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EFFECT OF LACOSAMIDE IN STREPTOZOTOCIN-INDUCED DAIBETIC NEUROPATHIC PAIN

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ABSTRACT

Objective: *The present study was carried out to investigate anti-nociceptive effect of Lacosamide in streptozotocin- induced diabetic rats.* ***Material & Methods:*** *Antinociceptive effect of Lacosamide (5, 15 & 45 mg/kg, i.p.) was evaluated in the streptozotocin -induced diabetes rat model (Streptozotocin 55 mg/kg i.p.) in total five group planned for neuropathic pain. Eddy's hot plate method and tail immersion test were performed on 1st, 2nd, 3rd and 4thweeks of experiment to assess thermal hyperalgesia and cold allodynia respectively. Thermal allodynia evaluated by hot plate (at 42 ±0.5^{0}C); Thermal hyperalgesia evaluated (at 55±0.5^{0}C) and tail immersion test (Cold water 10±0.5^{0}C and hot water 55±0.5^{0}C); and Rota rod test was carried out to examine motor co-ordination while pin-prick methods was mechanical hyperalgesia. Further thermal hyperalgesia & cold allodynia was observed for dose dependent improvement.* ***Results and conclusion:*** *A significant degree of thermal (Allodynia and hyperalgesia) and mechanical hyperalgesia was produced in all the treatment animal groups. Decreased grip strength in diabetic rat was indication of induction of neuropathy or nerve damage. The result of present study of Lacosamide demonstrate that significant anti-allodynic and antihyperalgesia effects on streptozotocin -induced diabetic rats. Lacosamide treatment increases the grip strength, licking time, withdrawal latency and loss of pain perception; this demonstrates its protective effect in diabetic neuropathy.* ***Conclusion:*** *Lacosamide was effective in reducing both the thermal and mechanical hyperalgesia means it has shown good efficacy in streptozotocin -induced diabetic model of neuropathic pain.*

KEY WORDS

streptozotocin induced Diabetic Neuropathy, Lacosamide, Behavioural Methods, Antinociceptive

INTRODUCTION

Pain is defined as an unpleasant sensation & emotional experience associated with actual or potential tissue injury. At some point everyone has experienced a painful sensation. Pain can cause unwanted physical, emotional& social anguish throughout one's daily life[1-2]. Painful diabetic neuropathy (PDN) is one of the leading cause of neuropathic pain in humans.[1-3]PDN is a chronic, usually symmetrical sensorimotor polyneuropathy that leads to significant morbidity which reflect negative impact on patient's general behavior viz. mood, mobility, work, sleep, social relations and affects overall quality of life[1-3].As exact mechanism behind PDN is not clear treatment of PDN is challenging while mechanisms of the action of drugs used to treat neuropathic pain have not been fully elucidated. This makes it difficult to match the type of pain to most appropriate medication. Pharmacological agents like tricyclic antidepressants, SSRI, opioid analgesics & anti-epileptic drugs are used in the management of PDN.

All available treatment options are not able to give total relief and also not effective in all patients. Only about one-third of patients may achieve more than 50% of pain relief.[5]Antiepileptic are increasingly playing key

role in the management of neuropathic pain. Antiepileptic drugs such as Lamotrigine, Gabapentin & Pregablin are demonstrating an analgesic effect in diabetic neuropathy.[1, 6-7]

Neuropathic pain is palliative care in population; inadequate treatment may lead to chronic anxiety, depression & social impairment. Though many treatments are proposed for PDN, as it is under diagnosed, under-treated & requires long term therapy with increased risk of adverse effects. Available treatment provides temporary relief from pain & must be taken consistently. Current developments provide understanding of mechanism of PDN, which contribute towards development of new target specific medications.

Lacosamide is R-enantiomer of l-acetamido-N-benzyl-3-methoxypropionamide. Though it was anticonvulsant drug various animal model have shown its anti-nociceptive efficacy. It showed equivalent or greater efficacy on measure of allodynia & hyperalgesia as compare to other anti- depressant or anticonvulsant drugs.[8-9]

Though gabapentin is very effective in diabetic neuropathic pain, it is lamotrigine which is superior to gabapentin in neuropathic pain induced by cancer chemotherapy. As there is difference in the analgesic action of various antiepileptic drugs. Also, the underlying mechanisms of neuropathic pain of different etiologies need to be understood. It is very exciting to see a compound with a novel mechanism of action with predictive validity in preclinical models of neuropathic pain. Ultimate goal should be to find out safe & effective drug for humans & that is major challenge. Improved understanding of mechanism of PDN along with development of valid animal model, efficacy of drugs can be assessed. Tricyclic antidepressants (TCAs), often the first choice has significant side effects[12] and antiepileptic are partially effective.[13]So it is difficult to select a right drug in different types of neuropathic pain. Multitude of neuropathic pain states & the complex pathophysiological mechanisms involved means that a drug effective in one pain state may not be effective in another; and the response produced may also not be adequate. But no drug, whether conventional or non-conventional, is fully effective in the treatment of this condition, and a drug that shows good efficacy in one neuropathic pain state may be ineffective in another. Thus, there is a continuous need to evaluate newer drugs in various models of neuropathic pain. To assess the sensory perception disturbances behavioral tests like thermal hypo or hyperalgesia is commonly used.

With the ever-increasing demand for newer treatment modalities, Lacosamide have recently investigated for its role in treatment of PDN in a rat but is in unclear and observer bias. With this background, a study has been undertaken to compare the efficacy of antiepileptic drug (lacosamide) for effectiveness in neuropathic pain model by STZ induced diabetes rats.

2. MATERIAL AND METHODS

2.1 Animals

Eight weeks old male Wister rats (180-250g) were used for the evaluation of the neuropathic pain activity. The animals were obtained from Wockhardt Research centre, D-4 MIDC, Chikalthana, Aurangabad. All animals are group housed for at least two weeks in the laboratory animal room prior to study. The selected animals are housed in polypropylene cages in the contolled standard conditions (20-25^{0}C), 12h: 12h light:dark cycle. Rats are fed on standard rodent diet (VRK Nutritional Solution, Sangali) & water *ad libitum*.

The experiments on animals were conducted in accordance with internationally accepted principle for laboratory animal use. The experimental protocols was duly approved (Proposal Number: CPCSEA/CBPCL/ IAEC/2015-16/03.) by Institutional animal ethical committee (IAEC) of Channabasweshwar Pharmacy College, Latur (MS) India

2.2 Drugs and Reagents

Lacosamide (5, 15 and 45 mg/kg body wt.) procured as a research gift sample from Micro Lab Pvt Ltd, Mumbai, Streptozotocin (STZ) injection 98% from SISCO Research laboratories Pvt. Ltd. All the chemicals were purchased from S.D. Fine Pvt. Ltd, Mumbai, India.

2.3 Experimental design and development of diabetes in the rat

Rats are divided randomly in two groups. Diabetes was induced by intraperitoneal (i.p.) injection of freshly prepared 0.1mol/l citrate buffer (pH4.5) of streptozotocin (60mg/kg). Control animals (n=06) receive equivalent volume of citrate buffer solution. Seventy-two hours later, the plasma glucose levels were estimated by using one touch ultra-blood glucose meter (Mfd. by Flextronic Industrial Co. Ltd. Shenzhen, Guangdong, marketed by Life Scan, Johnson & Johnson Pvt. Ltd, Mumbai). Rats showing blood glucose level

more than 16.7mmol/L indicated successful induction of diabetes. Rats with <14.3mol/L blood glucose levels were excluded from study. Animals were strictly monitored for their general health & body weight. After induction of diabetes, diabetic animals are grouped into five groups as mentioned below consisting of 6 animals in each group.

- **Group I (Control):** Rats were administered with normal saline (1ml/kg: i.p. Once daily) for 28th days.
- **Group II (Diabetic-control group):** Rats were administered with streptozotocin (55mg/kg: i.p; only once to induce diabetes)
- **Group III (LCM 5):** STZ+ LCM (5mg/kg; i.p.) treatment group
- **Group IV (LCM 15):** STZ+ LCM (15mg/kg; i.p.) treatment group
- **Group V (LCM 45):** STZ+ LCM (45mg/kg; i.p.) treatment group

2.4: Behavioral assessment

2.4.1. Hot plate test (Thermal allodynia and Thermal hperalgesia)

Hot Plate analgesia meter was used to determinate the central component of nociception. Individual animal was placed on a Hot Plate Analgesia Meter (Orchid Scientific and innovative India Pvt. Ltd., Nashik) maintained at constant temperature at 42 ±0.5^{0}C (Thermal allodynia) and at 55± 0.5^{0}C (Thermal hyperalgesia). The paw licking or jumping response whichever is the first to avoid thermal pain was first sign as an index of pain threshold. To avoid tissue, damage a cut off period of 15sec was predetermined.[14]

2.4.2 Tail immersion test (*Cold and hot hyperalgesia*)

Tail immersion test was performed to assess diabetic thermal hyperalgesia. Rat's tail was immersed in cold (10±0.5^{0}C) to study cold hyperalgesia & in hot water (55±0.5^{0}C) to study hot hyperalgesia. Flicking response of tail or struggle to escape was considered as the end point of the test. Test was repeated for three times for each animal with interval of 5 minutes& average was noted down. Meanwhile, the cut-off time of 15s was kept to avoid tissue damage to the tail.[15-16]

2.4.3 Acetone test (Cold thermal allodynia)

Cold thermal sensitivity test was carried out by using Acetone drop test (by Choi et al.). Rats were placed individually in compartments in a glass chamber with wire mesh floor and allowed to habituate for approximately 30 minutes in order to acclimatize. Freshly dispensed acetone drops (100µL) was applied gently on to the mid plantar surface of the hind paw. Digital stop watch was used to measure response. The test was carried out for three times with 5minute interval & average was noted down. Cold chemical sensitive reaction with respect to either paw licking, shaking or rubbing the hind paw and brisk foot withdrawal (typically 2–5 sec after application) was recorded as a positive response (nociceptive pain response). Absence or delay of these responses were considered as anti-nociceptive effect[17].

2.4.4 Rota rod test (Motor Co-ordination)

Changes in motor coordination and grip strength was investigated by using Rota-rod apparatus. Individual rat was placed on rotating rod having 15 rpm to find out the effect on motor performance. The latency of falling time in seconds was measured for three times with 5min interval & mean was noted down. Training sessions were carried out 1 and 2 days prior to the experiments, with three trials on each day. On the experimental day, a baseline response was obtained and the effects on motor coordination were observed. [18-19]

2.4.5 Pin prick test (*Mechanical hyperalgesia*)

Pin prick test described by Erichsen & Blackburn-Murno was used to evaluate mechanical hyperalgesia. Briefly, the plantar surface of the left hind paw was touched with the point of the bent 18-gauge needle (at 90 angles) at intensity sufficient to produce a reflex withdrawal response in rat, but at an intensity which was insufficient to penetrate the skin in all groups. The duration of the paw withdrawal was recorded in seconds. The test was carried out for 3 times & mean was noted down. A cut-off time of 20 s was maintained.[20]

3. Statistical analysis

All statistics tests were conducted using Graph Pad Prism (version 7) software. The values are expressed as mean ± SEM of six animals. Values with $P < 0.05$ or less were considered as statistically significant. Differences between the studied groups were examined for statistical significance as regards the various parameters using the analysis of variance test. This test is used to find a significance difference between more than two groups. Data were tabulated and represented graphically.

RESULT

3.1. Body weight & blood glucose levels in STZ treated rats

Rats are strictly monitored for their body weights & blood glucose levels. Body weight of STZ-treated animals had 24% less on day 21 while 25% on day 28 as compare to control rats. (Fig.1a). Though STZ-treated animal shows slight reduction in body weight all animals are active throughout the study. The average blood glucose levels of STZ-treated rats were350 mg/dl on day 7 and 420 mg/dl on day 28 while control animals had 116 mg/dl (Fig. 1b).

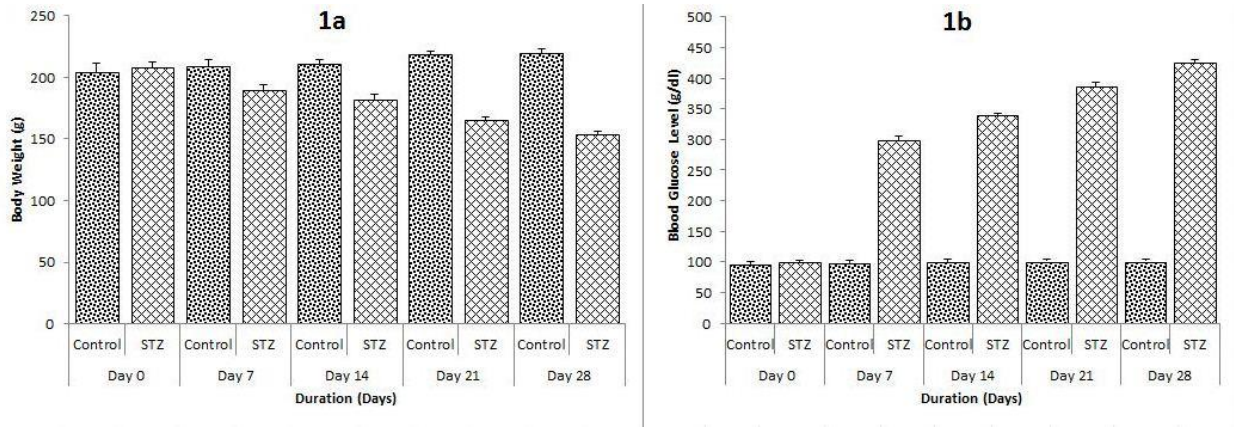

Fig. 1a. Shows body weight of all animals 1b. Blood glucose levels in STZ-treated rats (n=24) &control (n=06)) on day 7, 14, 21and 24 after STZ-treatment.

3.2 Hot plate test (Thermal allodynia and Thermal hyperalgesia)

3.2.1 Thermal allodynia

After four weeks of diabetes induction, as compare to control rats significantly lowered nociceptive threshold was ($p<0.0001$) was observed in all diabetic rats.STZ treated rats had significantly shorter ($p<0.001$) paw withdrawal latency than that of normal animals after four weeks of disease induction. Lacosamide (5 mg/kg, 15mg/kg and 45mg/kg, i.p.) treated groups showed significant increase in reaction time when compared with diabetic control. The therapeutic combination groups of Lacosamide (45mg/kg, i.p.) showed much more significant ($p<0.0001$) increase in reaction time when compared to diabetic controlled rats. (Fig 2).

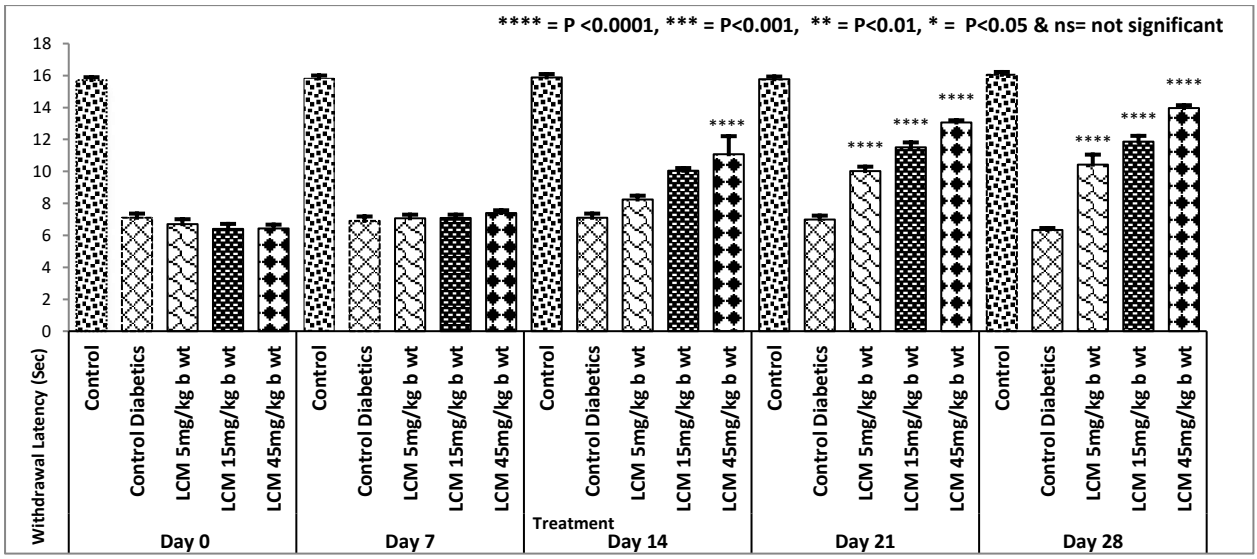

Figure 2: Effect of lacosamide on thermal allodynia test (at 42±0.5^{0}C) Data are expressed as mean ± SEM, n = 6 rats per group.

***3.2.2*Thermal hyperalgesia**

The groups treated with lacosamide (5 mg/kg, 15mg/kg and 45 mg/kg, i.p) showed significant increase in reaction time when compared with diabetic control. The therapeutic dose of lacosamide (45 mg/kg, i.p) showed much more significant (p<0.0001) increase in reaction time when compared with diabetic control on 28th day (Fig 3).

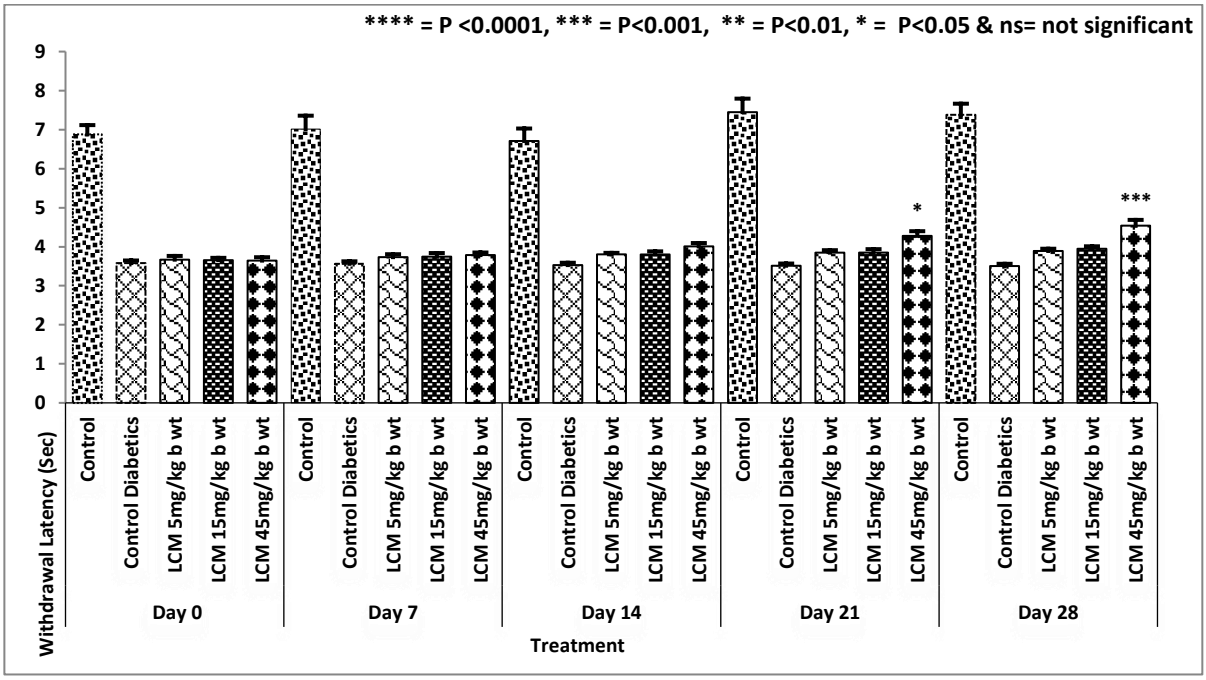

Figure 3: Effect of lacosamide on thermal hyperalgesia test (at 55±0.5^{0}C) (Tail withdrawal threshold). Data are expressed as mean ± SEM, n = 6 rats per group.

3.3 Tail immersion (Cold and hot allodynia) test

3.3.1 Hot water test

The diabetic control group showed significant decrease (p<0.0001) in reaction time when compared with normal control. The groups treated with lacosamide Lacosamide (15 and 45 mg/kg; i.p.) showed significant increase in reaction time (Tail withdrawal latency) when compared with diabetic control. The therapeutic effect of lacosamide on 28th day (45mg/kg,i.p) showed more significant (p<0.0001) increase in reaction time (Tail withdrawal latency) when compared with diabetic control(Fig. 4).

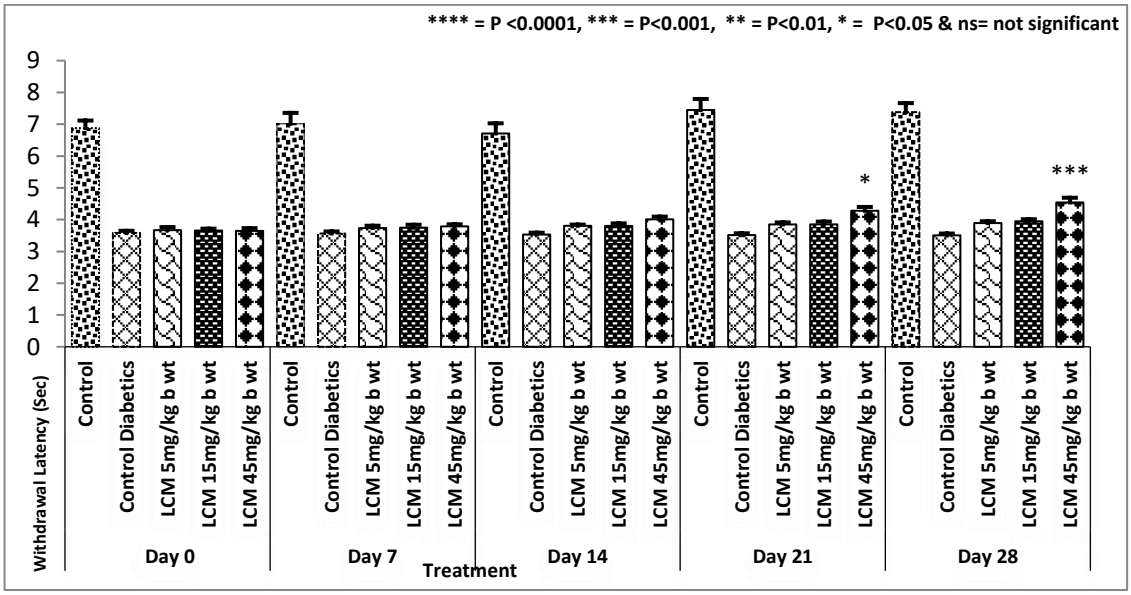

Figure 4: Effect of lacosamide on Tail immersion hot water test (at 55±0.5^{0}C) (Tail withdrawal threshold). Data are expressed as mean ± SEM, n = 6 rats per group.

3.3.2 Cold water tail immersion test

Pain elicited by cold is the major feature of many neuropathic pain states. Especially in cold allodynia normal cool stimuli elicits pain in animal models. For testing cold allodynia two standard animal models, namely Acetone drop test and Tail immersion test were used in the present study.

Streptozotocin-treated animals which received the vehicle exhibited a very short mean threshold latency in the cold bath test (approximately 6 s) in contrast to control/vehicle-treated animals (>15 s) which indicates that cold allodynia developed (Fig. 3). Treatment of streptozotocin-animals with lacosamide 15 and 45 mg/kg (i.p.) produced statistically significant increases in the threshold latency (P<0.05, Dunnett's test). In fact, lacosamide at 45 mg/kg doses produced full reversal of streptozotocin-induced cold allodynia. However, although the threshold latency was greater at the 5, 15 and 45 mg/kg dose of lacosamide than that in vehicle-treated streptozotocin-animals, the difference was not statistically significant. (Figure 6).

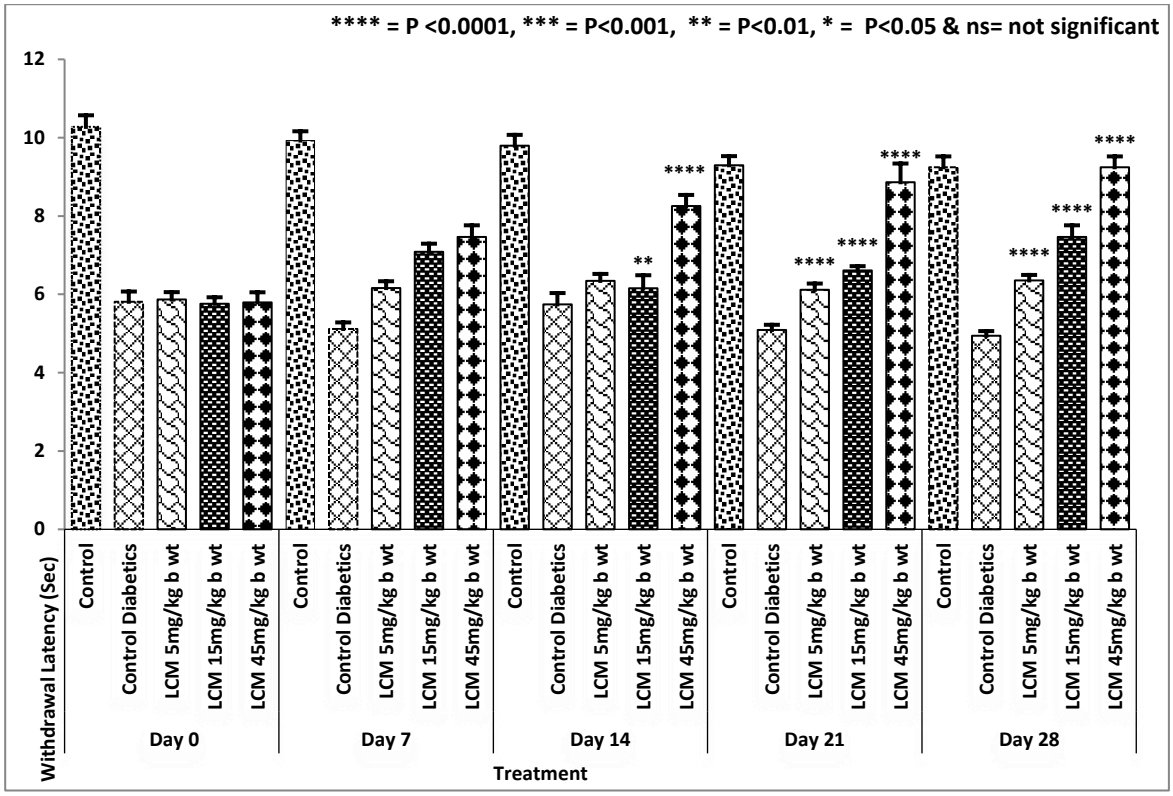

Fig.5.: Effect of lacosamide (i.p.) on tail withdrawal latency in cold water model (10±0.5^{0}C). Data are expressed as mean ± SEM, n = 6 rats per group.

3.3 Acetone test (Thermal allodynia)

In this method the brisk foot withdrawal response, paw licking, shaking or rubbing the hind paw and its frequency was considered as positive response. Lacosamide treated group resulted a significant reduction in foot withdrawal response when compared to STZ-control group (p< 0.0001). Furthermore, in lacosamide group, the foot withdrawal response re-appeared at dose of 45mg/kg on 28th day of treatment. Lacosamide treated group resulted inhibition of foot withdrawal response, paw licking, shaking or rubbing the hind paw noticed in all periods of observation by dose dependence manner (Fig.6).

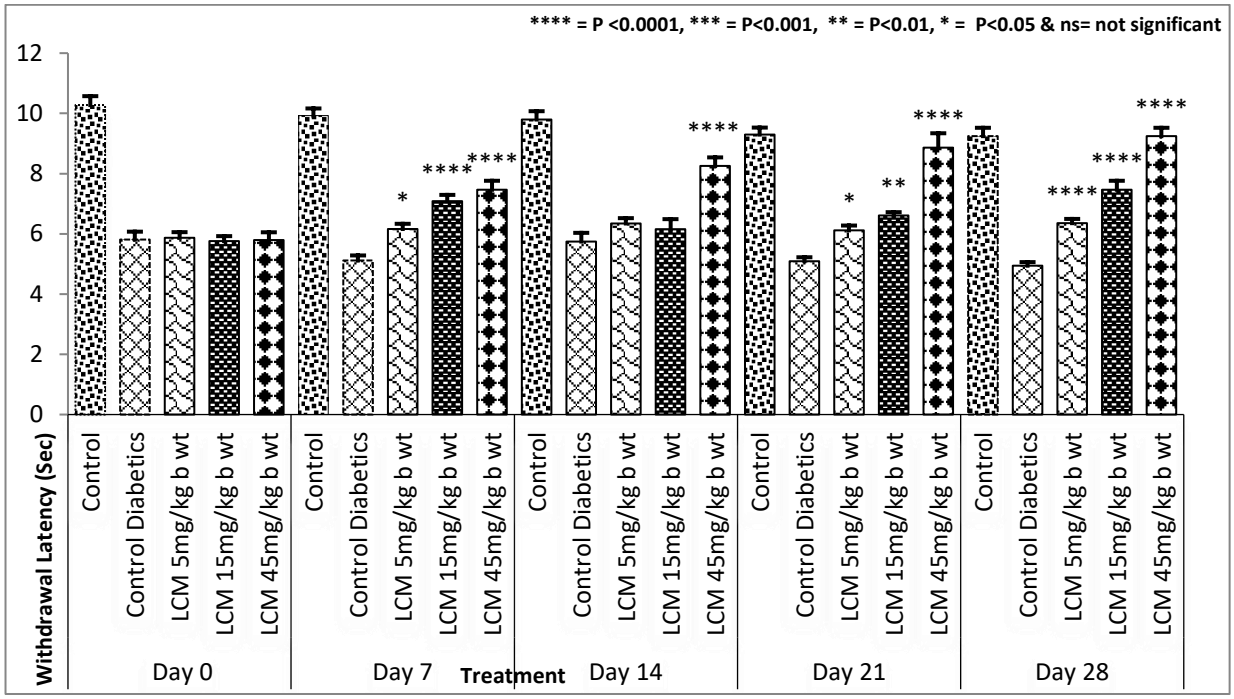

Fig.6.: Effect of lacosamide (i.p.) on paw withdrawal latency in cold water model (10±0.5^{0}C)**. Data are expressed as mean ± SEM, n = 6 rats per group.**

3.4 Rota rod Test (Motor coordination)

After four weeks of diabetes induction muscle spindle get damage and can lead to deficits such as motor incordination. In rota rod test fall down latency time of animals on rotating rod was calculated. The diabetic control group animals showed significant decrease in fall latency time (p<0.0001) when compared with normal group. The groups treated with lacosamide 5, 15 and 45 mg/kg,i.p showed significant increase in fall latency time (p<0.0001) when compared with diabetic control. However, LCM 45 mg/kg i.p. did not produce any significant change in fall off time as compared to the normal control group (Figure 7).

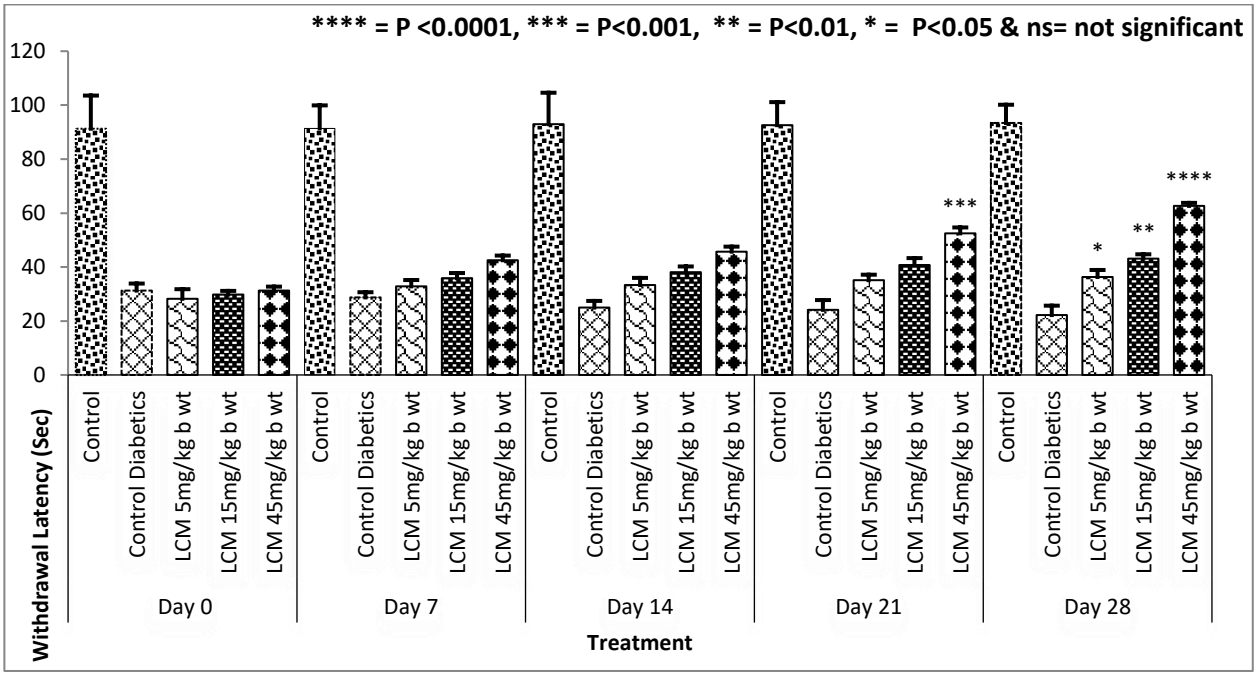

Figure 7: Effect of lacosamide on muscle grip strength (i.e. Fall off time). Data are expressed as mean ± SEM, n = 6 rats per group.

3.5 Pin prick test (Mechanical hyperalgesia)

In this method mechanical hyperalgesia was evaluated by the pin prick test and withdrawal latency was recorded as second. Treatment of lacosamide at dose 45mg/kg has shown highly significant activity as compare to 5 and 15 mg/kg. All the treatment dose is showing the positive response and values are scientifically significant (p>0.05) compare to the STZ control group (Fig 8)

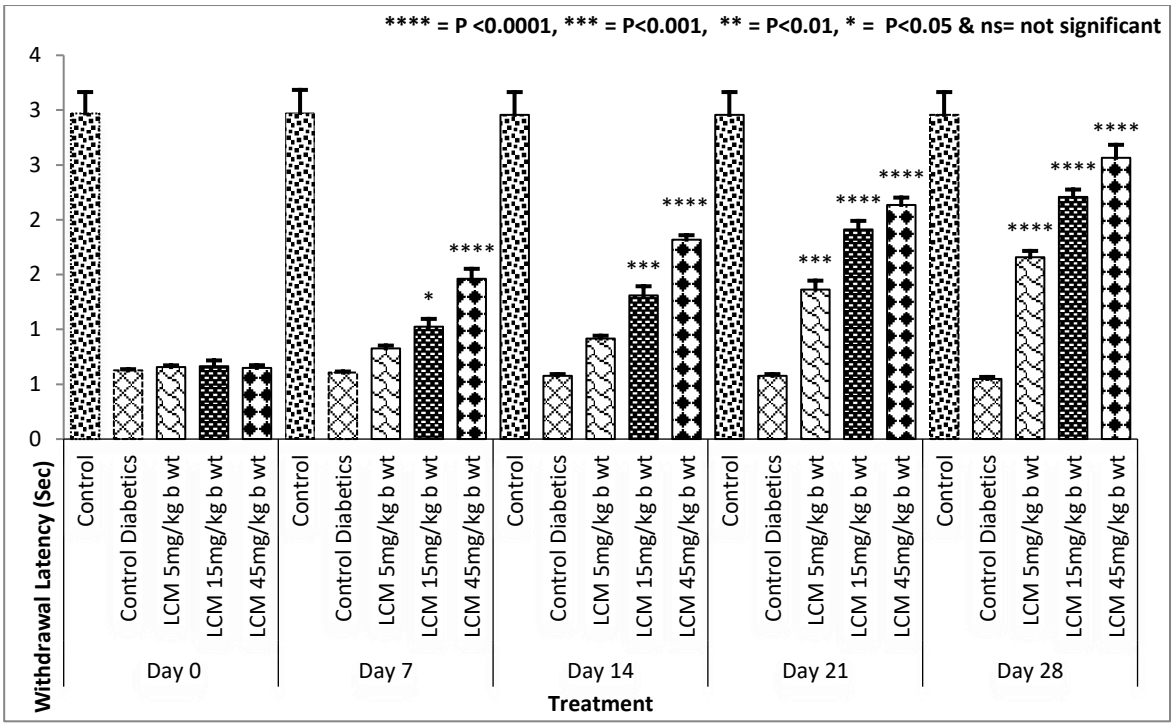

Figure 8: Effect of lacosamide on pinprick test. Data are expressed as mean ± SEM, n = 6 rats per group.

DISCUSSION

Neuropathic pain is a chronic pain that affects the quality of life of millions of people. It is a debilitating condition arising from injury to somatosensory neurons. It triggers allodynia & hyperalgesia in patients. Various surgeries, traumatic accidents, and diseases those affects PNS & CNS contribute to etiopathogenesis of neuropathic pain. The inflammatory cytokines & oxidative stress along with allogenic mediators released subsequently to a nerve injury induce neuropathic pain. This process is through sensitization of nociceptive receptors.

Due to availability of limited treatments for PDN, a lot of patients are using opioids. Long term use may lead to severe effects as tolerance directing towards addiction. Opioid hyperalgesia & risk of death. Neuropathic pain is an important public health problem for which only a few treatments are available. Current treatments have deleterious side effects. Therefore, identifying novel analgesics with safety & efficacy is of keen interest. To evaluate potent drug for maximum pain relief & minimize morbidity to improve quality of life is the challenge.

New approaches to treat the neuropathic pain are slowly emerging. Regulation of N-type voltage-gated calcium channel (CaV2.2) can be done by targeting the protein interactions. This is an alternative method instead directly blocking the channel. This action is antinociceptive with no effect on memory, depression and addiction. This act by peptide uncoupling calcium channels interaction with axonal collapsing response mediator protein 2(CRMP2). This treatment is with improved efficacy.[22]

Though the same type of animal models performed by different laboratories, it reflects different in their characteristics, differences in induction of hyperalgesia.[23-24]Like other antiepileptic drugs lacosamide does not bind to various receptors, ion channels. It is specific in action. Lacosamide binds to slow inactivated form of the channel. It promotes the time spent in refractory period. This affects hyper-excitability by limiting availability of voltage gated sodium channels those can conduct action potentials

along the neuron. This has direct impact on neuronal firing rate, finally normalize activation threshold, controls hypersensitiveness. These in vitro experiments indicate the exact mechanism of action. Lacosamide is more potent & also has efficacy in various animal models of neuropathy. Specific mechanism of action of it indicates its efficacy than various other sodium channel inhibitor like lamotrigine, calcium channel modulators like pregablin, neuronalsynchronization modulator like levetiracetam & venlafaxine (serotonin- and weak noradrenalin reuptake inhibitor& other antidepressants.[25-27]

Streptozotocin, an antibiotic extracted from Streptomyces acromogenes. It is diabetogenic in nature due to its selective cytotoxic action on pancreatic βcell. [28-30]Earlier research reported that rats induced with streptozotocin has diabetic neuropathy characterized with allodynia & hyperalgesia.[31-32] This is due to elevated nociceptive response. Also, these rats exhibit clinicopatological features like biochemical, oxidative & metabolic changes as observed in humans[28-30]. It was also found in the present study following STZ injection. A decrease in pain threshold to mild noxious stimulus like mechanical force was observed, while thermal stimuli had found increased thermal hyperalgesia in diabetic rats than normal rats. In the present investigation, we found that dose dependent reversal of thermal hyperalgesia & mechanical alloynia was found after administration of LCM. Its novel mechanism of action could be a base for its efficacy in epilepsy & Diabetic neuropathy treatment and diabetic neuropathic pain and potentially slow or even stop the progression of disease. “Based on proposed modes of action, patients might be able to get a significant benefit in the treatment of their diseases: Lacosamide seems not only to be an efficacious treatment option in epilepsy and neuropathic pain but might have the potential to directly affect the progression of the diseases”

In the present study decreased pain threshold was observed with mildly noxious stimulus after streptozotocin induced diabetic neuropathy but this threshold was improved by using Lacosamide.The percentage increase in reaction time in case of Thermal allodynia and Thermal hperalgesia shown that more than 75 % increase in case of Lacosamide at dose 45 mg/kg,i.p which was more as compared to Lacosamide at dose 5 and 15 mg/kg,i.p. on day 28 ($p<0.0001$)..

In tail immersion (Hot water) model lacosamide 45mg/kg,i.p had shown more than 75% increase in withdrawal latency of tail which was more as compared to Lacosamide at dose 5 and 15 mg/kg,i.p. on day 28($p<0.0001$)..

In the present study, lacosamide significantly attenuated diabetes induced hyperalgesia. It is evidenced by increased tail withdrawal latency in tail flick method in first two weeks of lacosamide treatmentas compared to diabetic treated rats. In third &fourth week showed even improved responses observed in lacosamide treated groups dose dependently.

In tail immersion (cold water) model lacosamide 45mg/kg,i.p tail withdrawal latency was significantly increased which was more than in Lacosamide at dose 5 &15mg/kg, i.p. on day 14 and day21. In Tail flick model percent increase in tail withdrawal latency observed that lacosamide 45mg/kg,i.p had shown more than 75% increased tail withdrawal latency which was more as compared to Lacosamide at dose 5 &15 mg/kg, i.p. on day 28.

The anti-hyperalgesic activity was evaluated in case of Rota rod model by % increase in fall latency time. lacosamide 45mg/kg,i.p had shown more than 50% increase in fall latency time which was more as compared to Lacosamide at dose 5 & 15 mg/kg,i.p. on day 28.

In this present study, STZ-induced rats had significantly higher blood glucose level, decreased body weight & significantly lowered nociceptive threshold than non-diabetic rats in tail immersion test, hot plate method, and pin prick test. This indicated that STZ-induced rats exhibited significant thermal & mechanical hyperalgesia. This condition was reversed following the treatment of Lacosamide at dose 45mg/kg,i.p on 28th day of treatment($p<0.0001$). Lacosamide was effective in reducing both the thermal and mechanical hyperalgesia means it has shown good efficacy in different models of neuropathic pain.

Another study reported anti-allodynic effect of Lacosamide for 12 days,while in our study, it produced prolonged effecti.e. 4 weeks. This was further confirmed by results of various tests like foot withdrawal, paw licking, jumping response, shaking & rubbing on given stimuli in all four weeks study.The results obtained are consistent with previous findings that lacosamide has

anti-nociceptive properties in experimental neuropathy.[34-36]These study results suggested that Lacosamide reduced severity of diabetic neuropathy in STZ-induced diabetic rats & beneficial in reducing progression of diabetic neuropathy.Similar to finding of other anti-epileptic drugs (AEDs) in the treatment of neuropathic pain lacosamide can well established as per previous study and finding.[37-42] Similar incident by allodynia and hperalgesia on STZ induced diabetics in line with previous study.[43]

CONCLUSION

These results indicated a loss of pain perception in diabetic rats in all the behavioral models attributed to nerve damage resulting due to the development of diabetes neuropathy, while treatment of Lacosamide treatment groups caused an increase in the latency time or withdrawn time dose dependently. Thus, from the result it indicates that chronic treatment of Lacosamide prevent progression of painful diabetic neuropathy in STZ-induced diabetic rats. Lacosamide treated animals had decreased thermal hyperalgesia and possessed anti-allodynia effect. Drug was most effective in attenuating STZ-induced diabetic neuropathic pain. So, in conclusion, Lacosamide can be used as broad-spectrum potential drug which could offer a better treatment for the diabetic neuropathy.

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CONFLICT OF INTEREST:

The authors declare that they have no conflicts of interest.

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