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RESEARCH PAPER

Lamotrigine Versus Pregabalin in the Management of Refractory Trigeminal Neuralgia: A Randomized Open Label Crossover Trial

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Abstract
Background Carbamazepine (CBZ) formed the gold standard drug in trigeminal neuralgia (TN) treatment but faces high therapeutic failure. This defined the need to explore a second line of drug therapy. The study aimed at comparing two alternate drugs i.e. Lamotrigine (LTG) and Pregabalin (PGB), in the management of TN refractory to therapeutic doses of CBZ.
Methods Twenty-two patients with diagnosis of refractory TN were enrolled and randomly allotted into 2 groups of 11 each. Each group was subjected to a crossover analysis using LTG and PGB together with CBZ, for a period of 6 weeks. Patients maintained a pain diary, the scores of which, along with global evaluation scores, determined the primary outcome. Reevaluation of symptoms after 6 months was done to assess long term efficacy with study drugs.
Results Both LTG and PGB were effective over CBZ alone ($p < 0.05$); however, statistically insignificant difference ($p > 0.05$) was observed between the two groups using Mann–Whitney tests. Unlike LTG, side effects like nausea, insomnia and concentration loss were minimal with PGB thus exhibiting greater patient compliance. Secondary analysis showed complete relief in 4 patients on PGB (mean dose 240.68 mg/day) while 6 had partial relief. Three patients on LTG (mean dose 310.90 mg/day) reported relapse of acute symptoms and required peripheral alcohol blocks.
Conclusion Pregabalin has potential anti-neuralgia properties comparable to LTG. However, the level of patient's tolerance seen with PGB exceeds that with LTG. 6 months follow-up records suggest that PGB together with CBZ offers a more reliable pain control than with LTG.

Keywords Lamotrigine · Pregabalin · Refractory trigeminal neuralgia

Introduction

The standard drug management of trigeminal neuralgia (TN) includes Phenytoin or Carbamazepine (CBZ). Recently, drugs including Gabapentin, Oxcarbazepine, Lamotrigine (LTG), Pregabalin (PGB) and Topiramate, amongst others, have shown positive results in limited researches for the medical management of TN [1].

The condition most commonly affects the elderly in the age range of 50–70 years [2]. This poses a major therapeutic challenge, as most patients are medically compromised and under variety of medications. Thus, drug interactions may be common often reducing efficacy to a significant level. Moreover such patients may be unfit for any invasive surgical procedures due to associated co-morbidities. Apart from this, surgical procedures have been associated with a mortality rate of 0.7–1 % and significant morbidity [3]. Thus, drug management remains the treatment of choice in majority of patients.

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However, most drugs in current use face therapeutic failure owing to development of refractoriness or severe adverse effects with higher doses. It has been seen that up to 30 % patients may be initially resistant to CBZ while further 50 % may become refractory on subsequent usage [4]. This may be partly due to the fact that CBZ induces its own metabolism by means of auto induction, usually within 3–5 weeks of first dosage [5]. Thus, patients become unresponsive to therapeutic doses of CBZ and attain relief only at higher doses, which in turn increases potential side effects and the risk for toxicity. In addition, certain patients may be intolerant to CBZ initially, owing to its central nervous and hematologic side effects [6]. This poses a major therapeutic challenge and thus, defines the need to explore a second line of drug therapy in the current management of TN refractory to CBZ.

Both LTG and PGB have been extensively reviewed in the past for management of painful neuropathic conditions [7–13], with only few establishing their efficacy in TN. In addition, both drugs have minimal effects on hematological and biochemical indices [11, 14]; are not associated with hepatic enzyme induction, have minimal drug interactions and protein binding which makes them suitable for use in the elderly [15, 16]. Also, in comparison to other drugs, both require only twice daily administration, increasing the patient's compliance substantially. The adverse-effect profiles of both the drugs have also been found to be acceptable [11, 14].

Paucity of literature describing management of refractory cases leads to uncertainty in diagnoses and initiating early treatment, which often leaves the patient with great psychological and economic burden. This study was undertaken to assess and compare clinical efficacies of two recently used drugs (LTG and PGB), in patients, refractory to therapeutic doses of CBZ over a short and long term period.

Aims and Objectives

The study aimed at testing the intra/inter patient efficacy of LTG and PGB in the management of refractory TN using the cross-over design. At the same we sought to test the hypothesis that both LTG and PGB are comparable, in terms of (1) improvement in pain scores, (2) increased daily activities by the patient and, (3) generating minimal adverse effects for maximum patient compliance. The secondary objective was to test the long term efficacy of these drugs at a 6-month follow up period, at a dose established by the trial.

Materials and Methods

The study was a prospective, single centre, open-label, active-comparator controlled, cross-over trial conducted from March 2008 till 2009. The study centre is a tertiary care hospital and one of the largest referral centres in India with about 2,500 registered cases of TN in the out-patient department. The location, New Delhi, has a humid, sometimes extreme, sub-tropical climate [17], and majority of the sample constituted the local population. All registered patients of TN (defined by clinical description using Short-Form of McGill's pain questionnaire or SF-MPQ), in the age group of 18–65 years, and under CBZ therapy for a minimum of 4 weeks, were screened for refractoriness. The criteria for refractoriness were: (1) minimal/no improvement in pain dairy scores (which each patient was required to fill for the 4 weeks preceding to inclusion), on a minimum dose of 600 mg/day of CBZ; (2) having serum CBZ level within the therapeutic range of 4–12 mcg/ml; and (3) pain score of >40 mm on the visual analogue scale (VAS) of SF-MPQ.

Patients who had undergone invasive treatment for TN during the past 1 year preceding to inclusion (to avoid unpredictable course of disease/false outcome), pregnant/lactating women (risk for teratogenicity), patients on antidepressants like sodium valproate or any other hepatic microsomal enzyme inhibitors (to avoid risk for toxicity); history of excessive alcohol intake, hepatic or renal insufficiency or a known intolerance/allergy to study drugs or those who were found to be non-compliant during the screening period (owing to psychological or logistic reasons) were excluded from the study.

Institutional ethical clearance was obtained and 136 patients with TN reporting during the one-year period were screened for eligibility. While 27 patients were initially found to be eligible, five did not consent for the study. Thus, twenty-two eligible patients who consented to the study were included and randomly allocated into two groups of eleven each using a computer generated random table. The two groups [Group 1 (LTG/PGB) and Group 2 (PGB/LTG)] differed only in the sequence of drugs administered and followed a similar protocol (Fig. 1). The cross-over design required patients to undergo one regime, followed by a "wash-over" period of 2 weeks, before he/she was "crossed-over" to the other drug regime. All throughout the trial, CBZ formed the baseline drug that was maintained at 600 mg/day in thrice daily regime. The exposure of patients to "no drug" during the wash-over period would, otherwise, be unethical.

Oral CBZ tablets, dispersible tablets of LTG and PGB capsules were supplied to the subjects from the hospital (open label). Each enrolled patient (taking only CBZ) was required to record pain scores in the pain diary for 1 week prior to randomization (baseline scores). Pre-randomization composite efficacy index (CEI) scores were used to compare baseline characteristics of the two groups using non-parametric tests. Patients (after allocation) were started on the study drug that was titrated to the desired dose over

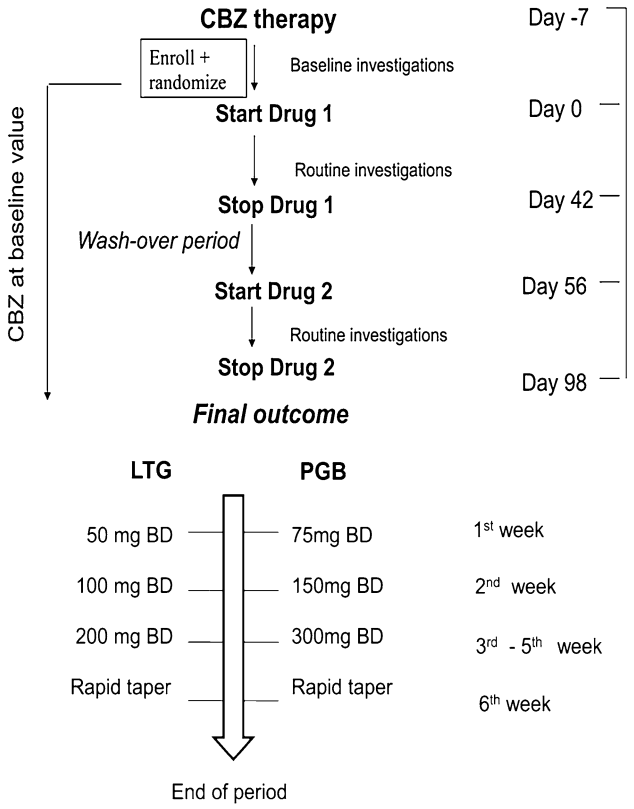

Fig. 1 Group protocol and drug regime

the next 2 weeks period (Fig. 1). This was followed by a maintenance phase of another 3 weeks during which all investigations were undertaken. Here, the dose of study drug that provided maximal relief with minimal adverse effect was maintained and every patient was required to fill a pain diary at the end of each day that consisted of three parameters to assess changes in pain perception, quantitatively. These included: (a) total number of pain episodes (on a scale of 1- none to 6- >20 episodes; (b) severity of pain (on a scale of 1-no pain to 4-severe) and (c) degree of relief obtained (on a scale of 1-complete to 5-no relief). The mean of these recordings formed the mean total pain diary score for that treatment period (Table 2).

Additionally, patients were allowed to use an "escape medication" in the form of an extra 200 mg CBZ tablet, if the relief obtained with study drug was considered to be inadequate. The use of this escape medication was noted in patient diary and the total exposures were calculated. Further, at the end of each arm of trial, global evaluations for response to current treatment were recorded to analyze any improvement in conduct of daily activities like brushing, washing face and eating. The adverse events with either drug therapy were also noted in the adverse drug reaction chart. At the end of maintenance phase, the drug was rapidly tapered off over 1 week. All recordings were maintained by a single investigator and were analyzed only two times; individually at the end of treatment for each patient and collectively at the end of trial (after recruitment of the last patient).

The data was collected and digitalized in Microsoft Excel™ (version 2007) sheets and analyzed using SPSS™ software (version 11). The three parameters taken for evaluation constituted the CEI that included total exposures to escape medication; mean pain diary scores and global evaluation scores. The analysis of CEI was carried out using Mann-Whitney tests to rule out possible period or treatment-period effects following which the actual treatment efficacy was compared. In general, presence of these interactions would indicate biased estimate of the treatment effect and that the results depended upon the order in which the treatments were administered.

The drug showing greater efficacy or fewer side effects was continued for that patient at the end of the trial. Patients were reviewed after 6 months for assessing long term efficacy with the study drugs. The SF-MPQ recordings were used to formulate the secondary outcome.

Results

Baseline Analysis

A total of 136 patients with a diagnosis of TN were seen at the centre in the 1-year duration. The allotment scheme is presented in Fig. 2.

The demographic analysis of the 22 study subjects (Table 1) showed an equivocal distribution with a male to female ratio of 1.2:1. The mean age at the time of presentation was found to be 44.5 years with a range of 25–58 years. Majority (55 %) of the patients were in the age group of 40–49 years. Overall 30 branches of trigeminal nerve were involved in 22 patients with a definite right sided predisposition (14, 63 %) while only one case (4.5 %) showed bilateral involvement. The mandibular division was involved in 19 (63 %) instances, with the rest (11/30) involving the maxillary division, while no case of ophthalmic branch involvement was seen. Individually, the inferior alveolar nerve (56.6 %) was the maximally affected followed by the infra-orbital branch (26.7 %) of maxillary division.

More than one branch was seen in 8 (26.6 %) cases. A history of multiple dental extractions could be elicited in majority (15/22, 68.2 %) of patients. However, only 6 (27.2 %) related the onset of pain to traumatic extractions.

All the patients enrolled had been under CBZ therapy for varying durations. Eight patients had been previously on drugs like Gabapentin (n = 5), Tryptomer (n = 2) and Baclofen (n = 1) along with CBZ, but had discontinued these at least 1 month prior to enrolment. The serum CBZ levels ranged from 4.68 to 9.42 μg/ml with a mean level of

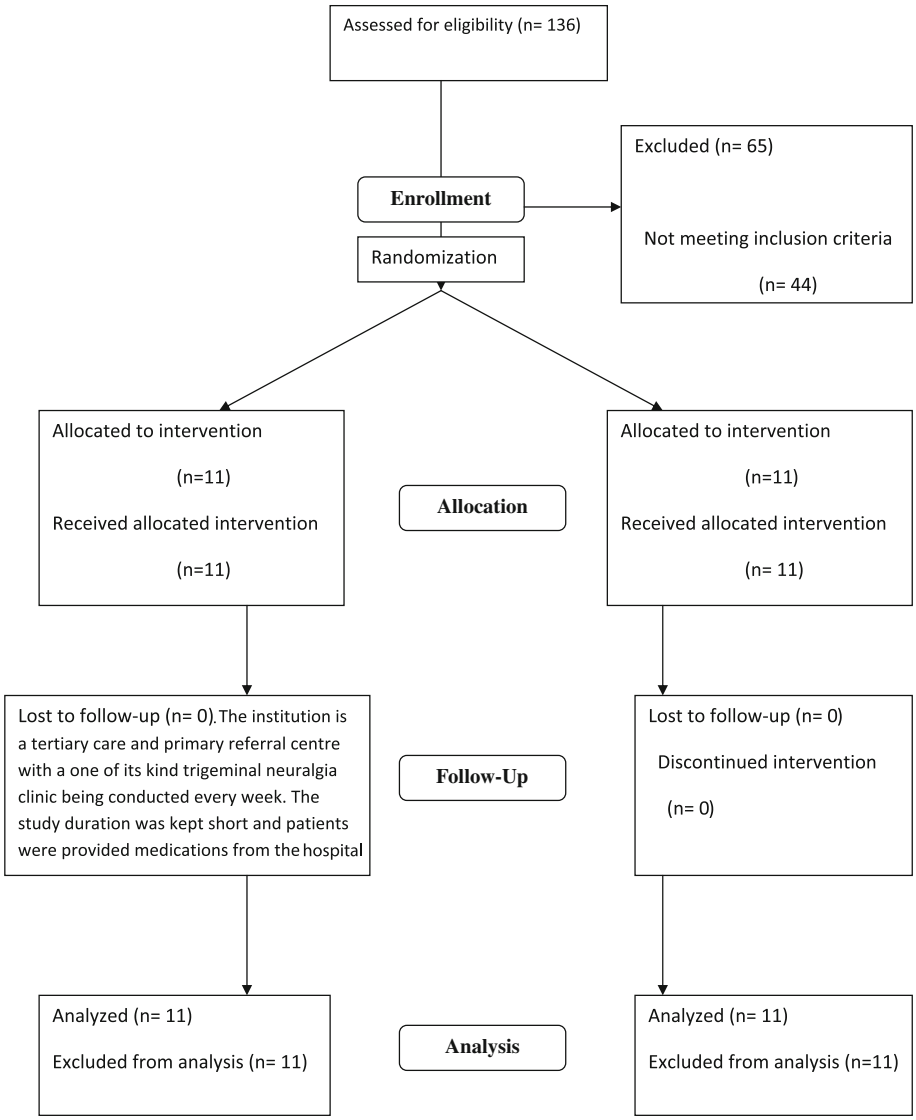

Fig. 2 The consort E-flowchart Aug. 2005

Table 1 Demographic characteristics of patients after randomization

Patient characteristics	Group A (LTG/PGB)	Group B (PGB/LTG)	Overall
Number	11	11	22
Mean age (years)	44.8	45.8	45.3
M:F	5:6	7:4	12:10
Average duration since diagnosis of TGN (months)	28.2	24.1	26.7
Mean duration on CBZ therapy (months)	26.3	23.4	24.9
Mean duration of CBZ refractoriness (months)	3.36	3.45	3.4
Mean serum CBZ levels (μg/ml)	6.64	7.08	6.86

6.86 μg/ml. No significant alterations in the hemogram or electrolyte profiles of the patients were found during the trial.

For the purpose of comparison of baseline recordings, Mann-Whitney tests were applied and the difference was statistically insignificant ($p > 0.05$). Thus, post randomization, both the groups were comparable in their response to baseline drug i.e. CBZ (Table 2). The difference in scores of treatment periods from the baseline readings were used to generate the percentage reduction in pain scores offered by the study drugs. As can be seen in Table 3, statistically significant improvement in pain scores was observed using the unpaired t test ($p < 0.05$), with either drug, when compared to CBZ alone.

Crossover Analysis

The cross-over analysis of the two study drugs LTG and PGB was done using the CEI index. After the end of trial, the CEI readings with both drugs were compared by determining the

Table 2 Baseline (on CBZ) CEI scores of two groups

Parameter	Group A			Group B		
	Mean	Median	Range	Mean	Median	Range
Average exposures	1.60 ± 0.58	1.57	0.86–2.71	1.24 ± 0.66	1.14	0.43–2.43
Total mean pain diary scores	12.70 ± 0.79	12.78	10.92–14.05	12.12 ± 0.98	12.44	10.89–13.41
Patients' global evaluation	1.18 ± 0.75	1.00	0–2	1.27 ± 0.79	1.00	0–2

Table 3 Comparison of the baseline pain diary scores (CBZ) with study drugs

Parameter	Average daily score ($S_{CBZ} = \Sigma CBZ/n$)	Δ_1 (S_{LTG}–S_{CBZ})	% Reduction	Δ_2 (S_{PGB}–S_{CBZ})	% Reduction
Number of pain paroxysms	4.60	−2.49	53.09 $p < 0.0001$	−2.41	51.38 $p < 0.0001$
Severity of pain	3.84	−1.57	40.80 $p < 0.0001$	−1.55	40.36 $p < 0.0001$
Degree of relief	4.25	−1.98	46.58 $p < 0.0001$	−1.93	45.41 $p < 0.0001$

S_{LTG} average score with LTG, S_{PGB} average score with PGB

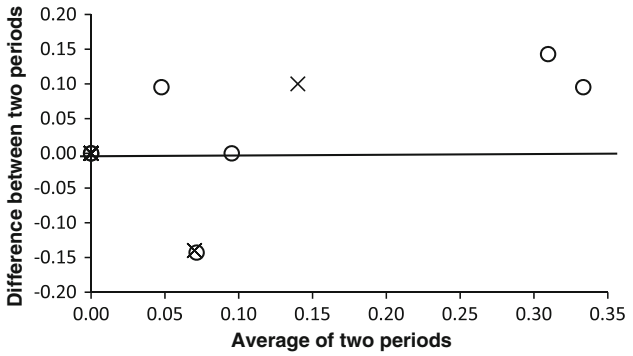

Fig. 3 Plot of difference between the periods against average exposures to escape medication in the two periods for patients receiving LTG followed by PGB (*circle*) or PGB followed by LTG (*times symbol*)

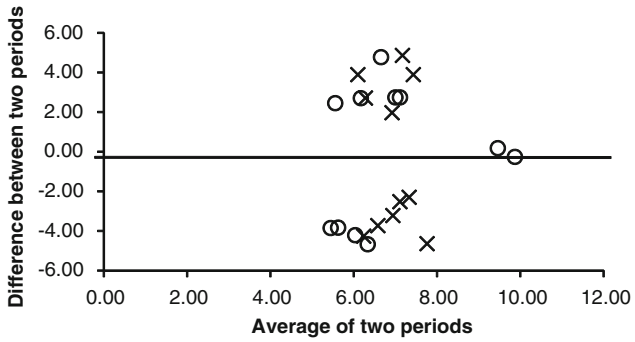

Fig. 4 Plot of difference between the periods against total mean pain scores of two periods for patients receiving LTG followed by PGB (*circle*) or PGB followed by LTG (*times symbol*)

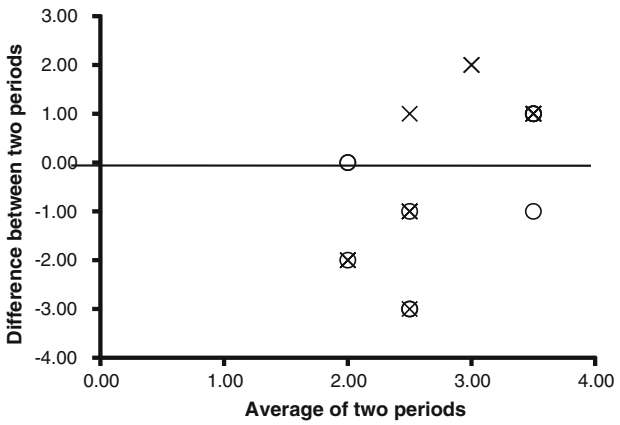

Fig. 5 Plot of difference between the periods against global evaluation scores of two periods for patients receiving LTG followed by PGB (*circle*) or PGB followed by LTG (*times symbol*)

treatment effect in the two groups. However, before the treatments can be compared using a cross-over design, two additional tests need to be performed to investigate possible "period" effect or "treatment-period" interaction. The comparison was done by calculating the differences (d1, d2) of the mean recordings and average responses (a1, a2) in the two groups and applying Mann–Whitney test to generate the p value. Additionally, presence of any treatment-period interaction was ruled out by plotting a scatter-plot of the difference between the two periods (−d1 and −d2) against the average of the two periods (a1 and a2). No period or treatment-period interaction was seen. Further, the distribution of treatment effects was also found to be comparable (Figs. 3, 4, 5).

The pain diary recordings were plotted showing daily variations during the interventional periods of the trial (7 days on CBZ and 3 weeks observation period in both arms). For this purpose, mean scores for each day of intervention were plotted against time for the two groups (LTG/PGB and PGB/LTG). As can be seen in Fig. 6, a

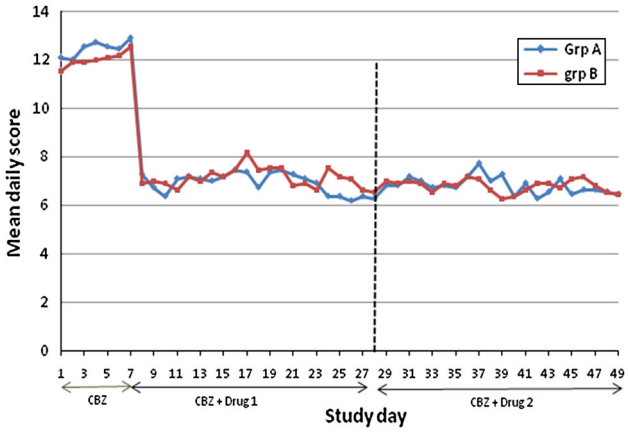

Fig. 6 Total mean pain diary scores of patients showing daily variation with study drugs

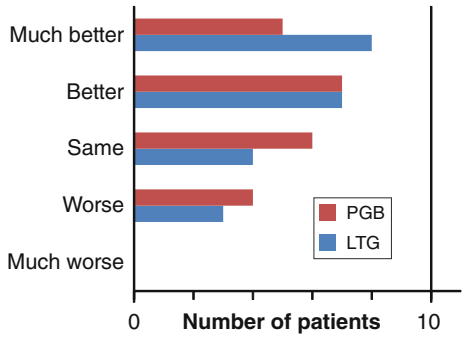

Fig. 7 Global evaluations of patients taking the study drugs

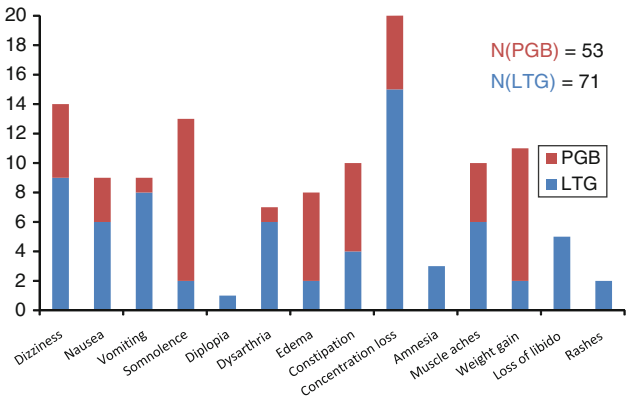

Fig. 8 Adverse reaction profile of the two study drugs

sudden drop (manifested as clinical improvement) is noted when the patients are shifted from CBZ to either study drug. Both the groups show similar pattern of relief over their respective 3 week period.

The evaluation of daily activities was done at the end of each treatment period and it was found that both the drugs were associated with significant improvement in the conduct of activities like shaving/washing face, combing and speaking (>50 %). Other activities like eating and brushing could be executed by less than 50 % of patients while on either drug.

Next, a subjective analysis of the global evaluations was done wherein each patient was asked about how they felt with the current drug regime. As seen in Figs. 7, 8 patients felt "much better" with LTG as compared to 5 when on PGB. Fourteen patients could not differentiate between the two treatments while no patient felt "much worse" during either period.

The adverse events with either drug are noted in Fig. 8. No case of serious adverse effect was observed with either treatment during the trial. Minor adverse effects were seen with both therapies; however, none of the patients discontinued the treatments in between the trial. The most common side effects seen with LTG included nausea, vomiting, dysarthria, loss of concentration and amnesia while 5 patients reported decrease in libido. On the other hand, PGB was most commonly associated with dizziness, nausea, peripheral edema, muscle aches, weight gain and somnolence. The concomitant use of CBZ potentiated the "excessive sleepiness" with PGB, making its use slightly uncomfortable in some of the patients. Overall, 53 instances of adverse reactions were reported by the patients when on PGB as compared to 71 experiences with LTG. However, adverse effects seen with both treatments were reversible and generally regarded by the patients as "mild" to "moderate".

Secondary Outcome

At the end of crossover, 11 patients continued on PGB (mean dose = 240.68 mg/day; range = 150–300 mg/day) while 2 patients reporting inadequate relief during the trial were given peripheral alcohol injections for the same. The rest (9/11) continued with LTG (mean dose = 310.90 mg/day; range = 200–400 mg/day) divided in two doses. At the end of 6 months, 20 patients reported for follow-up visits. Out of 11 patients on PGB, complete relief was present in 4 (36.3 %) while 6 patients had partial (>50 %) relief and 1 was lost to follow-up. Of the 9 patients taking LTG (dose range of 200–400 mg/day), 2 (25 %) had complete relief while 4 reported partial relief with another 3 patients requiring alcohol blocks due to recurrence of acute symptoms.

Discussion

Amongst the diverse orofacial pain syndromes, neuralgia of the trigeminal nerve is associated with the highest pain intensities that affect even the basic activities of the patient

[18, 19]. The sudden trigger mechanism of the pain leaves the patient in constant fear of inducing pain paroxysms. The uncommon occurrence together with limited treatment options makes the management of TN highly unpredictable. Medical therapy forms an epitome in long term management of TN [1, 20]. However, the drugs once considered to be the gold standard, are gradually becoming obsolete owing to development of resistance in high percentages [4]. This often leads to a great economic burden on these patients who have to travel long distances because of the lack of sufficient expertise in its management. Additionally, their lifestyle is affected either due to sudden attacks of pain or the associated drug side effects. A concoction of treatments often results in an inverse cost-benefit ratio for these patients. These reasons encouraged us to explore the efficacies of two new drugs, LTG and PGB, and compare their effect on patient's daily activities using a crossover design where the comparison is "within subject" rather than only "between-subjects" and hence each patient acts as a control for the second treatment [21].

Since the occurrence of TN is comparatively rare than other orofacial pain syndromes, cross-over design was best suited to provide adequate comparison with a smaller sample size. Also, since medical therapy is not a cure for the condition [22], a cross-over was quite applicable as complete cure after first arm may not be seen normally.

Majority (55 %) of the patients who consented were in the age group of 40–49 years. The mandibular division was the most commonly affected (63 %). In particular, the inferior alveolar branch (56.6 %) was the most frequently involved followed by infra-orbital nerve (26.7 %). These findings are consistent with those reported previously [2, 18]. Overall, 15 patients (68 %) had undergone tooth extractions in association with the facial pain prior to reporting at our centre. Not surprisingly, majority (60 %) of these extractions resulted as a sequel to the pain. This is an important finding that highlights the general inability of dentists and clinicians to accurately diagnose this condition in the early stages of progression. The McGill's pain questionnaire and its shorter format (SF-MPQ) have been shown to be effective in differentiating between pain conditions like TN or atypical facial pain [23]. Since this form addresses both the descriptive nature of pain and its intensity, we used the same during the screening period to formulate an unbiased diagnosis of TN.

Thus, the inclusion criteria for patients were based on both subjective (pain diary scores and SF-MPQ scores) and objective parameters (serum CBZ level). Patients who consented to the study were asked to fill pain diaries for 7 days preceding to randomization so that their level of compliance in filling the diary could be known. The serum levels were analyzed to check compliance with drug regime and lay down refractory criteria (patients within therapeutic serum levels unresponsive to CBZ). The long term use of CBZ is known to be associated with potential CNS side effects and sometimes, electrolyte imbalance particularly hyponatremia [4]. However, no case of hyponatremia was seen in our study and baseline hematological investigations remained grossly unaltered. Patients mostly reported with complaints of somnolence, extreme exhaustion, nausea and loss of appetite with higher doses of CBZ (up to 1200 mg/day). However, the effects were more tolerable with a regime of 600 mg/day divided into three doses. According to previous studies this regime is best suited for TN patients [4, 24].

Current models regarding the patho-physiology of TN, regards either central or peripheral mechanisms in the origin of pain [18]. Membrane-stabilizing drugs like AEDs either control the pain via suppressing the ectopic transmission of Na+ channels (like LTG) or increasing the rate of pain suppressing neurotransmitters like gamma- aminobutyric acid (PGB). A similar drug to PGB, gabapentin has shown efficacy in TN previously [25]. Thus, a comparable effect in controlling the TN pain can be expected with PGB. However, PGB offers higher effective pain relief and compliance as compared to gabapentin [16]. Thus, both LTG and PGB offer great potential for management of TN.

Although LTG has been shown to be effective for refractory TN management in a placebo-controlled trial [26]; the small sample and short duration of their study was accompanied with a low statistical power. Further their study was a sequential trial and elements of interactions associated with cross-over design were not addressed to. PGB, on the other hand, had not yet been tested in refractory cases of TN, although a single series does mention about its role as an adjunct in non-refractory patients [27]. A maximum dose of 400 mg/day for LTG was used in most trials [8, 9, 26, 28] while the dosing range of 150–300 mg/day for PGB was considered to be the most effective in other reports [11–13, 27]. The management in case of acute toxicity revolves around supportive care [29].

A composite efficacy index constituting exposures to escape medication, pain diary, and global evaluation scores has previously been used here to determine treatment efficacy in TN [26]. Marked reduction in exposures was noted with both LTG and PGB signifying that these drugs provide greater relief than CBZ alone (Table 3). Same inference was drawn after assessment of pain diary, which analyzed the total episodes (or paroxysms) of pain, the intensity of pain and the degree of relief obtained with the drug. Figure 6 shows that both the investigational drugs were effective in bringing about pain relief when compared to CBZ alone. The last parameter of the CEI was global evaluation scores that were noted by the patients at the end of each treatment period. Global evaluations take into

account the overall benefits experienced by the patient. Both treatments groups were found to be comparable. It is, however, interesting to note that 8 patients felt much better with LTG as compared to 5 on PGB. LTG is known to be an effective drug for the management of bipolar affective disorders. It has a potent anti-depressant activity, which could relate to the higher global evaluation scores given by the patients during its use. However, one of the biggest problems that made LTG unpopular with patients seemed to be its ability to cause insomnia and increased sleep disorders. It thus seems logical to use LTG in early evening regime to avoid this. On the other hand, PGB provided good sleep and was generally more compatible with the patients. Its action in improving pain-related sleep interference has been shown previously in patients with postherpetic neuralgia [30].

Studies have shown that both LTG and PGB do not affect CBZ or its metabolite [11, 31]; therefore, serum level monitoring for CBZ was not considered in the post randomization period. Patients were aware of the drugs being dispensed at all times and different formulations of the study drugs meant that they could memorize the regime providing greater relief amongst the two. Records were analyzed for each patient (intra-patient comparison) at the end of cross-over and collectively (inter-patient) at the end of trial. As seen in Table 2, average pain diary scores with CBZ for all three parameters were high. Significant reduction was seen with both LTG and PGB, for all the parameters (Table 3). This clearly shows that both drugs are effective as compared to CBZ in management of refractory TN.

As the study centre is a primary referral hospital and the fact that the cohorts were carefully screened, all patients entering the study completed the trial with no premature withdrawal seen. The treatment period for both drugs was kept short to prevent premature withdrawals from other reasons. To avoid a possibility of spontaneous remission [19], the study duration was optimized to meet the drug specifications (need to titrate the dose) while maintaining the validity of the recordings at the same time. To overcome any carry-over effect, a wash over period (2 weeks) was given in between the two treatments that were preceded by a rapid taper off over a week's period. Since the average half-life varies from 14 h for LTG [15] to 6.5 h for PGB [11], the stipulated wash-out period was considered to be adequate to prevent any carry-over. Ideally, baseline recordings before the onset of second treatment provide good evidence for testing this effect. However, this was omitted in our study for the fear of making the analysis more complex and that it may affect patient compliance.

The period effect was tested using the values of observed differences between the periods (d1 and d2). Again, a p value of >0.05 was observed with all three parameters of CEI thus indicating that there was no general tendency of the patients to do better in one of the periods. In our study, no treatment period interaction was found indicating that the average response to the two treatment groups was same regardless of the order in which they were received. The comparison of the two treatments (LTG and PGB) was then simply carried out, by applying the Mann-Whitney test to the observed difference in values (d1 and d2) with the drugs. A p value >0.05 was observed, thus indicating that no significant difference exists between the two treatments. As seen in Figs. 7 and 8; the data lie symmetrically on line $y = 0$ with no or little horizontal difference being observed between the groups. These clearly suggest absence of any treatment-period interaction. Vertical separation of the two groups is an indication of a difference between the treatments. As seen in Figs. 3, 4 and 5, both groups lie symmetric in vertical axis around $y = 0$; thus, both the treatments (LTG and PGB) are equally efficacious when the CEI is compared.

The daily activities chart recorded by the patients showed significant improvement in basic activities like speaking and washing face while majority of them reported some but not complete improvement while eating or brushing as compared to baseline. Often, patients avoid activities that they feel might "trigger" attacks. A good pain control and reassurance from the doctor plays an important part in encouraging these patients to lead a normal life. The adverse effects profile of the two drugs is shown in Fig. 8. As seen, both drugs were generally well tolerated by all patients with no major event noted throughout the trial. The minor events included mostly dizziness, vomiting, insomnia and inability to concentrate with LTG while somnolence, weight gain and peripheral edema were most commonly observed on PGB therapy. However, the events were reversible and the introduction of a titration regime markedly reduces the intensity of such adverse drug reactions [14, 26, 27, 32].

At the end of trial, 11 patients continued PGB along with CBZ while 9 were put on LTG. The remaining 2 patients found the relief "inadequate" and were given peripheral alcohol injections. At the end of 6 months, 20 patients reported for check-up with 2 being lost to follow-up. The visual analog scale (VAS) readings of the SF-MPQ were used to determine the pain intensity at the follow-up visit. Out of 11 patients on PGB, complete relief was present in 4 (36.3 %) while 6 patients had partial (>50 %) relief and 1 was lost to follow-up. Of the 9 patients taking LTG, 2 (25 %) had complete relief while 4 reported partial relief with another 3 patients requiring alcohol blocks due to recurrence of acute symptoms. To avoid sleep complications patients were advised to take a lower dose of LTG (100–150 mg) in the evening while the morning dose was adjusted at 200–300 mg. The 2 patients with previously

administered alcohol injections reported relapse of pain and required another block while 1 did not return for check up.

An important consideration with the new anti-epileptic drugs (including LTG and PGB) is the cost factor that affects the long term maintenance regime by the patient. Since patients, in a developing country like ours, are usually limited by economic factors; frequent follow-ups to monitor multiple drug treatment severely hampers compliance and may cause relapse in such cases. Not surprisingly, out of 136 patients screened in the 1 year period, only 27 eligible patients could be isolated as most patients refuse drug treatment for logistic reasons. Another drawback with the newer drugs is the requirement of a titration regime before the therapeutic doses can be administered, thus, making them unavailable for use in acute onset pain syndromes. Peripheral alcohol blocks remains the mainstay of treatment at our centre for the above cited reasons and has been shown to have high success rate initially [33]. However, the cost-effectiveness of these is often over-shadowed by the limitations of the procedure including persistent numbness and reduced efficacy with repeated blocks [34].

The present cross-over study was undertaken as a prospective, randomized, single centre and open label trial to compare the efficacies of two anti-neuralgic drugs viz. LTG and PGB, in patients who were found to be refractory to therapeutic doses of CBZ. Both LTG and PGB, in combination with CBZ, were found to offer significant improvement in pain diary scores than that with CBZ alone. The analysis of composite efficacy index for 22 patients enrolled in the trial highlighted that both LTG and PGB are equally effective with regards to dependence on escape medication, improvement in pain diary scores and global evaluations. In addition, the adverse drug profiles of the two drugs suggest that overall tolerability of PGB exceeded that of LTG in the current sample population.

Conclusion

Under the limitation of a small sample size and subjective nature of the assessments, the efficacies of both LTG and PGB may be considered "comparable" in terms of pain relief and prevention of pain attacks. The secondary outcome suggests that in long term management of refractory TN, PGB (150–300 mg/day) along with CBZ (up to 600 mg/day) may provide better pain control with minimal drug adverse effects when compared to LTG (250–300 mg/day). It is thus prudent that continuous research is carried out to avail a therapy for refractory patients, one that is cost-effective and carrying good anti-neuralgic properties with minimal adverse effects.

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