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COMPARISON OF QUALITY OF LIFE IN PATIENTS OF TRIGEMINAL NEURALGIA WHO ARE RECEIVING PREGABALIN AS AN ADD ON THERAPY TO CARBAMAZEPINE

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ABSTRACT

Objective: Patients with trigeminal neuralgia suffer pain episode for months or years before the condition is finally diagnosed and unfortunately episodes of trigeminal neuralgia have a devastating impact on patients Quality of life. This study was done with an aim to compare the quality of life in patients of trigeminal neuralgia who are receiving pregabalin as an add on therapy to carbamazepine. **Materials and Methods:** A prospective, open label, randomized, comparative clinical study conducted on 50 patients. The patients were randomly divided in two groups of 25 patients to receive following two treatments. Group I (n=25) received tablet carbamazepine as a monotherapy initially 200 mg daily per orally in divided doses and gradually built up as per clinical response with maximum titrated dose upto 1000mg/day**.** Group II (n=25) received capsule pregabalin 75 mg OD and tablet carbamazepine 200 mg daily per orally in divided doses and dose gradually built up as per clinical response with maximum titrated dose upto 300mg/day for pregabalin for a period of 12 weeks. Quality of life assessment was done by Pain disability index (PDI). The patients were assessed at the end of 4^{th}, 8^{th} and 12^{th} weeks. **Results:** On intragroup analysis there was statistically significant reduction in mean PDI score ($p<0.05$ indicating improvement in quality of life) when compared to baseline values at the end of 4^{th}, 8^{th} and 12^{th} weeks with both the drugs. In group I mean score at baseline was 48.08 ± 1.03, (43.52 ± 1.07) at 4^{th} week, (40.24± 0.95) at 8^{th} week and (37.44 ± 0.94) at 12^{th} week. In group II mean score at baseline was 47.80 ± 0.53, (41.60 ± 0.51) at 4^{th} week, (37.20± 0.52) at 8^{th} week and (33.12 ± 0.60) at 12^{th} week. On intergroup analysis it was observed that there was no statistically significant difference (improvement in quality of life) between the two treatment groups at the end of 4 weeks (43.52±1.07 vs 41.60±0.51; *p=0.15*), although statistically significant better quality of life was observed with pregabalin as an add therapy to carbamazepine at the end of week 8^{th} (40.24 ±0.95 vs 37.20±0.52; *p<0.05*), and 12^{th} (37.44±0.94 vs 33.12 ±0.60; *p<0.05*), indicating better quality of life with pregabalin. **Conclusion:** The present study suggested that pregabalin as an add on therapy to carbamazepine was found to cause significant improvement in quality of life & reduction in pain scoring at 8^{th} & 12 weeks.

KEYWORDS: Carbamazepine, pregabalin, trigeminal neuralgia, pain disability index.

INTRODUCTION

Trigeminal neuralgia (TN) which is also known as Fothergill disease or Tic douloureux disease is a form of neuropathic pain characterized by the occurrence of abrupt pain which is generally one-sided, severe, brief, sharp and recurrent in the distribution area of one or several branches of the V^{th} nerve.[1] Pain is commonly evoked by trivial stimuli including washing, shaving, smoking, talking and brushing the teeth but may also occur spontaneously.[2] The International Headache Society (IHS) in year 2013 defined strict clinical criteria for trigeminal neuralgia diagnosis.[2] According to these criteria a diagnosis can be made when there is at least three attacks of unilateral facial pain i.e occuring in one or more division of the trigeminal nerve with no radiation beyond the trigeminal distribution. Pain with atleast three of the following four characteristics i.e recurring in paroxysmal attacks lasting from a fraction of a second to two minutes, severe intensity, electric shock-like shooting, stabbing pain, precipitated by innocuous stimuli to the affected side of face. Trigeminal neuralgia is further divided as typical and atypical.[3] In Typical

type there is an idiopathic episodic pain lasting for several seconds, with pain-free intervals between the attacks whereas in atypical type there is continuous or repeated pain between transient paroxysms.[3] The prevalence of trigeminal neuralgia in the general population is 0.015%[4] and overall incidence ranges from 12.6 to 27 per 100,000/year[5] which increases with the advancing age. Middle aged and elderly persons are primarily affected, higher incidence is seen in women with 5.9 cases per 100,000 in females as compared with men with 3.5 cases per 100,000 in males. The diagnosis of trigeminal neuralgia is purely clinical and is made on the basis of characteristic pain in the trigeminal nerve distribution. Patients with trigeminal neuralgia suffer pain episode for months or years before the condition is finally diagnosed and unfortunately episodes of TN have a devastating impact on patients Quality of life. A timely accurate diagnosis of trigeminal neuralgia is therefore particularly important, because a variety of specific treatments can greatly reduce or totally eliminate trigeminal neuralgia pain symptoms in most patients. There have been surprisingly few studies relating to quality of life outcomes in TN. A couple of long term cohort studies have demonstrated that many TN patients suffer depression, which can be alleviated following curative surgical procedures.[6]

The first-line of treatment is always medical therapy. Of the drugs currently used to treat trigeminal neuralgia, most of them are anticonvulsants. Additionally only a handful of these drugs have been investigated in small randomized control trials for the treatment of trigeminal neuralgia and many of these trials have methodological flaws and are outdated.[7] Carbamazepine is the most studied medication for treatment of trigeminal neuralgia and is therefore the drug of choice. It is a sodium channel blocker and promotes the inactivated state of voltage activated sodium ion channels.

Pregabalin is a calcium channel blocker which shows specific affinity for the alpha2delta (α2δ) auxiliary subunits of voltage dependent calcium channels. The pregabalin exhibits analgesic, anxiolytic and anticonvulsant properties. It is structurally related to gabapentin and absorbed orally. It is not bound to plasma protein and is excreted unchanged mainly in urine without undergoing metabolism, its half life is approximately 6 hour. In randomized, placebo-controlled clinical trials pregabalin has demonstrated efficacy in reducing pain in patients with diabetic neuropathy and post herpetic neuralgia thereby significantly improving affective symptoms, sleep and quality of life.[8] Furthermore the pharmacokinetic profile of pregabalin allows for easy management and rapid dose escalation to therapeutic dosages.

Presently, surgical treatment options for trigeminal neuralgia are generally explored only when patients are refractory to medical management. A patient is said to be refractory when he/she cannot bear the adverse effects of the medication, experience breakthrough pain or cannot take the medications because he/she are medically complex patients with polypharmacy for other conditions.[9]

The present study has been planned in the view of the fact that, trigeminal neuralgia is common neuropathic pain disorder. Also it has a potential risk for causing depression and poor quality of life if left untreated. Despite the fact that many standard drugs such carbamazepine and other anticonvulsants are available for treatment of trigeminal neuralgia, but still there is a search for an ideal analgesic with minimal side effects, maximal analgesia and improved patient compliance. Pregabalin is a commonly used therapy currently recommended as first line treatment for a number of neuropathic pain conditions such as diabetic peripheral neuropathy, postherpetic neuralgia, spinal cord injury etc. Pregabalin has been used as an add-on therapy along with NSAIDS, opioids, antiepileptic drugs and antidepressants drugs in uncontrolled neuropathic pain and its administration resulted in significant reduction in pain and improvement in the psychological well-being. So a comparative study was planned where combination of carbamazepine and pregabalin was compared with carbamazepine as a standard line of drug.

MATERIAL AND METHODS

This was a prospective, open label, randomized, comparative clinical study conducted by the Department of Pharmacology in collaboration with the Department of Neurology at Pt. B.D. Sharma PGIMS, Rohtak. In present study patients of either sex of more than 18 yrs of age attending the OPD in Neurology department with facial pain of trigeminal neuralgia were selected. The study was conducted over a period of 1 year and 50 patients were included. The Study was in accordance with the principles of good clinical practice (ICH-GCP) and declaration of Helsinki. The study was conducted after obtaining ethical clearance from institutional ethical committee (IEC). An informed consent was obtained from all the patients enrolled in this study.

The eligible patients were randomly divided into two study groups i.e. Group I and Group II with the help of computer generated random numbers. Each study group had 25 patients and were found to be comparable at the time of their initial visit with regard to demographic parameters such as age, gender, side involved and other parameters (as shown in table 1). Patients were allocated to receive one of the 2 different treatments in an open fashion. Group I (n=25) received tablet carbamazepine as a monotherapy initially 200 mg daily per orally in divided doses and gradually built up as per clinical response with maximum titrated dose upto 1000mg/day. Group II (n=25) received capsule pregabalin 75 mg OD and tablet carbamazepine 200 mg daily per orally in divided doses and dose gradually built up as per clinical response with maximum titrated dose upto 300mg/day for pregabalin for a period of 12 weeks and subjected to

clinical assessment for safety and efficacy of drug(effect on quality of life). During the study, patients were not permitted to take any non-study drugs. Inclusion criteria were diagnosed cases of trigeminal neuralgia, patients of either gender of more than 18 years of age, patients who are ready to give written informed consent. Exclusion criteria were patients with history of psychiatric illness, patients with severe hepatic and renal disorders and other co-morbid conditions, pregnant and lactating women, history of known hypersensitivity to pregabalin and carbamazepine, patients who refused to give informed consent.

Quality of life assessment was determined by Pain disability index (PDI). This index was developed at St. Louis University Medical Center which was designed to measure the degree to which aspects of life are disrupted by chronic pain. In other words, one would like to know how much pain is preventing you from doing what you would normally do or from doing it as well as you normally would. There are 7 categories of life activity listed and patients responded to each category indicating the overall impact of pain in one's life, not just when pain is at its worst. Patients will circle the number on the scale that describes the level of disability ones typically experience. In each category a score of 0 means no disability at all, and a score of 10 signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your pain. So this scale can be used to evaluate patients initially to monitor them over time and to judge the effectiveness of interventions. Measures of disability related to pain:

(1) Family and home responsibilities: activities related to home and family
(2) Recreation: hobbies sports and other leisure time activities
(3) Social Activity: participation with friends and acquaintances other than family members
(4) Occupation: activities partly or directly related to work including housework or volunteering
(5) Sexual Behavior: frequency and quality of sex life
(6) Self Care: personal maintenance and independent daily living (bathing dressing etc.)
(7) Life-Support activity: basic life-supporting behaviors (eating sleeping breathing etc.)

Data Analysis

Data was expressed as Mean ± SEM. Both intragroup and intergroup statistical analysis was done. Intragroup analysis was done by using ANOVA. Intergroup analysis was done by using unpaired't' test. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

Table. 1: Demographic Profile of Study Participants in Both The Groups.[N= 25 IN EACH GROUP].

Demographic Profile	Group I (n=25)	Group II (n= 25)
Age in years	52.9 ±3.59	51.3 ±3.33
Gender **Male** **Female**	 19 (76%) 06 (24)	 18 (72%) 07 (28%)
Side of face involved **Right side** **Left side**	 16 (64%) 09 (36%)	 18 (72%) 07 (28%)
Vascular loop around Trigeminal nerve	4 (16%)	6 (24%)
Drug allergy	NO	NO

Age is expressed as Mean ± SEM (standard error of mean) while categorical values are expressed as actual number of patients and their percentage.

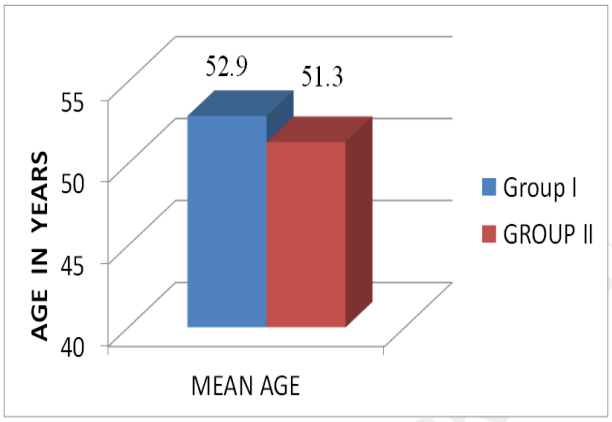

Figure. 1: Study Population-Age Characteristics.

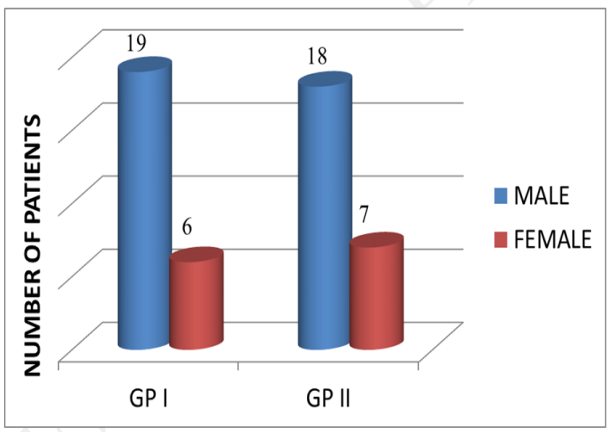

Figure. 2: Sex Distribution in Two Groups.

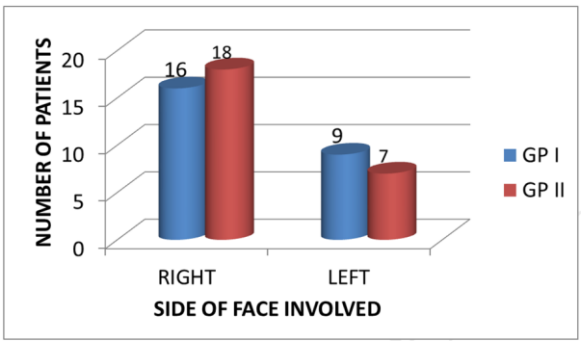

Figure. 3: Facial Pain in Two Groups.

PDI SCORING IN GP I

Intragroup analysis (Table 2; Figure 4): At baseline mean PDI score was 48.08 ± 1.03. There was clinically significant reduction in mean pain disability index scoring at week 4 (43.52 ± 1.07), 8 (40.24± 0.95) and 12 week (37.44 ± 0.94), as compared to baseline.

Table. 2: Intragroup Comaparision of Pain Disability Index In Group I (N=25).

Time interval	Group 1	
	Mean ± SEM	Change from baseline
Baseline	48.08 ± 1.03	----
4nd week	43.52 ± 1.07	4.56*
8th week	40.24± 0.95	7.84*
12th week	37.44 ± 0.94	10.64*

- * p < 0.05 indicates significant values at 4,8 and 12 week.
- All values are expressed as Mean ± SEM
- Gradual decrease in pain disability index score with initiation of treatment at the end of 4, 8 and 12 week signifies improvement in Quality of life

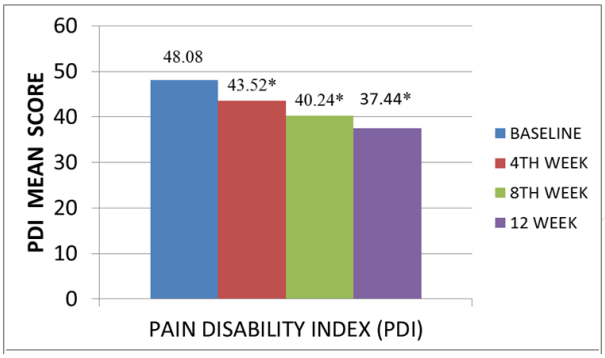

Figure. 4: PDI Scoring in Group I.

PDI SCORING IN GP II

Intragroup analysis (Table 3; Figure 5)

At baseline mean PDI score was 47.80 ± 0.53. There was statistically significant reduction in mean pain disability index score at week 4 (41.60 ± 0.51), 8 (37.20± 0.52) and 12 (33.12 ± 0.60), when compared to baseline.

Table. 3: Intragroup Comaparision O Pain Disability Index in Group II (N=25).

Time interval	Group II	
	Mean ± SEM	Change from baseline
Baseline	47.80 ± 0.53	-----
4th week	41.60 ± 0.51	6.20*
8th week	37.20 ± 0.52	10.60*
12th week	33.12 ± 0.60	14.68*

- * p < 0.05 indicates significant values at 4,8 and 12 week.
- All values *are* expressed *as* Mean ± SEM

Gradual decrease in pain disability index score with initiation of treatment at the end of 4, 8 and 12 week signifies improvement in Quality of life.

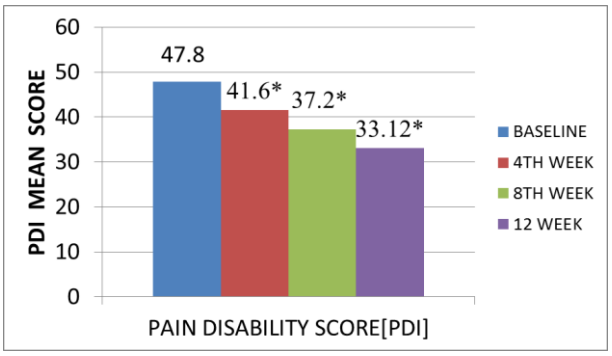

Figure. 5: Pdi Scoring In Group II.

Intergroup analysis (Table 4; Figure 6)

At the end of 4 weeks reduction in pain disability index score was 4.56 and 6.20 which was not significant (p >0.05). But at the end of 8 weeks better response was seen with group B i.e more reduction in pain disability index scoring value by (10.60) as compared to (7.84) group A which was statistically significant reduction (p<0.05). Also at the end of 12 weeks again better response was seen in group B with more reduction in pain disability index scoring value (14.68) as compared to (10.64) group A which was statistically significant (p<0.05).

Table. 4: Intergroup Comparision Of Pain Disability Index[Pdi] Between Both The Groups At Baseline, 4, 8 And 12 Weeks.

Time interval	Group 1 (N=25)	Group II (N=25)	p-value
Time point	Mean ± SEM	Mean ± SEM	
Baseline	48.08 ± 1.03	47.80± 0.53	0.82
4th week	43.52 ± 1.07	41.60 ± 0.51	0.151
8th week	40.24± 0.95#	37.20± 0.52#	< 0.05
12th week	37.44 ± 0.94#	33.12 ± 0.60#	<0.05

- All values are expressed as Mean ± SEM
- # p < 0.05 at 8th and 12th week.

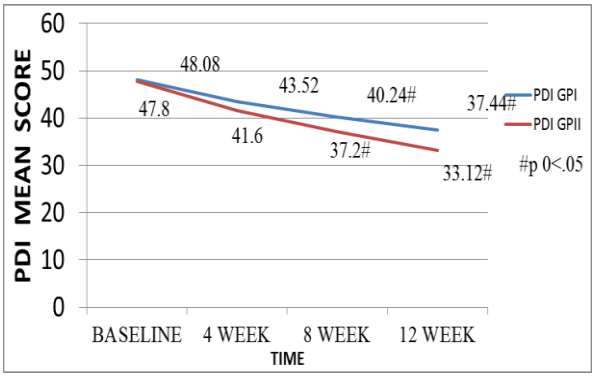

Figure. 6: Profile Plot of Qol Scoring Between Two Groups.

DISCUSSION

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage".[10] Trigeminal neuralgia (TN) is a notable facial pain disorder characterized by sudden, severe, brief, stabbing or lancinating recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve. It is one of the classical neuropathic pain condition that have been known for centuries. Gilron I[11] showed in randomized, placebo-controlled clinical trial that pregabalin demonstrated efficacy for pain relief in patients with diabetic neuropathy and peripheral post herpetic neuralgia, significantly improving affective symptoms, sleep and quality of life. Our study has an additional benefit that it was a randomized, active comparator controlled study. Pérez C et al.[12] studied the effects of pregabalin (PGB) on patient-reported health outcomes in 65 PGB-naive subjects with trigeminal neuralgia refractory to previous analgesic therapy in a prospective, multicentre observational study carried out in primary care. 12 weeks monotherapy with PGB (n = 36) or add-on (n = 29), reduced baseline intensity of pain by a mean ± S.D. of -40.0 ± 22.1 mm[-55.4%, effect size (ES) 2.32; P < 0.0001] with 59.4% of responders (pain reduction ± 50%), and produced 34.6±29.3 additional days with no/mild pain. Anxiety/depression symptoms decreased by -3.8 ± 3.5 and -4.5 ±4.2 points (ES 0.95 and 1.02; P < 0.0001), respectively. PGB improved sleep by -17.9 ± 19.6 points (ES 1.18; P < 0.0001) and improved patient functioning by decreasing overall scoring on Sheehan disability index by -8.6 ± 5.9 points (ES 1.59; P < 0.0001). Health status as assessed by (EQ-5D), increased by 31.6 ±22.2 mm (ES 1.67; P < 0.0001), with 0.0388 ± 0.0374 gained quality-adjusted life-years(QALY). Our study results also matched with the above study quoted but QOL in our study was assessed by PDI scoring instead of EQ-5D scoring.

In a study done by Campbell et al, in which carbamazepine has been shown to be much more effective than a placebo in the treatment of trigeminal neuralgia and improved quality of life.[13] Vranken J.H et al[14] conducted a randomized, double-blinded, placebo-controlled trial evaluated the effects of pregabalin on pain relief, tolerability, health status, and quality of life in patients with central neuropathic pain caused by brain or spinal cord injuries. At baseline and 4 weeks after the start of treatment subjects were evaluated with standard measures of efficacy. Pain intensity measured by visual analogue scale, health status by Pain Disability Index and EQ-5D whereas quality of life by SF-36. 40 patients received escalating doses of either pregabalin (150, 300, and 600 mg/day) or matching placebo capsules. In both groups, patients started with 1 capsule per day (either 150 mg of pregabalin or placebo). If pain relief was insufficient, patients were titrated to a higher dose. There was a statistically significant decrease in mean pain score at endpoint for pregabalin treatment, compared with placebo (P = 0.016) and also led to a significant improvement in bodily pain domain of SF 36 and pain disability index. Pregabalin in a flexible dose regimen produced clinically significant reduction in pain and improves health in patients suffering from neuropathic pain. Few other randomised controlled study conducted also documented significant reduction in neuropathic pain at the end of study (p< 0.05). In our study quality of life was assessed by PDI scoring. In group I at baseline PDI score was 48.08 ±1.03 and it was 37.44 ± 0.94 at the end of 12 weeks, with a overall reduction of 10.64 ±0.09 while in group II, PDI score at base line was 47.80 ± 0.53 and 33.12 ± 0.60, with an overall reduction of 14.68 ± 0.07 at the end of 12 weeks. Thus there was a better quality of life observed in group II patients receiving pregabalin as an add on therapy to carbamazepine.

Crawford M et al[15] provided evidence regarding the real-life efficacy of pregabalin in the treatment of peripheral neuropathic pain (NeP) in Denmark. In this prospective, observational, noninterventional study, pregabalin was prescribed and compared with baseline. . A total of 86 of the 128 patients included were regarded as efficacy evaluable (those completing 3 months of pregabalin treatment). A clinically and statistically significant improvement of 2.2 points in the average level of pain intensity was found after 3 months. Positive results were also found for pain-related sleep interference, patients global impression of change, quality of life and work and productivity impairment. So this real-life study indicates that for some patients (two-thirds), addition of pregabalin for peripheral NeP helps to reduce their pain intensity and improves quality of life significantly. Our study also showed that there was significant change in quality of life in both the groups. To best of our knowledge very few studies have assessed the quality of life in trigeminal neuralgia patients and we have assessed it by observing improvement in pain disability index scoring

CONCLUSION

There was statistically significant improvement in quality of life at 4th, 8th and 12 week, in both the groups when compared to the baseline i.e both carbamazepine and pregabalin as an add on therapy to carbamazepine

were effective in improving the quality of life in patients of trigeminal neuralgia. However on intergroup comparison, pregabalin as an add on drug to carbamazepine(Group II) produced statistically significant improvement in quality of life at 8th and 12th weeks when compared to carbamazepine alone (Group I). The present study suggested that pregabalin as an add on therapy to carbamazepine was found to cause significant improvement in quality of life and reduction in pain scoring. So pregabalin as an add on could be a promising drug in patients of trigeminal neuralgia when therapeutic options are limited.

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