ORIGINAL ARTICLE

A retrospective review of efficacy of combination therapy with pregabalin and carbamazepine versus pregabalin and amitriptyline in treatment of trigeminal neuralgia

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ABSTRACT

Aims: Trigeminal neuralgia is a rare cause of neuropathic pain and carbamazepine (CBZ) is its main treatment. However, its adverse effects sometimes compel the physicians to substitute or use it concurrently with other drugs. This study aimed to retrospectively compare the effects of combination therapy with pregabalin and carbamazepine versus pregabalin and amitriptyline, in the treatment of patients with refractory trigeminal neuralgia.

Methodology: Hospital records of 37 patients with refractory trigeminal neuralgia and no favorable response to the primary treatment without pregabalin, were retrospectively reviewed. Demographic information, drug doses and response to the treatment were recorded in a proforma. Visual Analogue Scale (VAS) was used as the tool for measuring pain intensity. Pain reduction equal or less than 50% based on VAS score after eight weeks of treatment was defined as no response to therapy, and pain reduction of more than 50% was considered as positive response.

Results: Twenty eight patients received pregabalin and carbamazepine, three patients received combination of pregabalin and amitriptyline and six received pregabalin, carbamazepine and amitriptyline combination. The mean dose of pregabalin and carbamazepine was 125.68 ± 63.87 and 283.78 ± 193.66 mg/day, respectively. After 8 weeks of treatment, 18 patients (64.3%) in pregabalin and carbamazepine group, six patients (100%) in triple therapy group and two cases (66.7%) in pregabalin and amitriptyline group had responded to treatment.

Conclusion: The effect of combination therapy with pregabalin and carbamazepine was comparable with pregabalin and amitriptyline. Using these combinations may be beneficial in patients with severe trigeminal neuralgia unresponsive to primary treatment.

Keywords: Trigeminal neuralgia; Pregabalin; Carbamazepine; Refractory pain

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INTRODUCTION

Trigeminal neuralgia (TN) is a rare cause of neuropathic pain, which manifests itself as a recurrent, sudden, transient, paroxysmal, severe sharp electric shock-like or lancinating pain that is commonly felt on one side of the jaw or cheek. This syndrome can influence one or more divisions of the trigeminal nerve. Pain may be initiated by stimulation of a trigger point on the face, lips, or gums or by movement of facial muscles or chewing.[1,2] The goal in the management of TN includes achieving long-lasting relief of pain and its prevention.[2] The first choice for treatment of TN is drug therapy administered singly or in combination.[1,2] The

anti-epileptic drug, carbamazepine (CBZ), is the initial choice.[1,2] However several adverse effects are linked with CBZ use, and physicians substitute it with other second line agents like phenytoin, oxcarbazepine and gabapentin (GBP).[1,2] Third line agents (lamotrigine and baclofen) can be tried in cases in which monotherapy is inadequate for relief.[2] To the best of our knowledge, GBP has saturable absorption rate within the usual dosing range. Pregabalin (PGB) exerts the biological activity of GBP and also shows improved pharmacokinetic properties.[3,4] PGB modulates the voltage-gated calcium channels and thus lessens the release of excitatory neurotransmitters.[3,4] PGB is completely absorbed from the gut and does not bind to the plasma proteins and is not metabolized.[3,4] In clinical trials, PGB has been shown to be effective in relieving neuropathic pain linked with post herpetic neuralgia and diabetic peripheral neuropathy.[5-10] PGB has also been demonstrated to be effective in the treatment of TN especially in those patients without concomitant chronic facial pain.[4] It has also been shown that PGB is effective in the management of TN refractory to primary analgesic therapy.[11] Evidence suggests that PGB, both in monotherapy and in combination with other drugs, is an effective drug for the short-term treatment of TN.[11] One major question that still needs to be answered is whether PGP plus CBZ is a better therapeutic choice than PGB and Amitriptyline in the management of TN patient's refractory to primary treatment.

The aim of this retrospective review was to investigate and compare the therapeutic effects of PGB in combination with CBZ versus PGB and amitriptyline in the treatment of TN refractory to primary analgesic therapy.

METHODOLOGY

This retrospective study reviewed hospital records of 37 patients with refractory TN and no favorable response to the primary treatment without PGB, who were referred to the pain clinic of Ami-Alam Hospital, Tehran (Iran) from 2010 to 2013. TN diagnosis was made based on the current version of the International Classification of Headache Disorders (ICHD-II).[12] TN was considered refractory if it had not responded to the previous analgesic therapies and chronic neuropathic pain was constant for more than six months. The term refractory was defined[11] as the lack of pain reduction after treatment with at least one course of an analgesic medications or pain reduction less than 50%.

The study protocol was approved by Institutional Review Board (IRB) at Tehran University of Medical Sciences, Tehran (Iran) and patients' anonymity was ensured during data collection.

Patients with TN refractory to the primary therapies without receiving PGB were included. Those with other severe medical or psychiatric disorders and pregnant and lactating women were excluded.

Demographic information, drug doses and response to the treatment were recorded in a proforma. Pain intensity which was measured by using Visual Analogue Scale (VAS) at beginning and after 8 weeks of treatment, was noted.

Response to therapy was the main outcome measure of the study. Pain reduction of equal or less than 50% based on VAS score was defined as no response to therapy and a pain reduction of more than 50% was considered as a positive response.

Statistical Analysis: All analyses were performed using SPSS for Windows version 16.00 (SPSS Inc., Chicago, IL, USA). Continuous data was presented as mean and SD and categorical data was shown as number and percentage. To compare categorical data such as response to therapy between the two groups, chi-square test was used. Paired t-test was used to evaluate the changes in VAS pain score before and after treatment. P value less than 0.05 was considered significant.

RESULTS

Hospital records of 37 patients with refractory TN including 22 male (59.5%) and 15 (40.5%) females with mean age of 56.92 ± 13.61 were reviewed. Patient demographics and clinical characteristics are shown in Table 1.

Twenty eight patients received PGB and CBZ, three patients received a combination of PGB and Amitriptyline and 6 patients received triple therapy with PGB, CBZ and Amitriptyline. The mean dose of PGB and CBZ were 125.68 ± 63.87 and 283.78 ± 193.66 mg/day respectively.

The mean VAS score after 8 weeks of treatment decreased significantly in all patients ($p<0.001$). VAS score reduction in PGB and amitriptyline group was borderline (p: 0.057).

After 8 weeks of treatment, 18 patients (64.3%) in PGB and CBZ group, six patients (100%) in triple therapy group and two cases (66.7%) in PGB and amitriptyline group and in overall 26 patients (70.3%) responded to treatment (Table 1).

Table 1: Demographic and clinical characteristics of patients in the three study groups

	TN (total)	PGB + CBZ	PGB and Amitriptyline	PGB, CBZ and Amitriptyline
Number of patients	37	28	3	6
Age (mean ± SD) in yrs	56.92 ± 13.61	56.21 ± 14.65	60.0 ± 17.57	58.67 ± 6.25
Gender [n (%)] M F	 22 (59.5) 15 (40.5)	 15 (53.6) 13 (46.4)	 3 (100) 0 (0.00)	 4 (66.7) 2 (33.3)
VAS score before treatment	8.97 ± 1.70	9.00 ± 1.80	10.00 ± 0.00	8.33 ± 1.50
VAS score after treatment	1.92 ± 2.22	1.57 ± 1.81	3.33 ± 2.88	2.83 ± 3.40
Previous treatment				
No treatment [n (%)]	2 (5.4)	1 (3.6)	1 (33.3)	0 (0.0)
CBZ [n (%)]	28 (75.7)	22 (78.6)	2 (66.7)	4 (66.7)
Gabapentin [n (%)]	6 (16.2)	6 (21.4)	0 (0.00)	6 (100)
Pregabalin [n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Amitriptyline [n (%)]	1 (2.7)	1 (3.6)	0 (0.00)	0 (0.00)
Other [n (%)]	13 (35.1)	10 (35.7)	1 (33.3)	2 (33.3)
Interventions				
CBZ [n (%)]	34 (91.9)	28 (100)	0 (0.0)	6 (100)
Gabapentin [n (%)]	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.0)
Pregabalin [n (%)]	37 (100)	28 (100)	3 (100)	6 (100)
Amitriptyline [n (%)]	9 (24.3)	0 (0.0)	3 (100)	6 (100)
Pregabalin dose (mg/day)	125.68 ± 63.87	133.93 ± 68.79	100±43.30	100.00±38.73
CBZ dose (mg/day)	283.78±193.66	325.00±193.64	0.00	233.33±81.65
Response to Intervention >50% [n (%)]	26 (70.3)	18 (64.3)	2 (66.7)	6 (100)

Legend: CBZ = carbamazepine, PGB = pregabalin, TN = trigeminal neuralgia

Table 2: Patients characteristic regarding response to intervention

Variable	Response to intervention			
	< 50%	> 50%	P-value	Statistics
Number of patients	11	26		
Gender Male [n (%)]	6 (54.5)	16 (61.5)	0.69	Chi-square
Female [n (%)]	5 (45.5)	10 (38.5)		
Age (Mean ± SD)	53.73 ± 18.30	58.27 ± 11.24	0.361	t-test
VAS before treatment (Mean ± SD)	10.00 ± 0.00	8.54 ± 1.88	0.015	t-test
VAS after treatment (Mean ± SD)	1.09 ± 1.86	2.27 ± 2.30	0.116	t-test
Pain Location				
Left [n (%)]	5 (45.5)	8 (30.8)	0.593	Chi-square
Right [n (%)]	6 (54.5)	17 (65.4)		
Bilateral [n (%)]	0 (0.0)	1 (3.8)		

Table 2 summarizes characteristics of patients regarding response to the therapy. There was no significant difference in the doses of PGB and CBZ between responders and non-responders (p=0.284 and p=0.612, respectively).

There was no significant difference between those who received PGB + CBZ and those who received PGB + amitriptyline regarding the response to treatment (pain reduction of more than 50%) (p>0.05) (Table 2).

DISCUSSION

This retrospective study suggests that PGB might be effective in the treatment of TN. We found that PGB in combination with CBZ or amitriptyline exerted a remarkable analgesic effect. Also, we found that triple therapy with PGB, CBZ and amitriptyline had a superior analgesic effect. These findings are in line with the studies of Obermann et al[4] and Pérez et al [11]. These studies demonstrated comparable effects of combination therapy with PGB + CBZ and PGB + Amitriptyline in the treatment of refractory TN. However, the small number of patients in our second group may limit our interpretation.

PGB has superiority over the other treatment options because of fewer side effects, more rapid titration potential, shorter onset of action and the fact that can be administered twice daily (BID) which might increase patients' adherence to treatment.[4] Membrane-stabilizing agents such as anticonvulsants are believed to be effective in the management of paroxysmal pain through suppressing ectopic transmission and blocking Na+channels.[3,4] This mechanism is operative for CBZ and lamotrigine, while gabapentin and pregabalin exert their role through interaction with the $a_2\delta$ subunit of voltage dependent Ca^{2+} channels thus increasing the cerebral concentration and synthesis of g-aminobutyric acid (GABA).[3,4] The neurotransmitter GABA is demonstrated to reduce central pain. PGB has been demonstrated to be effective in relieving neuropathic pain, though its exact mechanism remains enigmatic.[3,4]

One review[13] has summarized several randomized, placebo-controlled clinical trials investigating efficacy of PGB in the management of diabetic neuropathy. A total of 1068 patients receiving PGB 300–600 mg/day showed significantly greater pain reduction than placebo. Patients with post herpetic neuralgia had significantly greater pain reductions with PGB doses between 450–600 mg/day than placebo recipients. Study of Pérez et al[11] supports the effectiveness of PGB for the improvement in pain and related health symptoms of TN patients' refractory to previous analgesic therapy. Prisco et al also, reported successful treatment of TN in three refractory cases with combination of PGB and CBZ.[14] Our retrospective review confirmed this finding in the management of Iranian refractory TN patients; moreover, it demonstrated that PGB + CBZ as well as PGB + amitriptyline therapy are encouraging in the management of refractory TN. The efficacy of combination therapy of refractory TN has not been assessed in other studies to the best of our knowledge.

Interestingly, we observed that by combination therapy we could achieve a desirable reduction of pain by lower dosages of PGB and CBZ. This finding provisionally confirms that combination approaches like this can prevent adverse side effects of high dose monotherapies, but requires prospective data collection.

The main limitations of our study were the retrospective nature of our study and small number of patients that may limit our interpretation and generalization of results.

CONCLUSION

In conclusion, this study demonstrated that refractory trigeminal neuralgia patients receiving pregabalin plus carbamazepine as well as pregabalin and amitriptyline had considerable reduction in VAS pain score in spite of lower dosages compared to previous studies. Combination of these three medications in non-responders may have superior analgesic effects rather than combination of pregabalin with one of carbamazepine or amitriptyline.

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ACADEMIC ACTIVITIES

58th Post Graduate Course, DMC / CHK Karachi

Dr. Safia Zafar Siddiqui

Course Organiser

Department of Anesthesiology, Surgical Intensive Care & Pain Management

Dow Medical College & Civil Hospital, Dow University of Health Sciences, Karachi

For the last 29 years, we have been holding preparatory classes for candidates of MCPS and FCPS exams, biannually, under the name of Post Graduate Course. 58th Post Graduate Course started on 9th March, and ended on 19th March 2015. It covered almost all of the important topics related to exams and practical approach to the patient. This academic program comprised of interactive lectures, as well as a hands-on workshop on CPR and TOACS. More than 25 tutors and facilitators from around the country assisted us in conduction of this program. Forty postgraduates (MCPS, FCPS, DA and MD), including some qualified anesthetists registered for the course. The program was approved by the DUHS CME department, and credits hours awarded to registered delegates and facilitators.

I am thankful to all the tutors and facilitators for their immense support in the conduction of this course.