

**Efficacy and safety of lamotrigine in patients with trigeminal neuralgia: a comparison with carbamazepine****Mahesh Goel<sup>1</sup>, Rajiv Tanwar<sup>1\*</sup>, Janardhan Singh<sup>2</sup>, Shruti Kirti Tripathi<sup>1</sup>**<sup>1</sup>Department of Oral and Maxillofacial Surgery, PGIDS, Rohtak, Haryana, India,<sup>2</sup>Department of Pharmacology, Pt. BDS, UHS, Rohtak, Haryana, India**Received:** 01 March 2015**Accepted:** 04 April 2015**\*Correspondence to:**Rajiv Tanwar,  
Email: rajivraj.124@gmail.com**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.**ABSTRACT****Background:** Antiepileptic drugs are increasingly used in the treatment of pain syndromes. This study evaluates efficacy and safety of lamotrigine in comparison with carbamazepine (CBZ) in trigeminal neuralgia (TN) patients.**Methods:** A total of 50 previously and newly diagnosed patients of TN were administered with lamotrigine (LTG) in comparison to CBZ. The final titration in dose for LTG was 400 mg/day and 1200 mg/day for CBZ. Clinical assessment (pain relief) was done before and after 15, 30, and 60 days of drug administration by visual analog scale and verbal rating scale. Side effects were recorded during study in both groups.**Results:** Of 25 patients in Group I who received CBZ, 16 patients (64%) experienced complete pain relief, while in Group II (LTG), 21 patients experienced complete pain relief. LTG was generally well tolerated except one patient was withdrawn due to skin rashes. CBZ was associated with mild hematological and central nervous system side effects.**Conclusion:** LTG is as effective and safe treatment for the management of TN as compared to CBZ.**Keywords:** Lamotrigine, Carbamazepine, Trigeminal neuralgia pain**INTRODUCTION**

Trigeminal neuralgia (TN) is the most frequently diagnosed form of facial pain with a prevalence of 4 per 1,00,000 in the general population.<sup>1</sup> This condition has been known since ancient time and has been investigated extensively by clinicians of various fields neurosurgeons, neurologists, ophthalmologists, dentists, psychiatrists, and pathophysiologists. Still, many problems related to TN remain unknown. Currently, there are 3 most popular theories regarding etiology of TN. One is related to other disease, second is direct trauma to the nerve, and third theory propagates the polyetiologic origin of the disease. However, as yet no cause has been identified for most of the patients with TN.<sup>2</sup> Treatment of TN continues to be a major therapeutic challenge. Antiepileptic drugs are also commonly utilized for pain syndromes including neuropathic pain. Despite the entry of several new drugs for this condition over the last few decades carbamazepine (CBZ) has still retained its position as the drug of choice

for TN.<sup>3</sup> However, a number of patients tolerate this drug poorly mainly due to serious side effects such as vertigo, ataxia, diplopia, stupor blurred vision, respiratory depression, aplastic anemia, hypersensitivity reaction, and retention of water.<sup>4</sup> If pain relief is incomplete with CBZ or contraindicated, other drugs such as phenytoin, gabapentin, sodium valproate, topiramate, clonazepam or lamotrigine (LTG) are suggested.<sup>4</sup> Many patients with TN eventually become refractory to drug treatment and are then offered surgery. Surgery itself is associated with morbidity and mortality. Hence, there is always scope to develop safe and effective drug for TN.

LTG is a novel antiepileptic drug with at least two anti-nociceptive mechanisms. It stabilizes the neuronal membrane by blocking the activation of voltage-sensitive sodium channels and inhibits the presynaptic release of the excitatory neurotransmitter glutamate.<sup>5</sup> It can also act at calcium channels.<sup>6</sup> Glutamate is an excitatory neurotransmitter candidate in nociceptive pathways in the spinal cord which

has been implicated in the mechanisms that may be involved in chronic pain such as central sensitization and wind up, both of which can be inhibited by N-methyl D-aspartate (NMDA) receptor antagonists.<sup>7</sup> By inhibiting the release of glutamate, LTG has the potential to be antinociceptive and to prevent the mechanisms responsible for establishment of chronic pain. LTG, a phenyltriazine derivative was initially developed as an antifolate agent.<sup>8</sup> It is useful as monotherapy and add-on therapy for partial and secondarily generalized tonic-clonic seizures in adults.<sup>9</sup> LTG was found to be efficacious in a placebo controlled crossover trial in 14 patients of TN.<sup>5</sup> Kaminow et al. in an open-label study demonstrated better clinical outcomes of LTG monotherapy compared with CBZ, phenytoin or valproate monotherapy in patients with epilepsy.<sup>10</sup> The efficacy and safety of LTG when used as monotherapy in comparison with CBZ rather than placebo has yet to be studied in patients with TN. Therefore, the present study is undertaken to evaluate the role of LTG in patients with TN in direct comparison to an active control, i.e., CBZ.

## METHODS

Total 50 previously and newly diagnosed patients suffering from TN, who met the inclusion criteria were enrolled in the study. The study was conducted at the Department of Oral and Maxillofacial Surgery, Post graduate Institute of Dental Sciences, Rohtak. Ethical approval was granted by the Institutional Ethics Committee, PGIDS, Rohtak. Patients who were eligible as per the inclusion and exclusion criteria of the study were allotted to receive one of the two different treatments in an open fashion and were subjected to clinical assessment including efficacy and safety. All the participants were provided with patient information sheet containing detailed information regarding this study. Informed consent was obtained from all patients before their enrollment. Patients of either sex, more than 18 years of age were eligible for the study. Patients were ineligible if any of the following were evident, psychiatric illness, severe liver or cardiovascular disease, renal impairment, low white blood cell count, malignancy, pregnancy or lactation, alcohol or recreational drug abuse, HIV or hepatitis B or C positive patients, and hypersensitivity to CBZ or LTG. Previously diagnosed patients with TN were also recruited who were being treated with CBZ monotherapy only and had not discontinued CBZ.

### *Diagnosis of TN*

Patients with pain in and around the face were diagnosed for TN using detailed clinical history and thorough examination of face and facial pain questionnaire.<sup>11</sup>

### *Drug interventions*

This study was of interventional type, comparative and open label. CBZ was used as the control for comparison purpose

in order to evaluate the efficacy (pain relief) and occurrence of side effects (safety) of LTG. Patients were divided in to two groups of 25 each.

Group I: Patients were given standard treatment, i.e., CBZ tablet 200 mg per day in two divided doses. The dose was increased gradually on every 10<sup>th</sup> day and was titrated up to 1200 mg/day.

Group II: Patients were given drug LTG started at a dose of 100 mg/day equally divided with a dose escalation of 100 mg per day on every 10<sup>th</sup> day, titrated up to 400 mg per day.

Patients who developed intolerable side effects during treatment were withdrawn from the study and were given with best possible treatment.

### *Clinical assessment*

Clinical assessment was done before treatment and after 15, 30, and 60 days of drug administration.

### *Efficacy end point for TN*

Outcome measures related to efficacy (pain relief) of medications were made through the usage of various diagnostic tools such as visual analog scale (VAS)<sup>12</sup> and verbal rating scale (VRS).<sup>13</sup>

The patients rated their current pain intensity and pain relief on a VAS, a 100 mm vertical line with no pain marked at one end and worst pain at the other, and on a 3 category parametric VRS, before the start of treatment (CBZ and LTG) and at each follow-up visit. VAS rating of 0-4 mm was considered no pain, 5-44 mm mild pain; 45-74 mm moderate pain and 75-100 mm severe pain. Toward pain relief, VAS rating of 0-4 mm was 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 the severity of pain (0, none; 1 mild; 2 moderate; 3 severe). The difference between each pre-treatment VAS and VRS scores and the post-treatment scores were calculated and represented each patient's VAS and VRS difference scores. Results were statistically analyzed using SPSS version 17 chi-square test comprised the statistical analysis. A  $p < 0.05$  was considered to be statistically significant.

## RESULTS

### *Patients characteristics*

Of 50 patient (male  $n=15$ ; female  $n=35$ ) assessed in this study, female comprised 70% of the patients, representing a female to male ratio of 2.3:1. The mean age of patients

in Group I was 51.08 years and in Group II was mean 55.68 years. The youngest patient in Group I was a female of 30 years and oldest patient was a male of 72 years. In Group II, youngest patient was a male of 38 years and oldest patients, a female, aged 71 years.

**Efficacy analysis**

Both on VAS and VRS assessments, out of total 25 patients in Group I who received CBZ, 16 patients (64%) experienced complete pain relief. Of 25 patients of Group II those received LTG, 21 patients (84%) experienced complete pain relief (Table 1 & 2).

**Safety**

General side effects observed during study in both groups i.e., active control (CBZ) and LTG are shown in Table 3. 12 patients (48%) out of 25 during therapy with CBZ were reported 17 side effects. Side effects of CBZ were usually well tolerated. There was no drop out in Group I due to serious side effects. Two patients in Group II developed skin rash and one was withdrawn from the study.

**Table 1: Mean score of pain assessed by visual analog scale in CBZ and LTG treated patients.**

Time interval	Group I VAS (n=25)	Group II VAS (n=25)	Statistical significance
Pretreatment	75.68±8.06	72.76±11.79	
After 15 days	29.8±10.94*	15.8±9.31*#	p<0.001 (highly significant)
After 30 days	31±12.33*	14.8±8.35*#	p<0.001 (highly significant)
After 60 days	30.4±17.49*	15.4±7.89*#	p<0.001 (highly significant)

\*p<0.001 when compared with pretreatment value (Chi-square test), #p<0.001 when compared with Group I (control), LTG: Lamotrigine, VAS: Visual analog scale, CBZ: Carbamazepine

**Table 2: Degree of pain relief assessed by VRS in CBZ and LTG treated patients.**

Time interval	Group I VRS (n=25)	Group II VRS (n=25)	Statistical significance
Pretreatment	2.52±0.50	2.44±0.50	
After 15 days	1.48±0.50*	1.04±0.611*#	p<0.001 (highly significant)
After 30 days	1.72±0.54*	0.84±0.74*#	p<0.001 (highly significant)
After 60 days	1.28±0.61*	0.64±0.56*#	p<0.001 (highly significant)

\*p<0.001 when compared with pretreatment value (Chi-square test), #p<0.001 when compared with Group I (control), LTG: Lamotrigine, VRS: Verbal rating scale, CBZ: Carbamazepine

Both CBZ and LTG had no effect on vision of the eye in both the study groups. Hematological, renal, and hepatic side effects were also reported in both the groups. LTG resulted in derangements of alkaline phosphatase (liver enzyme) in one patient (4%), while CBZ resulted in derangements of the same enzyme in two (8%) patients as determined by liver function test.

**DISCUSSION**

Results of the present study revealed that LTG is more effective than CBZ in controlling the pain of TN. As evidenced by significantly less VAS and VRS scores in LTG treated patients as compared to CBZ. Pain relief by LTG in patients with TN may be due to the effect of drug on sodium channels, by reducing the release of excitatory neurotransmitter glutamate or by modulating calcium channels. The possible efficacious characteristics of LTG observed in this study are in agreement with findings of Zakrzewska et al.<sup>5</sup> These workers also reported the efficacy of LTG in a placebo controlled crossover trials conducted in 14 patients with TN. In the present study, we evaluated efficacy and safety of LTG in direct comparison to an active control (CBZ) for TN patients because it is unethical to use a placebo alone due to severe nature of pain during TN.

Xie et al.<sup>14</sup> demonstrated that LTG acts by stabilizing the slow inactivated conformation of Type II A neuronal sodium channels, resulting in inhibition of repetitive firing of action potentials under conditions of sustained neuronal depolarization. By this mechanism, LTG is believed to suppress the excessive release of glutamate.

**Table 3: General side effects observed in CBZ and LTG treated patients (data represented as number of patients).**

Side effects	Group I (n=25)	Group II (n=25)	Statistical significance
Dizziness	2	1	$\chi^2=0.354$ ; df=1; p=0.551 (>0.05 NS)
Nausea/vomiting	4	2	$\chi^2=0.757$ ; df=1; p=0.384 (>0.05 NS)
Drowsiness	2	1	$\chi^2=0.354$ ; df=1; p=0.551 (>0.05 NS)
Skin rashes	1	2	$\chi^2=0.354$ ; df=1; p=0.551 (>0.05 NS)
Blurred vision	0	0	
Hepatic toxicity	2	1	$\chi^2=0.354$ ; df=1; p=0.551 (>0.05 NS)
Renal toxicity	2	1	$\chi^2=0.354$ ; df=1; p=0.551 (>0.05 NS)
Leukopenia	4	1	$\chi^2=2.0$ ; df=1; p=0.157 (>0.05 NS)

LTG: Lamotrigine, NS: Non-significant, CBZ: Carbamazepine

Glutamate is a neurotransmitter candidate in nociceptive pathway in the spinal cord which has been implicated in the mechanisms that may be involved in chronic pain such as central sensitization and wind up, both of which can be inhibited by NMDA receptors antagonist.<sup>7</sup> Therefore analgesic effect of LTG is mediated by inhibiting release of glutamate and thus prevents mechanisms responsible for development of chronic pain.

LTG inhibits voltage sensitive sodium currents through a preferential interaction with slow inactivated sodium channels, there by suggesting that it may act selectively against high frequency epileptiform discharge. As a cellular action, LTG suppress burst firing in cultured rat cortical neurons and sustained repetitive firing in the mammalian spinal cord, while having normal synaptic conduction unaffected. LTG inhibits sodium-dependent glutamate and aspartate release as well as GABA release from cortical slices.<sup>15</sup> LTG can also act at calcium channels.<sup>16</sup> Therefore, it is possible that the anti-nociceptive effect of LTG is mediated via modulating of voltage sensitive Na<sup>+</sup>, Ca<sup>2+</sup> channels and by reducing the release of excitatory neurotransmitter glutamate.

Efficacy of LTG in relieving painful diabetic neuropathy was tested in two large scale multicenter randomized controlled trials.<sup>17</sup> Each study randomized 360 patients to receive either LTG 200,300 and 400 mg/day or placebo. Both studies showed 2.5 and 2.7 points in improvements in mean pain intensity from baseline for the 300 mg/day and 400 mg/day dosages, respectively. Wiffen and Rees<sup>18</sup> reported that LTG is effective in TN refractory to other treatments, post-herpetic neuralgia, painful peripheral neuropathy, HIV neuropathy, post-stroke pain, pain related to spinal cord injury, and glossopharyngeal neuralgia.

More efficacy of LTG as compared to CBZ observed in the present study may be explained on the basis of decreased glutamate release by LTG. Excitatory neurotransmitter is involved neurotoxicity, neurodegeneration and oxidative stress and glutamate has well established a role in nociceptive mechanisms.

In the present study, LTG is generally well tolerated by patients except incidence of skin rashes observed in two patients and one patient was withdrawn from the study due to skin rashes, otherwise LTG was better tolerated than CBZ, no dropout was reported in CBZ group. LTG had no significant hematological, biochemical, and central nervous system related side effects, which is a common occurrence with CBZ.

At present, it is difficult to propose an exact molecular mechanism of analgesic effect of LTG in patients with TN, but the study suggests that LTG is more effective and better tolerated drug than CBZ.

## CONCLUSION

LTG is an effective and safe treatment for management of TN, compared to CBZ.

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