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ATTENUATION OF NEROPATHIC PAIN BY LACOSAMIDE IN AN EXPERIEMENTAL MODEL OF CHRONIC CONSTRIICTION INJURY IN RATS

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ABSTRACT

Aim: *The aim of the present study was to investigate effect of lacosamide (LCM) in chronic constriction injury of sciatic nerve by behavioral evaluation in rats.* ***Methods:*** *Chronic constriction injury (CCI) was induced by placing four loose ligatures around the sciatic nerve proximal part of the trifurcation with an approximate distance of one millimeter between each ligature. The mechanical hyperalgesia, cold allodynia, thermal hyperalgesia were evaluated by performing pin prick test & von frey filament; acetone drop; hot plate respectively. Rats were treated daily with lacosamide(5, 15 and 45 mg/kg i.p.) from the day of surgery (day 0) for 14 days in comparison with the positive control drug used (Pregabline 10mg/kg, i.p.). Chronic constriction injury was associated with the development of mechanical hyperalgesia, cold allodynia, heat hyperalgesia along with an assessment of spontaneous pain and postural index of foot deformity.* ***Result:*** *In the present study, we investigated the antiallodynic and antihyperlagesic properties of lacosamide, in chronic constriction injury (CCI)-induced neuropathic pain rat model. Our findings showed that single and repeated dose of intra-peritoneal administration of lacosamide (5, 15, 45 mg/kg) significantly inhibited (P<0.05) the chronic constriction injury induced neuropathic pain in dose dependent manner. Lacosamide showed ameliorating action against CCI induced neuropathic pain in all the tested models as the behavioral score of neuropathic pain.* ***Conclusion:*** *The results indicated that lacosamide significantly attenuated CCI-induced neuropathic pain. It may be concluded that the anti-nociception mediated by lacosamide are responsible for its beneficial effects in neuropathic pain in rats. Therefore, the present study suggests the potential use of lacosamide in the treatment of neuropathic pain, which merits further clinical investigation.*

KEY WORDS

Chronic Constriction Injury (CCI), Neuropathic pain, Lacosamide, Behavioral study, Anti-nociceptive.

1. INTRODUCTION

Up to one in four patients with diabetes may be affected by chronic diabetic painful neuropathy (DPN) [1-2] and suffer substantial morbidity and impaired quality of life.[3] Because the current treatment options are limited, there is continued need for new therapeutic approaches.[3-4]

The International Association for the Study of Pain defines neuropathic pain as “initiated or caused by a primary lesion or dysfunction in the nervous system” and defines neuropathic due to disordered peripheral or central nerves. Neuropathic pain is not a single entity; it is a heterogeneous group of conditions that differs in not only aetiology, but also in location, and symptoms respect neither cause nor anatomical site. Neuropathic pain is generally characterized by sensory abnormalities such as unpleasant abnormal sensation (dysesthesia), an increased response to painful stimuli (hyperalgesia), and pain in response to a stimulus that does not normally provoke pain (allodynia)[5-7]

The diagnosis and treatment of neuropathic pain remain as one of the major medical challenges. Existing treatment including nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids is not
completely effective in relieving neuropathic pain causing significant burden on the patient and on their quality of life.[8-10] These drugs cause various adverse effects[11] including drowsiness and dizziness. Other drugs used to manage this condition are usually non-specific in their actions.[12] The first choices of treatment that have been used till date include the antidepressants such as amitriptyline, venlafaxine and the anticonvulsants such as carbamazepine, gabapentin and pregabalin. It is well known that these groups of drugs only produce partial relief and are the cause of numerous adverse effects experienced by patients.[13] The diverse etiology and complex pathophysiology of neuropathic pain make it a challenge to be effectively treated[14] making way for newer pain management techniques and drugs.

Chronic constriction injury is a novel model of peripheral neuropathy as the alterations produced in this model of peripheral neuropathy are analogous to the human beings and the symptoms in this rat model are parallel to causalgia or complex regional pain syndrome. Chronic constriction injury produces unilateral peripheral neuropathy due to compression of the sciatic nerve and hence, it has been extensively used in research for the analysis of sensory abnormalities associated with entrapment neuropathy. Furthermore, the behavioral changes observed in this model are the most sustained and generalized ones with regards to other models of peripheral neuropathy.[15-17]

Unlike other types of pain, the paucity of human volunteer models for neuropathic pain means that animal models, in spite of their shortcomings, are the mainstay of research; with rodent models, especially rat models being by far the most commonly used.[18] Of the models used Sciatic nerve CCI resembles human neuropathy resulting from trauma of peripheral nerves, with some functional preservation of the innervations (nerve entrapment or compression). The model of CCI is one of the most commonly used models because it is reliable and easily reproducible.[19]

The mechanism of action of several antiepileptic drugs is based on their ability to modulate the activity of voltage-gated sodium current that are responsible for fast action potential generation. Recent studies have analyzed that lacosamide shares similar mechanism as an analgesic and anticonvulsant in comparison with other antiepileptic drugs lacosamide has the unique ability to with sodium channel slow inactivation without affecting fast inactivation. Lacosamide is a newer functional amino acid being developed as an adjunctive therapy for resistant partial-onset seizures owing to its activity of enhancing the slow inactivation of voltage-gated sodium channels thereby reducing pathologic hyperactivity in neurons. It has also being investigated for its role as anti-nociceptive in variety of pain scenarios specifically in diabetic neuropathic pain. It is well-absorbed orally, metabolized in liver and excreted by the kidneys. It has a favorable pharmacologic profile in having minimal drug interactions. The adverse effects include mild dizziness, behavioral changes and dose dependent prolongation. It has also shown to be beneficial in neuropathic pain as evidenced by animal studies and some clinical trials, but it is not approved by regulatory authorities for use in pain clinics.[20-23]

Lacosamide(LCM) is a novel anti-epileptic as well as anti-nociceptive drug with minimal drug interactions and controllable adverse reactions. However, many more randomized trials are needed to establish the potential benefi ts of lacosamide in other painful neuropathies as well. Therefore, the present study was designed to investigate the ameliorative role of lacosamide in another model of neuropathic pain i.e. chronic constriction-induced neuropathy.

2. MATERIAL AND METHODS

2.1 Animals

Wistar albino rats weighing 180-250 g, maintained on standard laboratory diet (VRK nutritionals. Pune, India) and having free access to tap water were employed in the present study. They were housed in the departmental animal house and were exposed to normal cycle of light and dark. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and the care of the animals was carried out as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forest, Government of India (Proposal Number: CPCSEA/CBPCL/ IAEC/2015-16/03.).

2.2 Drugs and Reagents

Lacosamide (5, 15 and 45 mg/kg body wt.) procured as a research gift sample from Micro Lab Pvt Lts, Mumbai.

2.3 Induction of Neuropathic Pain by Chronic Constriction Injury

Peripheral neuropathic pain was induced in rats by chronic constriction injury (CCI). In brief, rats were deeply anesthetized with ketamine 60mg/kg and Xylazin10mg/kg i.p. The hair of the rat's lower back and thigh were shaved, and the skin was sterilized with spirit. The skin of the lateral surface of the left thigh was incised and a cut was made directly through the biceps femoris muscle to expose the sciatic nerve, and four ligatures (silk 4-0) were placed around the nerve proximal part of the trifurcation with an approximate distance of one millimeter between each ligature. The ligatures were loosely tied until a short flick of the ipsilateral hind limb was observed. After performing nerve ligation, muscular and skin layer were immediately sutured with thread, and topical antiseptic (Tincture iodine) was applied. Due to the distinct development of postural defects in the paw of chronic constriction injury control animals, the behavioral studies could not be blinded for comparing normal control; sham control and chronic constriction injury control groups. However, for all other groups the behavioral tests were blinded.

2.4 Experimental Protocol

Animals were divided in five groups, each containing six animals. Three doses LCM (50 and 100 mg/kg) were studied

***Group I (control group)*:** Rats in this group were not subjected to any surgical procedure and were kept for 14 days. Behavioral tests were performed to assess nociceptive threshold on different days, i.e. days 0, 3, 7, 11 and 14. All the animals were sacrificed at the end of the 14 day, and biochemical analysis with histopathological examinations was carried out.

***Group II (Sham control group)*:** Rats in this group were subjected to surgical procedure to expose left sciatic nerve without any nerve ligation. After subjecting the rats to CCI, Water for injection was given. Behavioral tests were performed as mentioned in group I.

***Group III (CCI group)*:** Rats in this group were subjected to surgical procedure, to expose and ligate left sciatic nerve as described earlier. After subjecting the rats to CCI, distilled water was dministered orally for 14 consecutive days. Behavioral tests were performed as mentioned in group I.

Group IV (EP 5mg/kg in CCI): Rats in this group were subjected to surgical procedure, to expose and ligate left sciatic nerve. After subjecting the rats to CCI, LCM (5mg/kg) was administered i.p. for 14 consecutive days. Behavioral tests were performed as mentioned in group I.

***Group IV (EP 15 mg/kg in CCI)*:** Rats in this group were subjected to surgical procedure, to expose and ligated left sciatic nerve. After subjecting the rats to CCI, EP (15mg/kg) was administered i.p. for 14 consecutive days. Behavioral tests were performed as mentioned in group I.

***Group IV (EP 45 mg/kg in CCI)*:** Rats in this group were subjected to surgical procedure, to expose and ligated left sciatic nerve. After subjecting the rats to CCI, EP (45mg/kg) was administered i.p. for 14 consecutive days. Behavioral tests were performed as mentioned in group I.

2.5 General behavioral observation

Rats with CCI showed abnormal gait, posture, licking of hind paw of the ipsi-lateral side of sciatic nerve ligation on day three onwards. The rats could not put weight on affected site and hind limb of affected site was drawn close to body with distinctive guarding posture.

2.6 Behavioral Examination

For the establishment of chronic pain, a constriction injury was applied to the sciatic nerve, which induced neuropathic pain characterized by hyperalgesia and allodynia. The mechanical von Frey test, hot plate test, acetone test were performed to assess mechanical, thermal, and cold hyperalgesia, respectively. The rotarod test was used to examine potential motor dysfunction. In studies that examine the drug duration of actions, baseline measurement was immediately followed by an injection of the drug lacosamide and the paw withdrawal latency was then measured every 10 min until the drug effect dissipated to a level that the paw withdrawal threshold was not significantly different from the control level.

2.7.1Thermal* (heat) *allodynia and hyperalgesia

***a) Hot Plate test (Thermal allodynia)*[24]**

Thermal allodynia response was assessed according to the procedure described by Eddy and Leimbach. A total of six rats were assigned to this group. The temperature of eddy's hot plate was set at 45°C ± 0.5°C. The operated rats were placed on a heated surface and the time interval between placement and the shaking, licking or tucking of the affected hind paws was recorded as the latency response. If no paw withdrawal was shown within 22 s, the test was terminated, and animal was

assigned nonresponsive. For each measurement, three successive readings were taken with 3 min elapsed between each test and mean was calculated. The cut-off time of 15 s was set to avoid the injury to hind paw.

b) Hot plate test (Thermal hyperalgesia)[24]

Thermal hyperalgesia response was assessed according to the procedure described by Eddy and Leimbach. A total of six rats were assigned to this group. The temperature of eddy's hot plate was set at 55.0°C ± 0.1°C. The operated rats were placed on a heated surface and the time interval between placement and the shaking, licking or tucking of the affected hind paws was recorded as the latency response. If no paw withdrawal was shown within 22 s, the test was terminated, and animal was assigned nonresponsive. For each measurement, three successive readings were taken with 3 min elapsed between each test and mean was calculated. The cut-off time of 15 s was set to avoid the injury to hind paw.

2.7.2 Rota road test (Motor coordination) [25-26]

Rota-rod test at day 14th post-surgery, motor coordination was evaluated using the rota-rod test. This apparatus consists of a base platform and a rotating horizontal rod (7 cm in diameter, 50 cm in length) divided into three separate compartments. The rod was set to accelerate from 20 rpm in a 5 min period. Each rat was given 3 training sessions before testing. During the test session, the latency(s) for the first fall during a 5 min period *was observed.*

2.7.3 Paw cold-allodynia (acetone drop test) [27-28]

The extent of neuropathic pain development was also assessed by measuring the development of cold allodynia. It was measured using acetone drop test, in which 100 ml of acetone was sprayed on the plantar surface of hind paw of rat. The normal reaction of rat is quick withdrawal of paw in response to acetone application followed by quickly placing the paw on mesh wire. The quick recovery of paw was assigned a value of 0.5 s. However, in neuropathic pain, rat keeps its hind paw in air for a sufficient period of time and time taken to place its hind paw back to mesh wire is termed as paw withdrawal duration. In this study also, paw cold allodynia was assessed by measuring paw withdrawal duration in seconds in response to acetone application

2.7.4 Mechanical hyperalgesia (Pin prick test) [29]

A Pinprick test was used to assess the degree of mechanical hyperalgesia in which a bent gauge needle was slightly pricked on the planter surface of hind paw to induce a reflex withdrawal action. The time taken to return back the hind paw on the mesh wire was recorded in terms of paw withdrawal duration. A normal quick hind paw withdrawal followed by quickly placing the paw on mesh wire was assigned a value of 0.5 s

2.7.5 Von Frey filament test.[30]

Mechanical allodynia (non-noxious mechanical stimuli) was assessed as described by Chaplan and co-workers.21 Briefly, nylon filaments (von Frey hair), calibrated in terms of different bending forces, were applied to the mid plantar surface of left hind paw. The filaments were applied 10 times, starting with the softest and continuing in ascending order of stiffness. A brisk withdrawal of the left hind limb was considered a positive response. The criterion for the threshold value, in grams, was equal to the filament evoking a with-drawal threshold of the left hind paw five times out of 10 trials i.e. 50% response

Testing paradigm

Von Frey hairs were presented in ascending order of strength 24 hours after CCI. Each hair was presented 10 times and the number of positive responses multiplied by 10 was recorded as the percent response. For each rat, ascending stimuli were tested either until the maximum stimulus of 15.10 g was reached or until hair strength was reached that caused 100% response. The 50% paw withdrawal threshold was determined using the Dixon method (1980). Testing was initiated with the 2 g hair and stimuli were presented in consecutive fashion whether ascending or descending. In the absence of paw withdrawal to the initially selected von Frey hair, a stronger stimulus was presented; in the event of paw withdrawal, a weaker stimulus was chosen. According to Dixon, optimal threshold calculation requires 6 responses in the immediate vicinity of the 50% threshold. Since the threshold is unknown, strings of similar responses may be generated as the threshold is approached from either direction. Rats with a 50% paw withdrawal threshold (PWT) below 4g on the ipsilateral paw were considered alloydnic. The paw skin, lumbar spinal cords and sciatic nerve from the CCI's were dissected following cervical dislocation, 24 hours after CCI induction and frozen to be used in western blots.

2.8 Statistical analysis

The results were expressed in mean ±S.E.M. The data of behavioral tests were analyzed using GraphPad prism version 7.0, two-way ANOVA followed by Tukey's Post

hoc multiple comparison test. The P-value < 0.05 was considered to be statistically significant.

3. RESULT

3.1 Theramal (heat) allodynia and hyperalgesia

a) Hot plate (Thermal allodynia)

Figure1. Shown the change in response to painful heat stimuli in plantar test in sham operated and CCI induced neuropathic rats administered with vehicle, and LCM at 5, 15 and 45mg/kg i.p. on day o, 3, 7, 11 and day 14 post surgery. Baseline for heat allodynia was recorded before surgery and pharmacological testing. The marked decrease in the ipsilateral paw withdrawal latencies of CCI-induced neuropathic pain rat shows the development of thermal allodynia in response to the heat stimuli two weeks after surgery when compared to sham-operated rats. Intraperitoneal injection of LCM in different dosages (5, 15, 45 mg/kg i.e.) and pregabline (10mg/kg i.p.) on day 14 and followed by daily treatment until day 14 demonstrated significant and dose-dependent inhibition of thermal allodynia in CCI-induced neuropathic pain rat.

All the doses of LCM exhibited pronounced significant inhibition (P<0.001) of neuropathic pain when compared to vehicle group. Besides that, doses of 15mg/kg, and 45mg/kg of LCM has significant difference in the withdrawal latencies (P<0.01) when compared between day 7 and day 14. The data were shown as mean ± SEM. *P< 0.05* vs Sham, ### *P*< 0.001 vs CCI.

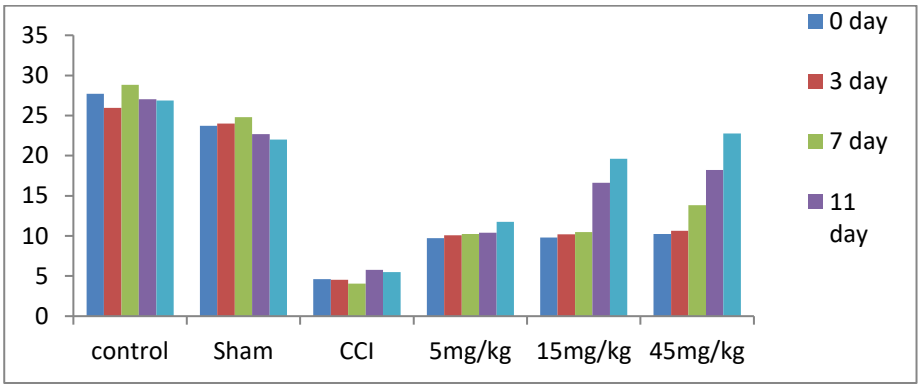

Figure1. The effect of LCM administration on CCI-induced heat allodynia(45^{0}C), assessed using the hot plate test. Rats were treated with vehicle or LCM at doses of 5, 15 and 45 mg/kg once daily for a period of 14 days. The data were shown as mean ± SEM. *P< 0.05* vs Sham, ### *P*< 0.001 vs CCI

b) Hot plate test (Thermal Hyperalgesia)

As shown in Figure 2, the neuropathic induction group after CCI of sciatic nerve showed significant (P < 0.05) duration dependent reduction in reaction time at 14th day as compared with sham control group. The administration of LCM 45mg/kg body weight showed significant (P < 0.05) and (P < 0.01) increase in reaction time at 11th and 14th day, respectively, when compared with neuropathic induction group. While lower dose of lacosamide (5 mg/kg) was ineffective on thermal hyperalgesia and did not reverse the hyperalgesic response during entire treatment period at same dose. Results obtained from thermal hyperalgesia revealed that induction of CCI significantly increased allodynia scores in days 3 (P<0.05), 7, 14, and 21 after surgery in comparison with sham groups (P<0.001).

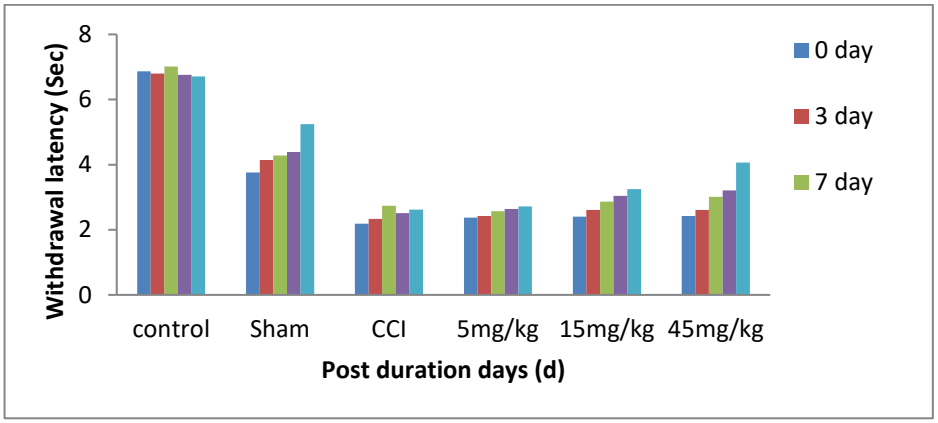

Figure2. The effect of LCM administration on CCI-induced heat hyperalgesia, assessed using the hot-plate test. Rats were treated with vehicle or LCM at doses of 5, 15 and 45 mg/kg once daily for a period of 14 days. The data were shown as mean ± SEM. ** *P< 0.01* vs Sham, ***P*< 0.001 vs Sham, *#P< 0.05* vs CCI, ## *P< 0.01* vs CCI, and ### *P*< 0.001 vs.

3.2 Rota road test (Motor coordination)

Figure3. Shown the change in response to motor coordination in sham operated and CCI induced neuropathic rats administered with vehicle, and LCM at 5, 15 and 45mg/kg i.p. on day 0, 3, 7, 11 and day 14 post surgery. Baseline for fall down latency time of animals on rotating rod was recorded before surgery and pharmacological testing. The marked decrease in the fall down latency time of CCI-induced neuropathic pain after surgery when compared to sham-operated rats. Administration of lacosamide to wister rat resulted in decreased muscle grip strength noted by the decrease in the fall of time from rota road as compared to the normal control group. While LCM (5, 15 and 45mg/kg) as well as pregabline significantly (P<0.01) decrease in fall off time.

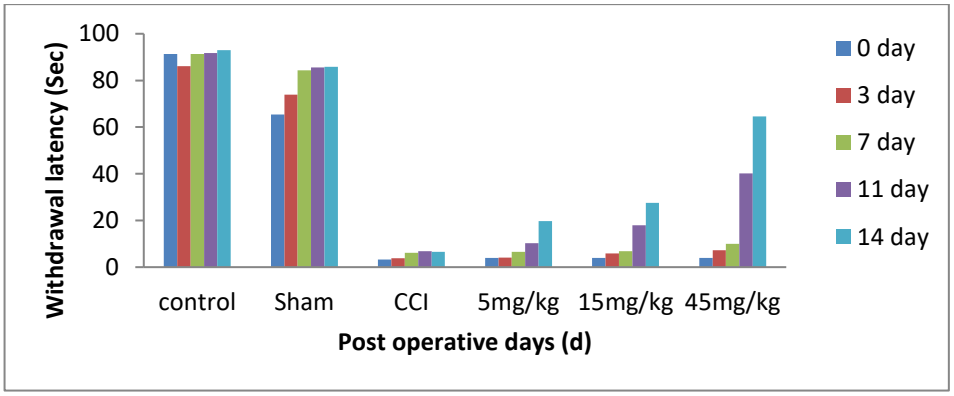

Figure 3: Effect of LCM on muscle grip strength (i.e. Fall off time). Data are expressed as mean ± SEM, n = 6 rats per group. p < 0.01 versus normal control group; p < 0.01 versus vc group; p > 0.05 non-significant versus normal control group.

3.3 Cold allodynia (Acetone test)

Figure4. Shown the change in response to painful cold stimuli in sham operated rats and CCI induced neuropathic rats administered with vehicle, and LCM at 5, 15 and 45mg/kg i.p. on day 0, 3, 7, 11 and day 14 post surgery. Baseline for withdrawal latency was recorded before surgery and pharmacological testing. The marked decrease in the withdrawal latencies of CCI-induced neuropathic pain rat shows the development of thermal allodynia in response to the cold stimuli two weeks after surgery when compared to sham-operated rats. Intraperitoneal injection of LCM in different dosages (5, 15, 45 mg/kg i.e.) and pregabline (10mg/kg i.p.) on day 14 and followed by daily treatment until day 14 demonstrated significant and dose-dependent inhibition of thermal allodynia in CCI-induced neuropathic pain rat.

All the doses of LCM exhibited pronounced significant inhibition (*P*<0.001) of neuropathic pain when compared to vehicle group. Besides that, doses of 15mg/kg, and 45mg/kg of LCM has significant difference in the withdrawal latencies (*P*<0.01) when compared between day 7 and day 14. The data were shown as mean ± SEM. *P< 0.05* vs Sham, ### *P*< 0.001 vs CCI.

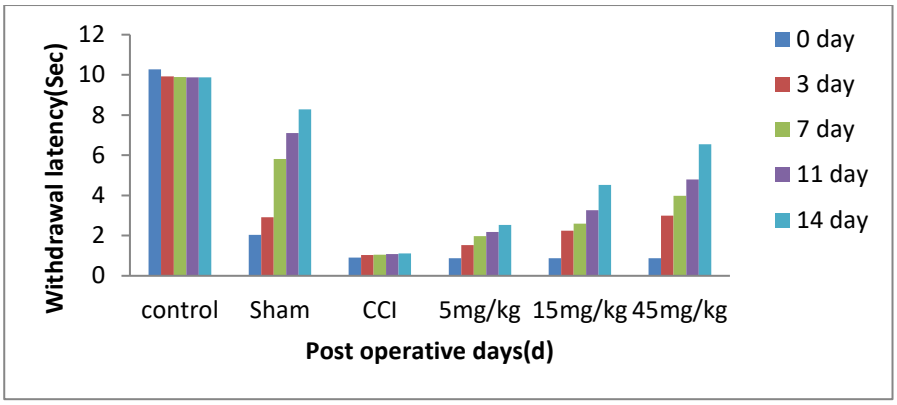

Figure4. The effect of LCM administration on CCI-induced cold allodynia, assessed using the acetone drop test. Rats were treated with vehicle or LCM at doses of 5, 15 and 45 mg/kg once daily for a period of 14 days. The data were shown as mean ± SEM. ** *P< 0.01* vs Sham, ***P< 0.001 vs Sham, *#P< 0.05* vs CCI, ## *P< 0.01* vs CCI, and ### *P*< 0.001 vs CCI.

3.4 Mechanical hyperalgesia (Pin prick test)

Figure5. Shown the change in response to painful mechanical stimuli in sham operated rats and CCI induced neuropathic rats administered with vehicle, and LCM at 5, 15 and 45mg/kg i.p. on day 0, 3, 7, 11 and day 14 post surgery. Baseline for withdrawal latency was recorded before surgery and pharmacological testing. The marked decrease in the withdrawal latencies of CCI-induced neuropathic pain rat shows the development of hyperalgesia in response to the mechanical stimuli two weeks after surgery when compared to sham-operated rats. Intraperitoneal injection of LCM in different dosages (5, 15, 45 mg/kg i.e.) and pregabline (10mg/kg i.p.) on day 14 and followed by daily treatment until day 14 demonstrated significant and dose-dependent inhibition of mechanical hyperalgesia in CCI-induced neuropathic pain rat.

All the doses of LCM exhibited pronounced significant inhibition (*P*<0.001) of neuropathic pain when compared to vehicle group. Besides that, doses of 15mg/kg, and 45mg/kg of LCM has significant difference in the withdrawal latencies (*P*<0.01) when compared between day 7 and day 14. The data were shown as mean ± SEM. *P< 0.05* vs Sham, ### *P*< 0.001 vs CCI.

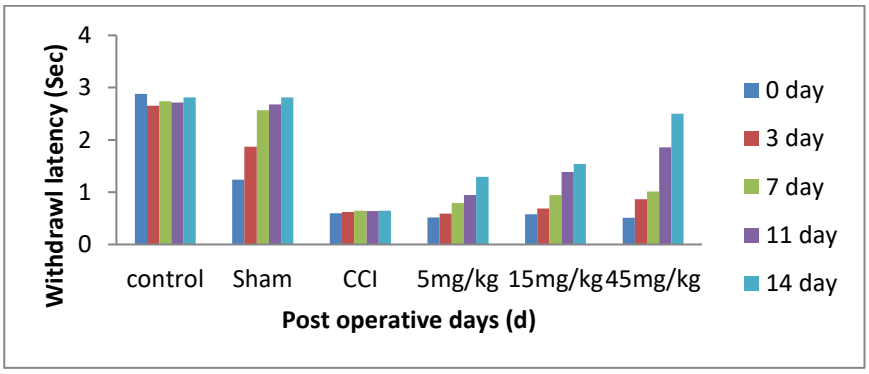

Figure5. The effect of LCM administration on CCI-induced Mechanical hyperalgesia, assessed using the pin prick test test. Rats were treated with vehicle or LCM at doses of 5, 15 and 45 mg/kg once daily for a period of 14 days. The data were shown as mean ± SEM. ** *P< 0.01* vs Sham, ***P< 0.001 vs Sham, *#P< 0.05* vs CCI, ## *P< 0.01* vs CCI, and ### *P*< 0.001 vs CCI.

3.5. Von Frey hair test (i.e. paw mechanical allodynia)

Figure6. Shown the change in response to painful mechanical stimuli in sham operated rats and CCI induced neuropathic rats administered with vehicle, and LCM at 5, 15 and 45mg/kg i.p. on day 0, 3, 7, 11 and day 14 post surgery. Baseline for withdrawal latency was recorded before surgery and pharmacological testing. The marked decrease in the withdrawal latencies of CCI-induced neuropathic pain rat shows the development of mechanical hyperalgesia in response to the mechanical stimuli two weeks after surgery when compared to sham-operated rats. Intraperitoneal injection of LCM in different dosages (5, 15, 45 mg/kg i.e.) and pregabline (10mg/kg i.p.) on day 14 and followed by daily treatment until day 14 demonstrated significant and dose-dependent inhibition of mechanical hyperalgesia in CCI-induced neuropathic pain rat. Treatment with pregabline (10mg/ kg, i.p.) also produced similar effects.

The doses of LCM (45mg/kg i.p.) exhibited pronounced significant inhibition (P<0.001) of neuropathic pain when compared to vehicle group. Besides that, doses of 15mg/kg, and 45mg/kg of LCM has significant difference in the withdrawal latencies (P<0.01) when compared between day 7 and day 14. The data were shown as mean ± SEM. *P< 0.05* vs Sham, ### *P*< 0.001 vs CCI.

DISCUSSION

It is a known fact that the diagnosis and treatment of neuropathic pain remain a major challenge globally[31]. Neuropathic pain is classified as chronic pain, a condition that is distinct to the normal physiological pain due to its diverse etiology and complex pathophysiology.[32-33] Thus far, no defined protocols have been agreed upon on the management of this serious debilitating condition.[34] In contrast to the nociceptive pain, the etiology of neuropathic pain is related to the neural pathway arising from damage to the, and dysfunction of the nervous system. These render some of the currently available drugs for neuropathic pain management ineffective.[35] Hence, there is an urgent need for in-depth studies both to further understand the pathophysiology of the disease as well as to discover better therapeutic approaches.

There has been growing interest in the potential utility of anticonvulsant drugs in the treatment of neuropathic pain, but systematic studies comparing the clinically used drugs have not been conducted. The present study, therefore, sought to directly investigate effects of clinically used anticonvulsant drugs with differing mechanisms of action by experimental peripheral neuropathy. The use of anti-epileptic drugs (AEDs) in the treatment of neuropathic pain is well established.[36-41] Lacosamide has been found to attenuate mechanical hyperalgesia in some animal models for acute and chronic inflammatory pain. [42-45]

The chronic constriction injury model is the most commonly employed neuropathic animal model of nerve damage induced allodynia/hyperalgesia. In this model, neuropathic pain is induced by entrapping the sciatic nerve through four loose ligatures and the model share the pathophysiology of carpal tunnel syndrome in humans due to entrapment of median nerve in narrowing carpal tunnel. Furthermore, this model has also been suggested to share the pathophysiology of complex regional pain syndrome in humans. In the presence study, chronic constriction injury led to significant development of cold allodynia, mechanical hyperalgesia, heat hyperalgesia and mechanical dynamics allodynia assessed on 7th and 14th day after surgery. Furthermore, the spontaneous pain assessed in terms of paw lifting and licking along with foot deformity was also with pronounced injury subjected rats. It has been reported that chronic constriction injury of the sciatic nerve causes dramatic alterations in morphology and physiology of an injury sciatic nerve as well as in the neurons of dorsal root ganglia, with a maximal effect at approximately 2 weeks after nerve injury.[46-50]

In the present study, systematic administration of lacosamide (5-45mg/kg, i. p.) demonstrated a significant dose-dependent inhibition of mechanical and thermal allodynia as well as mechanical and thermal hyperalgesia in the left-hand limb of the CCI-induced neuropathic pain animal model on day 14 post-surgery. Similarly, anti-hyperalgesia and antiallodynic effect of LCM were also observed on day 11after day 14 of daily lacosamide treatment. We found that lacosamide significantly attenuated hyperalgesia and allodynia assessed by Hot plate, Acetone drop test, rota road test, pinprick test and von frey hair test. [47]

In the present study, we investigated the antiallodynic and anti-hyperlagesic properties of lacosamide, in chronic constriction injury (CCI)-induced neuropathic pain rat model. Our findings showed that single and repeated dose of intra-peritoneal administration of

lacosamide (5, 15, 45 mg/kg) significantly inhibited (P<0.05) the chronic constriction injury induced neuropathic pain using the hot and cold plate test, pin prick test, von frey filament test and acetone test in comparison with the positive control drug used (Pregabline 10mg/kg, *i.p*.).

Two previous studies found clear evidence that LCM reduced experimental allodynia in painful peripheral neuropathies (partial peripheral nerve injury and spinal nerve ligation). A third study employed the nerve crush model and the CCI model and tested for allodynia (cold and mechanical) and hyperalgesia (heat and mechanical) in addition to measures of motor function and nerve degeneration.[48] The most significant effects of LCM were observed in measures of mechanohyperalgesia in the CCI model in-line with our findings. In animal studies, thermal sensitivity is mostly evaluated on the basis of nociceptive reaction latencies in response to a given thermal aversive stimulus, whereas nociceptive response was estimated by using the sum of paw lickings and withdrawals latency in seconds. These results demonstrate the interest of the dynamic hot and cold plate to study thermal nociception

CONCLUSION

In conclusion, our study showed that LCM was effective in reducing thermal & mechanical hyperalgesia produced by CCI of the sciatic nerve; Based on our current findings, we conclude that LCM possesses antiallodynic and antihyperalgesic properties in the CCI-induced neuropathic pain animal model. However, based on our current findings, we conclude that LCM possesses both antiallodynic and antihyperalgesic properties as shown in the CCI-induced animal model of neuropathic pain.

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CONFLICT OF INTEREST:

The authors declare that they have no conflicts of interest.

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