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ORIGINAL ARTICLE

Effectiveness of amitriptyline and lamotrigine in traumatic spinal cord injury-induced neuropathic pain: a randomized longitudinal comparative study

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Study design: Randomized longitudinal comparative study.
Objectives: To compare the efficacy of lamotrigine and amitriptyline in the management of traumatic spinal cord injury (SCI)-induced neuropathic pain (NP).
Setting: Sawai Man Singh Medical College and Hospital, Jaipur, India.
Methods: A total of 147 individuals with NP were randomized for a 3-week trial of either amitriptyline or lamotrigine. Amitriptyline was administered orally at doses of 25, 50 and 100 mg once daily at night time, and lamotrigine was administered orally at doses of 25, 50 and 100 mg twice daily, both for 1 week by means of optional titration. Assessment of NP was done at baseline and thereafter at 1, 2 and 3 weeks using Short–form MC Gill Pain Questionnaire-2 (SFMPQ2) scores.
Results: There was a significant difference between the mean values of the SFMPQ2 score at baseline and those at each follow-up for amitriptyline. Similar results were seen in the lamotrigine group. When the differences in mean SFMPQ2 scores at different time frames from baseline were compared with those of the other group, values were found to be nonsignificant as seen on the Mann–Whitney *U*-test.
Conclusions: These findings support the use of both amitriptyline and lamotrigine in the management of NP after traumatic SCI.
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INTRODUCTION

Traumatic spinal cord injury (SCI) is one of the most devastating types of injury and it results in varying degrees of paralysis, sensory loss and bladder/bowel dysfunction. In SCI patients, pain has a major impact in terms of reduced quality of life, functional impairment and restrictive social participation.

The average reported figure for the prevalence of chronic SCI-induced neuropathic pain (NP) is ~70%; one-third of patients describe it as an intense pain having a negative impact on their mood and activities of daily living.[1] Pain can slow down or even interrupt a rehabilitation program and be a major hurdle to a normal social life. When pain is not adequately managed or even neglected, it leads to physical and psychological disorders that are difficult to treat and can trigger a chronic pain syndrome.

Different types of pain are commonly observed in SCI patients, and taxonomy was proposed in 2012 as the International Spinal Cord Injury Pain (ISCIP) Classification.[2] It has a three-tiered division: tier 1 divides pain according to pain type—that is, nociceptive, neuropathic, other pain and unknown pain; tier 2 describes the pain subtype; and tier 3 describes the primary pain source. Tier 2 subcategories for NP are: at level SCI pain, below level SCI pain and other NP (not directly related to SCI). Among all pain types, chronic NP poses real problems in terms of identification and therapeutic strategies.

NP was defined[3] by the International Association for the Study of pain (IASP) as 'pain caused by a lesion or disease of the somatosensory nervous system.' It is present in 40–50% of individuals having SCI, usually develops within 1 year and tends to become chronic.[4]

Individuals with NP usually complain of spontaneous burning pain that is continuously present and may be accompanied by dysesthesias, often described as tingling or prickling, or may also describe electric shock or stabbing sensations that are intermittent. Some patients describe being hypersensitive in the area of NP, referring to the pain that is induced by light touch or moderate thermal stimuli (that is, allodynia) and to particularly severe pain elicited by normally mild nociceptive stimuli (that is, hyperalgesia).

Evidence-based symptomatic pharmacotherapy is the mainstay of the treatment of NP and it should be titrated individually according to the efficacy and possible contraindications or side-effects. NP is treated mainly with antidepressants and antiepileptics, whereas simple analgesics have not shown efficacy for this type of pain. Antidepressants have been used to treat pain in a number of populations and have been shown to have some benefit in conditions like diabetic neuropathy and fibromyalgia; however, only a limited number of studies have examined their use in post SCI NP. To our knowledge this is the first comparative study between amitriptyline and lamotrigine in the treatment of NP in persons with

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SCI. The objective of our study was to compare the effectiveness of amitriptyline with that of lamotrigine in NP following traumatic SCI.

MATERIALS AND METHODS

Subjects

Patients enrolled in the study were inpatients of the Department of Physical Medicine and Rehabilitation, SMS Medical College and hospital, Jaipur. Individuals aged 18 years and above with SCI-induced NP were eligible for the study. Written and informed consent was taken from each individual. History of cardiovascular diseases, seizures, hyperthyroidism or glaucoma or any known psychiatric illness and allergy to drugs used in this study were the exclusion criteria.

Baseline information including age, sex, education level, occupation, marital status, mechanism of injury, associated complications, dietary habits, family monthly income, family type, ASIA (American Spinal Injury Association) scale, neurological level, site, quality, time of onset and duration of NP were recorded.

The present study was approved by the ethics committee of Sawai Man Singh Medical College and Hospital Jaipur with reference number 2146/MC/EC/2016, which is in accordance with the Declaration of Helsinki.

Study design and procedure

This is a randomized, longitudinal, comparative study. Along with detailed clinical examination and radiological assessment, daily counseling for pain was also done. Motor and sensory examination was performed according to the Standards of the ASIA impairment scale and assessment of NP was made on the basis of DN4 (Douleur Neuropathic en 4 questions) score.[5]

Written informed consent was obtained for the study. All study patients were randomized into two groups, one for amitriptyline and the other for lamotrigine, by computer-generated randomized numbers.

DN4 was designed to discriminate between neuropathic and non-NP The tool was developed and validated in French and was translated into many languages. It consists of 10 items divided into seven symptoms and three items related to clinical examination. It includes two questions addressing symptoms:

1. Pain quality (presence of three symptoms assessed: burning, painful cold, electric shocks).
2. Non-painful symptoms (presence of four symptoms assessed: numbness, tingling, itching, pins-and-needles).

and two questions addressing sensory signs:

1. Assessment for mechanical hypoesthesia (two modalities assessed: touch and pinprick sensations).
2. Assessment for mechanical dynamic allodynia (one modality assessed: brushing).

Each of the 10 items is scored on a binary scale of 'Yes' or 'No'. A total score ranging from 0 to 10 is calculated by summing the 'Yes' responses. A cutoff score of 4 has been identified by the developers as indicating NP.

All patients were evaluated for pain at baseline using the SFMPQ2.[6] The patients in the amitriptyline group were started on an initial dose of 25 mg once daily and patients in the lamotrigine group were started on an initial dose of 25 mg twice daily. Short–form MC Gill Pain Questionnaire-2 (SFMPQ2) scores were reviewed at first follow-up (7th day), and doses were titrated to 50 mg once daily for amitriptyline and 50 mg twice daily for lamotrigine if no improvement (reduction in SFMPQ2 score values to half or more) or no adverse effects were observed by the treating physician. At the second follow-up (14th day), scores were reviewed and double the previous dose was given if no improvement or side-effects were observed. Final evaluation of SFMPQ2 scores was at third follow-up (21st day).

Table 1 Mean difference in SFMPQ2 scores

Drug	*Follow-up*[a]	N	*Mean*	*s.d.*	*Friedman's test*		
					χ^2	*Df*	P-*value*[b]
Amitriptyline	D-7	74	0.2149	0.2075	105.874	2	0.000
	D-14	74	0.3593	0.1939			
	D-21	74	0.4312	0.1812			

The *P*-value was significant; thus, we may conclude that amitriptyline was effective in neuropathic pain.
[a]Difference in SFMPQ2 scores on the 7th (D-7), 14th (D-14) and 21st day (D-21) from baseline in the Amitriptyline group.
[b]Statistically significant difference at various follow-up time points; $P<0.05$.

Outcome measure

Patients rated their average overall pain on the SFMPQ2 scale.

SFMPQ2 is composed of 22 items investigating four dimensions: continuous pain (Item 1, 5, 6, 8–10); intermittent pain (Items 2–4, 11, 16, 18); NP (Items 7, 17,19–22); and affective descriptors (Item 12–15). Each descriptor is rated on an 11-point Numeric rating scale ranging from 0 = 'none' to 10 = 'worst possible'. Subscale scores are computed by calculating the mean ratings for subscale descriptors. Total score is the mean of the four subscale scores.

Statistical analysis

Intention-to-treat analysis was performed. The mean difference in SFMPQ2 scores from baseline on the 7th day (D-7), 14th day (D-14) and 21st day (D-21) was calculated for both drugs. The Friedman test was applied for D-7, D-14 and D-21 in the amitriptyline group, and *post hoc* analysis was done using the Wilcoxon signed rank test for each pair of follow-up time points—that is, D-7 and D-14, D-7 and D-21, D-14 and D-21. A similar assessment was made in the lamotrigine group. Comparative analysis of mean difference at various check points was done for both groups using the Mann–Whitney *U*-test. *P*-values <0.05 were taken as significant.

Statement of ethics

I certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

RESULTS

Patients

There were a total of 147 patients, of whom 136 were male and 11 were female; 109 (74%) were in the age group of 18–40 years. A total of 83 (56%) were tetraplegics and 64 (44%) were paraplegics. According to ASIA, 112 (76%) were in grade A (neurologically complete), and the remaining 35 (24%) belonged to the neurologically incomplete category (B-D).

Table 2 *Post hoc* analysis

Drug	N	*Mean*[a]	*s.d.*	P-*value*[b]
Amitriptyline				
D-7	74	0.2149	0.2075	0.000
D-14	74	0.3593	0.1939	
Amitriptyline				
D-7	74	0.2149	0.2075	0.000
D-21	74	0.4312	0.1812	
Amitriptyline				
D-14	74	0.3593	0.1939	0.000
D-21	74	0.4312	0.1812	

[a]Mean difference in SFMPQ2 scores for each pair of follow-up time points—that is, D-7 and D-14, D-7 and D-21, D-14 and D-21—for the Amitriptyline group was compared using the Wilcoxon Signed Rank test.
[b]*P*-value was significant for each comparison; $P<0.05$.

Outcome measure

The *P*-value was significant for the mean difference in SFMPQ2 score from baseline at different follow-up time points—that is, 7th, 14th and 21st day—for the amitriptyline group (Table 1).

When post hoc analysis was conducted using the Wilcoxon Signed Rank test for each pair of follow-up time points, the *P*-value was found to be significant for each comparison (Table 2).

Significant changes were also seen in the lamotrigine group (Tables 3 and 4).

On application of the Mann–Whitney *U*-test between the amitriptyline and lamotrigine groups, comparing differences in mean SFMPQ2 scores from baseline on the 7th day (D-7), 14th day (D-14) and 21st day (D-21), the *P*-value was found to be nonsignificant at all three stages (Table 5).

Adverse events

Of the 74 studied patients on amitriptyline, only 10 reported one or more side-effects. The most common side-effects reported were dry mouth and drowsiness. Patients reported these adverse effects at doses exceeding 50 mg once daily. None of the patients on lamotrigine experienced any adverse events.

Withdrawn patients

A total of 147 subjects who satisfied the inclusion criteria were enrolled for study purpose. Of them, only 140 completed the 21-day follow-up period. One case dropped out at 1st follow-up, one at 2nd follow-up and three at 3rd follow-up. Two patients died during the study.

DISCUSSION

Different questionnaires have been developed to differentiate NP from other types of pain. In SCI patients, good reliability has been shown in particular for the DN4 questionnaire. It was developed by Didier Bouhassira *et al.*[5] and consists of both sensory descriptors and signs related to bedside sensory examination. In a study conducted by Hallstrom *et al.*,[7] the DN4 questionnaire was found to have maximum sensitivity (93%) and diagnostic accuracy (88%) with low specificity (75%) among the four scales used in individuals with SCI and pain.

Recent advances in identifying the mechanisms of NP and in improving its management have led to the development of new instruments designed to measure the unique aspects of pain. The SFMPQ score has been used successfully in treatment trials of NP. However, it does not contain certain descriptors that have been shown to be reliably associated with NP conditions. Dworkin *et al.*[6] developed the SFMPQ2, an expanded and revised version of the SFMPQ, designed to measure the qualities of both neuropathic and non-NP in research and clinical settings. They found that the SF- MPQ-2 has excellent reliability and validity, and results of both exploratory and confirmatory factor analysis revealed the presence of the following four factors or subscales—continuous pain; intermittent pain; predominantly NP; and affective descriptors. The following modifications were involved in the development of the SFMPQ2: (1) inclusion of seven new descriptors relevant to NP; (2) use of an 11-point Numeric rating scale for each descriptor; (3) addition of the qualifier 'pain' to 13 descriptors; and (4) expansion of the instructions to take into account 'different qualities of pain and related symptoms.

NP after SCI is characterized by loss of sensory modalities mediated by spinothalamic tract neurons, and abnormal pain perception (spontaneous continuous pain and abnormally evoked pain). Abnormal pain perception results from neuronal hyperactivity and hyper-excitability induced by abnormal impulse generation in damaged spinothalamic tract neurons. The neurochemical changes include increased excitatory glutaminergic activity involving *N*-methyl-D-aspartate receptor activation, changes in sodium ion channels and voltage-gated calcium channels. Other important mechanisms may be loss of endogenous inhibition, including reduced GABAergic, opioid and monoaminergic inhibition.

Lamotrigine acts at voltage-sensitive sodium channels to stabilize the neuronal membrane and inhibit sodium influx-mediated pathological release of excitatory amino-acid transmitters, principally glutamate; both are involved in neuronal hyper-excitability, which is an important mechanism of NP. Action of amitriptyline is multimodal, with contribution of monoamine reuptake inhibition and *N*-methyl-D-aspartate receptor and sodium channel blockade. Previously conducted studies on these drugs mentioned that there might be variable effects of drugs on NP in SCI individuals owing to a multimodal mechanism of action.

Three open studies of poor quality, two prospective (level 3) and one retrospective (level 4), suggested the efficacy of tricyclic antidepressants (mainly amitriptyline) combined with other treatments on SCI pain.[8–10]

More recently, two double-blind studies also compared the efficacy of amitriptyline with an 'active' placebo (mimicking the side-effects of tricyclic antidepressants) in patients with SCI pain. Cardenas *et al.*[11] studied amitriptyline in 84 patients of SCI pain with dose range from 10 to 125 mg over 6 weeks and failed to show any significant superiority of it over placebo. In this study, non-neuropathic SCI pain was also included. The median maximum and week-6 dose was 50 mg per day. These negative data, which are in contrast with most

Table 3 Mean difference in SFMPQ2 scores

Drug	*Follow-up*[a]	N	*Mean*	*s.d.*	*Friedman's test*		
					χ^2	*Df*	P-*value*[b]
Lamotrigine	D-7	73	0.2048	0.2245	106.351	2	0.000
	D-14	73	0.3622	0.2403			
	D-21	73	0.4432	0.2070			

P-value was significant; thus we may conclude that lamotrigine was effective in neuropathic pain.
[a]Difference in SFMPQ2 scores on the 7th (D-7), 14th (D-14) and 21st (D-21) day from baseline for the lamotrigine group.
[b]Statistically significant difference at various follow-up time points; $P<0.05$.

Table 4 *Post hoc* analysis

Drug	N	*Mean*[a]	*s.d.*	P-*value*[b]
Lamotrigine				
D-7	73	0.2048	0.2245	0.000
D-14	73	0.3622	0.2403	
Lamotrigine				
D-7	73	0.2048	0.2245	0.000
D-21	73	0.4432	0.2070	
Lamotrigine				
D-14	73	0.3622	0.2403	0.000
D-21	73	0.4432	0.2070	

[a]Mean difference in SFMPQ2 scores for each pair of follow-up time points—that is, D-7 and D-14, D-7 and D-21, D-14 and D-21—in the Lamotrigine group was compared using the Wilcoxon Signed Rank test.
[b]*P*-value was significant for each comparison; $P<0.05$.

Table 5 Comparison of the mean difference in SFMPQ2 scores

Follow-up	*Drug*	N	*Mean*[a]	*s.d.*	*s.e.m.*	*Mann–Whitney* U	P-*value*[b]
D-7	Amitriptyline	74	0.2149	0.2075	0.024	2636.000	0.799
	Lamotrigine	73	0.2048	0.2245	0.026		
D-14	Amitriptyline	74	0.3593	0.1939	0.023	2642.000	0.819
	Lamotrigine	73	0.3622	0.2403	0.028		
D-21	Amitriptyline	74	0.4312	0.1812	0.021	2583.500	0.648
	Lamotrigine	73	0.4432	0.2070	0.024		

P-value was found to be nonsignificant for all three comparisons; thus we may conclude that there was no difference in efficacy between the two drugs.
[a]Difference in SFMPQ2 scores on the 7th (D-7), 14th (D-14) and 21st (D-21) day from baseline in the Amitriptyline and Lamotrigine groups.
[b]Statistically nonsignificant difference using the Mann–Whitney *U*-test, $P > 0.05$.

study results, could be due to low dosages of amitriptyline and the poor assessment of NP. In fact, the main efficacy outcome of this study was pain in general (including musculoskeletal and visceral pain) as the trial did not compare treatment effects within subgroups of pain types.

Rintala *et al.*[12] conducted a randomized controlled, double-blind, triple cross-over 8-week trial study in 22 patients comparing the effects of amitriptyline, gabapentin or an active control (diphenhydramine) in the treatment of NP post SCI and found a moderate efficacy of high-dosage amitriptyline (150 mg per day) compared with gabapentin and placebo, but only in a subgroup of patients with depressive symptoms, suggesting that the analgesic effect of amitriptyline was related to its antidepressant efficacy.

Tricyclic antidepressants induced several adverse effects in both studies, consisting mainly of dry mouth, constipation, along with aggravation of spasticity and dysuria, which can be a genuine concern in the context of SCI.

In the present study, amitriptyline was found to be effective in the management of NP after traumatic SCI as the mean difference in SFMPQ2 score at a different time frame from baseline was significant. Of the 74 study patients on amitriptyline, only ten reported one or more side-effects. The most common side-effects reported were dry mouth and drowsiness, and patients reported these adverse effects at doses exceeding 50 mg once daily.

One placebo-controlled study on lamotrigine[13] in traumatic SCI patients (with pain at or below level) did not show efficiency in pain outcomes. However, in a *post hoc* analysis, lamotrigine was found effective in a subgroup of patients ($n = 7$) with incomplete SCI and mechanical allodynia (to brush) at level. A Cochrane review on lamotrigine[14] for chronic NP and fibromyalgia in adults published in 2013 included twelve studies in 11 publications (1511 participants), all with chronic NP: central post-stroke pain (1); chemotherapy-induced NP (1); diabetic neuropathy (4); HIV-related neuropathy (2); mixed NP (2); SCI-related pain (1); and trigeminal neuralgia (1). Lamotrigine did not help the pain, and was no different from placebo except in causing more side-effects. But it is important to mention here that only one study on SCI was involved in the Cochrane review with 22 participants, and in this trial lamotrigine reduced NP among incomplete SCI patients.

Lamotrigine was found to be effective in our experience in the management of NP after traumatic SCI as the mean difference in SFMPQ2 score at different time frames from baseline was significant. None of the patients on lamotrigine experienced any adverse events.

To our knowledge, this is the first study comparing the effectiveness of amitriptyline and lamotrigine in the treatment of NP in SCI patients. Earlier Jose *et al.*[15] compared the efficacy and safety of lamotrigine and amitriptyline in controlling chronic painful peripheral neuropathy in diabetic patients in a randomized, double-blind, cross-over, active control, clinical trial with variable dose titration ($n = 53$). This study showed similar benefits of both treatments; lamotrigine might be the first choice in peripheral NP as it is associated with fewer adverse events.

Our results showed that both amitriptyline and lamotrigine were similarly effective in the management of NP after traumatic SCI as the difference in mean SFMPQ2 from baseline at various follow-up time points was found to be significant for each drug separately. But on comparing differences in mean SFMPQ2 scores between two groups, the result was nonsignificant, suggesting that no drug was better than the other.

The prevalence of NP was not recorded, as the inclusion criteria of this study encompassed SCI patients having NP. Also denominator data for calculating prevalence were not recorded. The strength of the study was the large and complete follow-up and fewer dropouts.

In conclusion, comprehensive knowledge of the clinical characteristics of pain is important for proper management. The present study demonstrated the effectiveness of both amitriptyline and lamotrigine in SCI-induced NP; no difference in efficacy was noted between the two drugs. Because different mechanisms underlie SCI pain, it emphasizes the need for mechanism-based classification of patients with NP. Further large clinical studies are needed for established and novel management options.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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