Available online at www.sciencedirect.com
ScienceDirect
Journal of the Chinese Medical Association 74 (2011) 243–249
www.jcma-online.com

Original Article

Lamotrigine for trigeminal neuralgia: Efficacy and safety in comparison with carbamazepine☆,☆☆

Sameer Shaikh [a,*], Hashim Bin Yaacob [a], Rusdi Bin Abd Rahman [b]

[a] Department of Oral Medicine and Oral Pathology, Faculty of Dentistry, University of Malaya, Kuala Lumpur, Malaysia
[b] Hospital Raja Perempuan Zainab II, 15586 Kota Bharu, Kelantan, Malaysia

Received June 8, 2010; accepted December 16, 2010

Abstract

Background: Anticonvulsants are regarded as useful for the treatment of neuropathic pain. In this study, we evaluated the efficacy and occurrence of side effects of lamotrigine (LTG) in comparison with carbamazepine (CBZ), in trigeminal neuralgia (TN) patients.
Methods: The study was an interventional and crossover comparison. Twenty-one patients with TN were administered with LTG in comparison to CBZ. The clinical trials comprised two phases of 40 days each, with an intervening three-day washout period. The final titration in dose for LTG was 400 mg and 1,200 mg for CBZ. Efficacy of the medications involved was determined by visual analog scale (VAS) and verbal rating scale (VRS). Side effects were recorded through marking of the profiles of side effects encountered on administration of LTG and CBZ, together with baseline haematological, hepatic and renal investigations.
Results: Both on VAS and VRS assessments, in terms of proportion of patients, CBZ benefitted 90.5% (19/21) of the patients with pain relief ($p < 0.05$), in contrast to 62% (13/21) from LTG. On VAS assessment, of the 13 patients who gained pain relief from LTG and 19 from CBZ, 77% (10/13) obtained a "complete" degree of pain relief from LTG, as compared with 21% (4/19) from CBZ. On VRS assessment, with LTG, 84% (11/13) of the patients accomplished "much better" degree of pain relief, as compared with 26% (5/19) with CBZ. On LTG, 67% (14/21) of patients endured general pharmacological side effects, as compared with 57% (12/21) of patients on CBZ ($p > 0.05$). Meanwhile, LTG inflicted 14% (3/21) of the patients with haematological, hepatic and renal derangements, as compared with 48% (10/21) on CBZ.
Conclusion: LTG is generally an effective and safe treatment for management of TN, compared to CBZ.

Keywords: Carbamazepine; Lamotrigine; Pain relief; Side effects; Trigeminal neuralgia

1. Introduction

Trigeminal neuralgia (TN) is a rare form of chronic facial pain. Although not life-threatening, it can be excruciatingly painful and extraordinarily debilitating. Its uniqueness and peculiarity can be ascertained by the fact that TN may present to and be managed by dentists, neurologists, neurosurgeons, oral surgeons and ear, nose and throat surgeons. The dental surgeon is often the first to be consulted when patients confront this tormenting condition and should be familiar with it, in order to make an accurate diagnosis and initiate treatment.[1,2]

TN has an occurrence of approximately 4/100,000 individuals and occurs in both genders,[3] having a higher occurrence in women, with 5.9 cases per 100,000 females, as compared with men at 3.4 cases per 100,000 males.[4,5] It is a disease of older age groups, with a peak in the 50- to 70-year age group, and is rare below 40.[6]

TN is characterized by recurrent attacks of lancinating pain in the trigeminal nerve distribution. Typically, brief attacks are

☆ This study is registered at ClinicalTrials.gov. The corresponding ClinicalTrials.gov ID for this study is NCT00913107.
☆☆ The authors have no conflicts of interest to declare.

* Corresponding author. Dr. Sameer Shaikh, Department of Oral Medicine and Oral Pathology, Faculty of Dentistry, University of Malaya, 50603 Kuala Lumpur, Malaysia.
E-mail address: smrshaikh@gmail.com (S. Shaikh).

1726-4901/$ - see front matter
doi:10.1016/j.jcma.2011.04.002

triggered by talking, chewing, teeth brushing, shaving, a light touch, or even a cool breeze. The pain is nearly always unilateral, and may occur repeatedly throughout the day.[7] The pathophysiology of TN is thought to be focal mechanical compression of the trigeminal nerve at a point close to the brainstem, especially by an artery or tumor. This leads to demyelination of the nerve and the generation of ectopic impulses that spread ephaptically to precipitate the typical attack of TN.[7,8]

The management of TN is initially medical. Carbamazepine (CBZ) continues to be the treatment of choice,[9] however a substantial proportion of patients tolerate this drug poorly, predominantly because of side effects that include drowsiness, accommodation disorders, hepatitis, derangement in hepatic enzymes, renal dysfunction, congestive heart failure, delayed multi-organ failure, leucopenia, thrombocytopenia etc.[10,11] If pain relief for TN is incomplete with CBZ or it produces side effects, other anticonvulsant drugs are suggested as alternatives,[6,7] such as LTG, baclofen, phenytoin, gabapentin, clonazepam, valproate, mexiletine, and topiramate.[6]

Lamotrigine (LTG) has a bimodal mechanism of action: it inhibits release of the excitatory neurotransmitter glutamate, most likely by inhibiting voltage-sensitive sodium channels, and is antagonistic at neuroexcitatory *N*-methyl-D-aspartate receptors. It can also act at calcium channels.[11–13] Glutamate has been implicated in the mechanisms contributing towards the phenomenon of chronic pain, such as sensitization and wind-up. LTG, through its inhibition of pathological release of glutamate has the potential for management of chronic pain, particularly of neuropathic origin.[10]

LTG was found to be efficacious in a placebo-controlled crossover trial in 14 patients with TN.[10] An open-label study determined the better clinical and humanistic outcomes of LTG monotherapy compared with CBZ, phenytoin, or valproate monotherapy in patients with epilepsy.[14] The effectiveness of LTG when used as monotherapy in comparison with CBZ rather than placebo has yet to be evaluated in TN patients. And given the ethical and methodological dilemmas, a placebo-controlled, randomized trial raises ethical concerns in patients particularly with refractory TN, who are amongst the most difficult to treat.[10,15] This report presents the results of a clinical study to assess the efficacy and safety of LTG in direct comparison to an active "control" (CBZ), for TN.

2. Methods

2.1. Subjects

Sixteen previously and five newly diagnosed patients suffering from TN were recruited into this study, conducted at two centers within Malaysia. Ethical approval was granted by the Faculty of Dentistry Medical Ethics Committee, University of Malaya. All the prospective participants were provided with "Patient Information Sheets", containing thorough details and information regarding this clinical study. Informed consent was obtained from all patients before their enlistment. Patients with TN from either sex with no age limitation were eligible for the study. Patients were ineligible for inclusion if any of the following were evident: psychiatric illness, severe liver or cardiovascular disease, renal impairment, low white cell count, malignancy, pregnancy or lactation, alcohol or recreational drug abuse, and positive tests for human immunodeficiency virus or hepatitis B or C. Furthermore, it was ascertained that only those previously diagnosed patients with TN were recruited who were being treated with CBZ monotherapy only and hadn't undergone any cessation of CBZ (because of side effects or lack of pain relief) ever since its initiation.

2.2. Diagnosis of TN

Walk-in patients, with pain in and around the face were determined for the specific diagnosis of TN by using detailed clinical history and examination as indispensable tools. Furthermore, the Facial Pain Questionnaire (FPQ)[16] was employed to specify the TN patients into categories of Trigeminal neuralgia type 1 (TN 1) and Trigeminal neuralgia type 2 (TN 2). As per the FPQ interpretation, the explanation of diagnosis for TN 1 and TN 2 is as follows:

- *Trigeminal neuralgia type 1 (TN 1)*: "A facial pain of spontaneous onset characterized by brief electric shock-like pains, abrupt in onset and termination", such that the pain symptoms are limited to the duration of an episode of pain (temporary pain).[1,16]
- *Trigeminal neuralgia type 2 (TN 2)*: "A facial pain of spontaneous onset characterized by brief electric shock-like pains, abrupt in onset and with the features of a constant background pain which is dull and vague". This constant pain might persist from a few minutes to a few hours.[16,17]

2.3. Study design and procedures

This research study was of interventional type, having experimental design features of a comparative, open, and crossover clinical study. CBZ was employed as the "control" for comparative purposes in order to check and evaluate the efficacy (pain relief) and occurrence of side effects of LTG.

The clinical trials comprised two phases:

Phase 1 (clinical trial): At the start of Phase 1 of the clinical trials, the 16 previously diagnosed TN patients who were already receiving CBZ before this study as divulged through their medical histories, were asked to stop its administration, and subsequently after undergoing a three-day washout period, were prescribed with LTG for the following 40 days. Where as the 5 newly diagnosed patients with TN, enrolled in this study were immediately prescribed with CBZ for the next 40 days.

Phase 2 (clinical trial): At the end of the 40 days, 5 patients who were on CBZ in Phase 1 were put on LTG, for the next 40 days. Similarly, at the end of treatment with LTG in Phase 1, 16 patients were put on CBZ for the next 40 days. An intervening three-day washout period was observed between Phases 1 and 2.

Dispersible tablets of high and low strengths of each medication (LTG, 50 mg and 100 mg; CBZ, 100 mg and 200 mg) were provided to the patients. The regimes for prescription of LTG and CBZ for both Phases 1 and 2 of the clinical trials were as follows: LTG was started at a dose of 100 mg/d, and with a dose escalation of 100 mg/d on every 10th day, titrated up to a target dose of 400 mg. CBZ was a started at a dose of 300 mg/d, and with a dose escalation of 300 mg/d on every 10th day, titrated up to a target dose of 1,200 mg.

2.4. Outcome measures

The inquiry maneuvers related to the determination of efficacy of the medications involved was facilitated through the usage of various diagnostic instruments and tools such as the visual analog scale (VAS) and verbal rating scale (VRS). Detailed clinical history was also availed as an indispensable tool to divulge the required information about the nature of complaint, efficacy and safety of the medications (CBZ and LTG).

At the termination of each treatment phase, side effects were recorded through marking of the profiles of side effects encountered on administration of LTG and CBZ, together with baseline haematological, hepatic and renal investigations. These investigations included full blood counts (FBCs), liver function tests (LFTs) and renal function tests (RFTs). All these maneuvers were performed on the initiation, as well as at the termination, of each of the two phases of the clinical trials. Thus we compared the end of each treatment phase with the pre-trial condition, each for CBZ and LTG.

2.5. Interpretation of VAS and VRS

The patients rated their current pain intensity (pi) and pain relief (pr) on a VAS, a 100-mm vertical line with "no pain" marked at one end and "worst imaginable pain" at the other, and on a 3-category parametric VRS, before the start of treatments (LTG and CBZ) and at each follow-up visit. VAS ratings of 0–4 mm were considered no pain; 5–44 mm, mild pain; 45–74 mm, moderate pain; and 75–100 mm, severe pain. Toward pain relief, VAS ratings of 0–4 mm were considered complete relief; 5–44 mm, fair amount of relief; and 45–100 mm, incomplete relief. For VRS, pain intensity was determined through parameters related to severity of pain (0, none; 1, mild; 2, moderate; 3, severe) and its paroxysms (none, 1–3, 4–7, 8–12, 13–20, >20), where as pain relief was determined by a parameter based on three phrases related to the degree of pain relief (much better, better and minimal effect).

The difference between each post-treatment VAS and VRS scores and the pre-treatment scores were calculated and represented each participant's VAS and VRS difference scores.

2.6. Statistical analysis

Patients' pre and post medication (LTG and CBZ) responses towards their TN pain, recorded on VAS and VRSs, were translated into numerical values followed by statistical analysis using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Chi-square test comprised the statistical analyses. For analytical purposes related to the determination of efficacy and safety of LTG in comparison with CBZ, each of these two medications was taken as a separate entity, therefore the clinical effects (i.e. efficacy and safety) of each of these medications (LTG, CBZ) was subjected to statistical analysis separately. A p value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Patients characteristics

The two centres recruited seventeen and four patients respectively. Of these 21 patients (male, $n = 9$; female, $n = 12$) assessed under this study, female comprised 57% of the patients, representing a female to male ratio of 1.33:1. The mean age of patients was 64.66 years with a standard deviation of 13.22 years. The youngest patient, a female of 32 years and the oldest, a male, aged 84 years.

Eighteen cases (86%), through their clinical presentations and subsequent input of the features of their ailment into the online version of the FPQ, were diagnosed with TN 1,whereas three patients (14%) were diagnosed with TN 2.

3.2. Efficacy analysis

Both on VAS and VRS assessments, out of the total of 21 patients, 13 patients (62%) attained pain relief from LTG in contrast to 19 (90.5%) attaining pain relief from CBZ. Eight patients (38%) failed to achieve any benefit of pain relief from LTG, whereas 2 patients (10%) failed to achieve any benefit of pain relief from either drug. Under CBZ, the p value of the test was 0.001 (<0.05) indicating a large proportion of patients benefited in pain relief from CBZ. Table 1 illustrates the numbers of patients benefitting from pain relief under LTG and CBZ.

3.3. Degrees of pain relief assessed by VAS and VRS

On VAS assessment, of a total of 13 patients attaining pain relief from LTG, 10 patients (77%) experienced "complete" pain relief, whereas among the 19 patients who experienced pain relief with CBZ, only 4 patients (21%) experienced "complete" pain relief.

Table 1
Efficacy status in relation to number of patients

Pain relief with LTG	Pain relief with CBZ		Total
	Yes (n)	No (n)	
Yes (n)	13	0	13
No (n)	6	2	8
Total	19*	2	21

* A p value < 0.05.
CBZ = carbamazepine; LTG = lamotrigine; n = number of patients.

On VRS assessment, out of a total of 13 patients attaining pain relief from LTG, 11 patients (84%) accomplished "much better" degree of pain relief. While among the 19 patients who experienced pain relief with CBZ, only 5 patients (26%) accomplished "much better" degree of pain relief. Tables 2 and 3 elaborate the degrees of pain relief on VAS and VRS assessments.

3.4. Safety analysis

The general side effects reported on administration of LTG and CBZ are listed in Table 4. Fourteen patients (67%) out of a total of 21 patients during therapy with the LTG displayed 21 pharmacological side effects attributable to LTG, whereas 12/21 (57%) of the patients displayed 22 pharmacological side effects attributable to CBZ. Skin rash, headache and dizziness were the most commonly reported side effects on LTG. Eight patients (38%) withdrew from LTG because of development of skin rash (5 patients) and the failure to obtain pain relief (3 patients). Two patients (10%) withdrew from CBZ because of the development of Stevens-Johnson syndrome. Statistically, the proportion of patients with side effects was no different from that of those who did not have side effects, on either of the two treatments ($p > 0.05$).

For the sake of comparative assessment of the safety level of LTG and CBZ, patients were assigned into three categories based on affliction of side effects on administration of LTG and CBZ (Table 5). Patients who suffered side effects (8 patients), as well as no side effects (3 patients), through both treatments (LTG, CBZ) were classified as a group with "No difference". Patients who had side effects with LTG but not with CBZ were classified as "Worse" and patients having side effects with CBZ but not with LTG were classified as "Safer". On statistical comparison of the "Worse" and "Safer" statuses, the safety status of LTG was no different from that of CBZ ($p > 0.05$).

Haematological, hepatic and renal side effects with derangement values are illustrated in Table 6. LTG rendered 3 patients (14%) with these side effects. The most common of them pertains to the alterations within the red blood cell counts, haematocrit (packed cell volume) and haemoglobin levels. LTG had no effect on white blood cell and platelet counts. CBZ rendered 10 patients (48%) with haematological, hepatic and renal side effects. Derangements within the red blood cell counts and haematocrit levels were the most commonly reported events on CBZ. Regarding the derangements in LFT and RFT profiles (Table 6), LTG resulted in derangement of the alkaline phosphatase (liver enzyme) in two patients, while CBZ resulted in derangement of the gamma glutamyl transpeptidase (liver enzyme) in two patients, as determined by LFT. An abnormal shift in the creatinine levels determined by RFT was detected in one patient while on LTG and in two patients while on CBZ. No statistical analysis was appropriate, as a fewer number of patients were inflicted with haematological, hepatic and renal side effects on either drug.

Table 2
Degree of pain relief assessed by visual analogue scale

Degree of pain relief	LTG	CBZ
Complete	10 (77%)	4 (21%)
Fair	2 (15%)	8 (42%)
Incomplete	1 (8%)	7 (37%)
Total	13 (100%)	19 (100%)

CBZ = carbamazepine; LTG = lamotrigine.

Table 3
Degree of pain relief assessed by verbal rating scale

Degree of pain relief	LTG	CBZ
Much better	11 (84%)	5 (26%)
Better	1 (8%)	7 (37%)
Minimal effect	1 (8%)	7 (37%)
Total	13 (100%)	19 (100%)

CBZ = carbamazepine; LTG = lamotrigine.

4. Discussion

The design and methodology of clinical drug trials to investigate the efficacy (pain relief) and safety (side effects) of new drugs for managing TN presents a substantial challenge to the investigator as well as to the patients. The ethical considerations expect that the participants of the trial will not be subjected to unbearable afflictions of TN, at the expense of gathering some relevant clinical data pertaining to the new treatment in question. Sequential trials comparing new anticonvulsant drugs with a positive control have the potential to combine scientific validity, clinical relevance, and ethical acceptability. A trial of this sort involving evaluation of the "active" medication (LTG for this particular study) assessed in direct comparison to an active "control" (CBZ), serves two purposes. Firstly, it avoids the concerns raised by exposing patients with agonizing and distressing pain of TN to placebo. Secondly, it brings into limelight the side effects and shortcomings of the established treatment (CBZ). Finally the broader aim of such a design would be to show superiority, if

Table 4
General side effects attributable to lamotrigine and carbamazepine

Side effects	LTG ($n = 14$)*[a]	CBZ ($n = 12$)*[a]
Total side effects	21	22
Headache	4	10
Dizziness	3	5
Accommodation disorders	–	1
Mental irritability and distress	2	1
Nausea and GI troubles	–	3
Allergic reactions (skin rash & Stevens-Johnson syndrome)	5	2
Altered taste sensation	2	–
Hot flashes/pyretic feeling	3	–
Increased micturition (polyurea)	1	–
Resp. problems (asthma)	1	–

[a] Number of reported side effects.
* A p value > 0.05.
CBZ = carbamazepine; GI = gastrointestinal; LTG = lamotrigine; n = number of patients reporting side effects.

Table 5
Safety of LTG compared to carbamazepine

Safety status	Patients (%)
Worse with LTG	6 (29%)*
Safer with LTG	4 (19%)*
No difference	11 (52%)

* A p value > 0.05.
LTG = lamotrigine.

present, of the new over the established treatment, or to guarantee its equivalence if not.[15]

The clinical trials for this study were designed with the aforementioned considerations in mind. In this comparative study, LTG was assessed for its efficacious capability and the safety potential, for the management of TN. For that purpose, a comparative and sequential/ methodological approach was undertaken related to LTG administration in the TN patients, in direct comparison to an established effective treatment (CBZ). Important consideration was also given to the strategy of standardization related to the evaluation of the efficacy of the medications (LTG, CBZ). This was addressed through adoption of "Intention-to-treat" principle. When there is a drop in the number of patients along the way during an experiment because of the non-adherence to the procedures and protocols, or clinicians' recommendations for withdrawal of the medication(s) under study because of side effects, the end results become uncertain. "Intention-to-treat" is a strategy to account for this uncertainty which is generally interpreted as including all the patients, regardless of whether they actually satisfied the entry criteria, the treatment actually being received, on

Table 6
Haematological, hepatic and renal side effects

Side effects	LTG ($n = 3$)		CBZ ($n = 10$)	
	↓ in limit (# of patients)	↑ in limit (# of patients)	↓ in limit (# of patients)	↑ in limit (# of patients)
I. Cellular profiles				
(A) Full blood counts (FBCs)				
1) Derangements in RBC levels (*normal range*: 4.5–5.9 × 10^{12}/L)	4.18 × 10^{12}/L (2)	7.43 × 10^{12}/L (1)	3.62 × 10^{12}/L (5)	6.39 × 10^{12}/L (1)
2) Derangements in haematocrit levels (*normal range*: 36–46%)	30% (2)	72% (1)	33.1% (4)	62% (1)
3) Derangements in haemoglobin levels (*normal range*: 120–160 g/L)	115 g/L (2)	237 g/L (1)	112 g/L (2)	235 g/L (1)
4) Derangements in WBC levels (*normal range*: 4.6–10.2 × 10^9/L)	–	–	4.3 × 10^9/L (1)	11.5 × 10^9/L (1)
5) Derangements in platelet levels (*normal range*: 150–400 × 10^9/L)	–	–	143 × 10^9/L (1)	406 × 10^9/L (1)
6) Elevation in blood urea (*normal range*: 1.7–8.3 mmol/L)	–	–	–	13 mmol/L (1)
II. Molecular profiles				
(A) Liver function tests (LFTs)				
1) Derangement in liver enzymes				
1a) Alkaline phosphatase (*normal range*: 50–136 IU/L)	131 IU/L (1)	162 IU/L (1)	–	–
1b) Gamma glutamyl transpeptidase (*normal range*: 5–55 IU/L)	–	–	50 IU/L (1)	116 IU/L (1)
2) Derangement in globulin levels (*normal range*: 20–35 g/L)	30 g/L (1)	38 g/L (2)	17 g/L (1)	37 g/L (4)
(B) Renal function test (RFT)				
1) Creatinine levels (*normal range*: 53–100 μmol/L)	–	104 μmol/L (1)	42 μmol/L (1)	114 μmol/L (1)
2) Electrolytes:				
2a) Sodium (*normal range:* 136–145 mmol/L)	–	–	132 mmol/L (1)	–
2b) Chloride (*normal range*: 100–108 mmol/L)	–	–	99 mmol/L (1)	–

n = total number of patients reporting haematological, hepatic and renal side effects.

subsequent withdrawal or deviation from the protocol. Furthermore, this strategy takes the last observation as the end result.[18,19] During this study, if some patients were to be discontinued on either of the two treatments (LTG, CBZ), due to development of the side effects or because of unbearable TN pain as a result of failure of drugs' efficacy, the pain relief status at the time of discontinuation was considered as the outcome. This was in accordance with the "Intention-to-treat" principle.

CBZ, on initiation, has an elimination half-life of 20−40 hours. However, during chronic therapy, its half-life is decreased to 11−27 hours consequent to autoinduction (i.e. it induces its own hepatic metabolism). The mean elimination half-life of LTG is about 24 hours.[2] In this study of crossover comparison, a washout period of three days between the administration of two drugs was included to minimize carry-over effects, which was expected to be sufficient for both LTG and CBZ to be eliminated.

Because of scant numbers of patients suffering from trigeminal neuralgia and the reluctance of some patients to participate, it was imperative to include both the previously and newly diagnosed patients. To ensure fairness in comparison between LTG and CBZ, it was ascertained that only those previously diagnosed patients would be recruited who were solely on CBZ monotherapy ever since their diagnosis and (these 16 patients) hadn't discontinued CBZ in the past, either because of lack of pain relief or because of life-threatening/major side effects requiring withdrawal. Although they were all benefitting from varied degrees of pain relief from their CBZ medication before recruitment in this study, a washout period of three days (observed at the initiation of the study) was expected to be sufficient for the elimination of CBZ rendering these patients as "new entities" with minimal carryover effects. It is also pertinent to mention that no consideration was given to the degree of pain relief (whatsoever) from the CBZ treatment gained prior to enlistment in this study.

In this study, LTG was found to be an effective remedy for the management of TN, even though a sizeable proportion of patients derived benefit of pain relief from CBZ, but still, in terms of degree of pain relief a greater proportion of patients obtained a "complete" and "much better" degrees of pain relief from TN with LTG compared with CBZ. The positive efficacious characteristics of LTG shown by this study are in general agreement with the findings of Zakrzewska et al,[10] conducted to study the efficacy and tolerability of LTG in 14 patients with TN. In the present study, in terms of proportion of patients benefitting from the pain relief, efficacy of CBZ was found to be higher compared with that of LTG. This finding was in accordance with the two clinical studies.[20,21] Sato et al[20] demonstrated a beneficial efficacy rate of 90.5% for CBZ, in a diagnostic study to evaluate the significance of CBZ in 50 TN patients. Silver et al.[21] demonstrated a low efficacy rate of LTG (<50%), in a clinical study to evaluate the efficacy of LTG in 112 patients with neuropathic pain.

LTG, like CBZ, is not free from side effects. The numbers of dropouts from this clinical study because of a characteristic side effect of skin rash was found to be higher with LTG. Rapid dose escalation of LTG most likely increases the chances of dose-dependent side effects, particularly skin rash. The occurrence of skin rash requiring discontinuation of LTG can be reduced by using a gradual introduction of the drug.[10] The recommended dose escalation for LTG is to have it initiated at 25 mg daily and to increase it by 25 mg every seventh day as needed to a total daily dose of 400 mg.[22]

This clinical trial employed a far more rapid introduction of LTG than is recommended, and should not be used in clinical practice. However, gradual introduction of LTG can be a limitational factor precluding the use of LTG in the most severe cases of TN. LTG in this study proved to be a nominally tolerated option, particularly with respect to a lower occurrence of central nervous system and haematologically related side effects, which is a common occurrence with CBZ.[10] The present clinical trial was relatively short, with a total duration of 20 weeks. Because of the painful condition of TN, longer studies on the clinical trials would not be advisable. As such, the effectiveness of LTG in the long-term treatment of TN remains open to question. However, patients who are on treatment with LTG may be monitored for its long-term effects. It is also heartening to observe that thirteen (62%) of the twenty-one patients in this trial remained on LTG even after termination of the study and continued to receive the benefit of pain relief.

In conclusion, the results of this study suggest that LTG is an effective and safe treatment for management of TN, compared to CBZ.

Acknowledgments

The authors offer their sincere gratitude to Dr. Rusdi Bin Abd. Rahman, Oral and Maxillofacial Surgeon, Raja Perempuan Zainab Hospital 2, Kota Bharu, for giving unimpeded access to his patients with TGN. Clinical insight of Dr. Rusdi for proper assessment and management of patients with TGN contributed immensely to this study. This study was supported by a University Malaya Research Grant (PS287-2007B).

References

1. Scrivani SJ, Mathews ES, Maciewicz RJ. Trigeminal neuralgia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;**100**:527−38.
2. Zakrzewska JM. *Trigeminal neuralgia*. London: WB Saunders; 1995.
3. Zakrzewska JM. Trigeminal neuralgia. *Prim Dent Care* 1997;**4**:17−9.
4. Siddiqui MN, Siddiqui S, Ranasinghe JS, Furgang FA. Pain management: trigeminal neuralgia. *Hosp Physician* 2003;**39**:64−70.
5. Zakrzewska JM. Trigeminal neuralgia and facial pain. *Semin Pain Med* 2004;**2**:76−84.
6. Bennetto L, Patel NK, Fuller G. Trigeminal neuralgia and its management. *BMJ* 2007;**334**:201−5.
7. Krafft RM. Trigeminal neuralgia. *Am Fam Physician* 2008;**77**:1291−6.
8. Liu J, Dai J, E L, Wang D, Liu H. Trigeminal neuralgia may be caused by abnormality of the trigger zone. *Med Hypotheses* 2010;**74**:818−9.
9. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, et al. AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol* 2008;**15**:1013−28.

10. Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens EL. Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. *Pain* 1997;**73**:223−30.
11. Reisner L, Pettengill CA. The use of anticonvulsants in orofacial pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;**91**:2−7.
12. Tremont-Lukats IW, Megeff C, Backonja MM. Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. *Drugs* 2000;**60**:1029−52.
13. Chole R, Patil R, Degwekar SS, Bhowate RR. Drug treatment of trigeminal neuralgia: a systemic review of the literature. *J Oral Maxillofac Surg* 2007;**65**:40−5.
14. Kaminow L, Schimschock JR, Hammer AE, Vuong A. Lamotrigine monotherapy compared with carbamazepine, phenytoin, or valproate monotherapy in patients with epilepsy. *Epilepsy Behav* 2003;**4**:659−66.
15. Brodie MJ, Wroe SJ, Dean AD, Holdich TA, Whitehead J, Stevens JW. Efficacy and safety of remacemide versus carbamazepine in newly diagnosed epilepsy: comparison by sequential analysis. *Epilepsy Behav* 2002; **3**:140−6.
16. Oregon Health and Science University. Facial pain questionnaire. Available at: http://neurosurgery.ohsu.edu/tgn.php [accessed: 12. 12. 10].
17. Zakrzewska JM. Diagnosis and differential diagnosis of trigeminal neuralgia. *Clin J Pain* 2002;**18**:14−21.
18. Montori VM, Guyatt GH. Intention-to-treat principle. *CMAJ* 2001;**165**: 1339−41.
19. Heritier SR, Gebski VJ, Keech AC. Inclusion of patients in clinical trial analysis: the intention-to-treat principle. *Med J Aust* 2003;**179**: 438−40.
20. Sato J, Saitoh T, Notani K, Fukuda H, Kaneyama K, Segami N. Diagnostic significance of carbamazepine and trigger zones in trigeminal neuralgia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;**97**:18−22.
21. Silver M, Blum D, Grainger J, Hammer AE, Quessy S. Double-blind, placebo-controlled trial of lamotrigine in combination with other medications for neuropathic pain. *J Pain Symptom Manage* 2007;**34**: 446−54.
22. Prasad S, Galetta S. Trigeminal neuralgia: historical notes and current concepts. *Neurologist* 2009;**15**:87−94.