

Results

A total of 32 patients participated in the study out of which 6 were lost during follow-up. Of the remaining 26, 21 (80.76%) patients had pain relief while 5 (19.23%) reported no improvement in symptoms. Of the 21 patients with improvement in pain symptoms, 12 (57.14%) reported their pain as moderate after 3 months and 9 (42.85%) reported their pain level as mild.

From the 26 patients who were followed up for three months, the number of patients with severe pain was reduced from 14 to only 03 after a three-month treatment. The count of 12 patients with unbearable pain decreased to 4 patients. 3 patients now had a decrease in pain levels to severe while 10 patients pain decreased to moderate levels.

Regarding quality of life, patients reported an improvement in their ability to do their everyday jobs after the start of the new therapy with the impact of the pain of TN decreasing from a mean of 73.07% before therapy to 44.23% after 3 months. The adverse effect of TN pain on mood and behavior dropped from 48.07% to 31.73%. The ability to adequately maintain Orofacial hygiene improved by 33% while dietary habits improved by 16% after three months of observing the novel regimen. Overall Health increased from a mean score 50.96% to 78.84%.

فارم برائے تشخیص وعلاج درد منہ چہرہ وجبڑہ

نام:_____ عمر:_____ جنس: مرد/عورت تاریخ:_____

مختصر پتہ:_____ موبائل نمبر:_____

اس وقت آپ کے چہرے کے درد کی شدت کتنی ہے؟_____

بالکل بھی نہیں	ہلکی درد	درمیانی درد	شدید درد	بہت شدید/ناقابل برداشت

1۔ مجموعی طور پر آپ کی صحت کیسی رہتی ہے؟

بہترین	بہت اچھی	اچھی	مناسب	خراب

2۔ **اس وقت** آپ کے چہرے کا درد آپ کے **پیشہ یا کام کاج** میں کس حد تک رکاوٹ کا باعث بن رہا ہے؟

بالکل بھی نہیں	معمولی حد تک	مناسب حد تک	کافی حد تک	شدید حد تک

3۔ **اس وقت** آپ کے چہرے کا درد آپ کے **چہرے اور دانتوں کی صفائی ستھرائی** کو کتنا متاثر کر رہا ہے؟

بالکل بھی نہیں	معمولی حد تک	مناسب حد تک	کافی حد تک	شدید حد تک

4۔ **اس وقت** آپ کے چہرے کا درد آپ کی **طبیعت اور مزاج** پر کتنا اثر کر رہا ہے؟

بالکل بھی نہیں	معمولی حد تک	مناسب حد تک	کافی حد تک	شدید حد تک

5۔ **اس وقت** آپ کے چہرے کا درد آپ کے **کھانے پینے** کو کتنا متاثر کر رہا ہے؟

بالکل بھی نہیں	معمولی حد تک	مناسب حد تک	کافی حد تک	شدید حد تک

دستخط مریض:_____ دستخط ڈاکٹر:_____

Visit type:	Pre-Op	1 Month	3 Months

Figure 1: Questionnaire

Discussion

This study described the pain control and quality of life of 26 patients with intractable TN that had become unresponsive to conventional first line medical therapy. We evaluated mean pain levels, overall health, general mood and behavior, ability to work / maintain jobs, Orofacial hygiene and dietary habits using a five point scale (no effect, mild effect, moderate effect, severe effect to unbearable effect). Since there are no studies in the literature evaluating these as a group for patients with TN, there's a lack of numeric values for comparison. However, some studies with a similar general conclusion will be presented and discussed.

Mean pain levels for TN are usually assessed via a 100-mm visual analog scale (VAS) on which 0 represents no pain and 100 represents the worst ever pain. Cheng-Yin Tan et al evaluated the pain of 75 patients with TGN at its worst and at its least over a period of 4 weeks and obtained a mean score of 84.5 ±17.1 and 26.8 ± 21.8 respectively.[10] A study by Zakrzewska et all showed that pain control led to significant improvement in quality of life indices.[9]

In addition to the pain itself, there is a substantial burden on patients leading to an increased sense of fear that the pain could return suddenly at any time. During severe attacks, many patients are unable to speak or eat.[11] According to one study, 'many patients with trigeminal neuralgia live each day dreading the possibility of the unpredictable return of sudden severe facial pain. A single nerve holds the whole mind hostage, and safety from another assault of pain is never certain.[12]

The cumulative effect of all these conditions leads to increased difficulties in daily function which in turn affects the quality of life. Tolle et al showed that pain severity correlated with reduced daily function, well-being, quality of life, sleep and overall health status.[13] Regarding ability to hold jobs and participate in society, one study reports that TN impacted employment in 34% of patients and that depressive symptoms are frequent in patients suffering from TN.[14]

The novel drug regimen used in our study aimed to address both the refractory TN and the psychosocial aspects associated with the disease. Oxcarbazepine has been shown to have proven advantages over Carbamazepine that include safer drug profile, fewer interactions, comparable efficacy and improved tolerability.[15] Of particular concern is the slightly different mechanism of action which blocks L-Type Calcium channels in addition to the Sodium and NMDA channel blockade involved in the pain pathway, which makes it useful for the treatment of refractory TN.[16] Regarding the improvement in quality of life, there is evidence of improved cognition and alertness after substitution of oxcarbazepine for carbamazepine in some patients with epilepsy.[17]

There is debate in the literature about the natural course of TN and the mechanism of its evolution into atypical forms that are resistant to traditional therapy.[18] Gabapentin is thought to be effective in suppressing the central sensitization that leads to the intractable nature of medically unresponsive TN as it acts on the a2d (alpha2delta) calcium-channel subunit which results in the decrease of neurotransmitters release and suppression of central sensitization. This is possible as the proposed mechanism of the drug is not the reduction of ectopic discharges in the trigeminal ganglion directly, but rather to influence pain transmission or inhibition at the level of the central nervous system.[19]

Antidepressants are recommended as a treatment option for the pharmacological treatment of neuropathic pain of most causes, and current guidance suggest that when using an antidepressant a tricyclic antidepressant (TCA) should be the first-line choice.[20] The EFNS guidelines state that combination therapy with tricyclic antidepressant plus gabapentin or gabapentin

plus an opioid seems to be useful in some patients.[21] We have used once daily dosing of Amitriptyline which is the best and most widely used TCA with promising results and significant improvement in mood and behavior.

Conclusions

It can be concluded from the present study that combination therapy using Oxcarbazepine, Gabapentin and Amitriptyline for intractable Trigeminal Neuralgia leads to significant reduction in pain levels as well as improving the quality of life, the efficacy of which should be further evaluated.

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