

Original Research

Safety and Efficacy of Intravenous Lacosamide in Refractory Status Epilepticus

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ABSTRACT:

Introduction: SE has been defined as “a condition characterized by an epileptic seizure which is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition”. While there is a uniform agreement that SE should be treated on an emergent basis, treatment protocols of SE continue to be controversial. Refractory status epilepticus establishes in 23-43% section of the patients with SE. Lacosamide (LCM) is one of the newer antiepileptic drugs and since its introduction, use of this drug is steadily increasing. **Aim:** To evaluate the safety profile and efficacy of LCM in RSE, as compared to other conventional 2nd line agents. **Material and methods:** The present study was carried out on 52 patients of RSE, who were admitted in the Emergency Medical Department or Neurology ward, of our tertiary care hospital (Postgraduate Institute of Medical Education and Research, Chandigarh). The patients were randomly divided into two equal groups – Cases and Controls. Patients in Cases group (n=26) received IV LCM in a dosage of 200mg IV bolus, while patients in Controls group (n=26) received a second conventional AED (either phenytoin or levetiracetam depending upon the first used agent). Severity of status epilepticus (SE) was graded by the SE Severity Scale (STESS). All the patients underwent detailed investigations for determination of underlying etiology, as per the proforma attached. **Results:** On Comparisons of both demography and clinical characteristics including SE severity gradation by STESS, no significant differences in SE severity and etiology or critical medical conditions between both groups. However, requirement of add on AEDs was comparable in both the groups. It was observed that Phenytoin plus levetiracetam (Control group) achieved control of RSE in 6 (23.08%) patients compared to 10 (38.46%) patients who were infused phenytoin or levetiracetam plus lacosamide (Case group). None of patients in lacosamide group had adverse effects, while one female patient in phenytoin group developed hypotension, from which she recovered. Further, 25 (48.08%) expired during the course of the study, while 27 (51.92%) recovered. On comparing the two groups with respect to the outcome of treatment, the study observed no significant difference between the two groups. **Conclusion:** LCM appears to be a safe and effective alternative for treatment of seizures in critically ill patients. The low rate of response may be due to LCM being used as a 3rd line drug and dose used of LCM was 200 mg only. However, number of patients was relatively small and further large RCTs are required to confirm above findings.

Key words: Lacosamide, Refractory status epilepticus, safety, efficacy

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INTRODUCTION:

SE has been defined as “a condition characterized by an epileptic seizure which is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition”.¹ It represents one of the most severe neurological emergencies, with mortality rates ranging from 3% to 39% in different studies.²

While there is a uniform agreement that SE should be treated on an emergent basis, treatment protocols of SE continue to be controversial, despite more than one and a half century of research, much evidence is available only for the 1st line medications of SE that include drugs like

intravenous (IV) benzodiazepines.^{3,4} However, because this first-line drug therapy sometimes fail to control at least 35-45% of patients with SE and quite often more potent antiepileptic drugs are required to keep patients in seizure free state, virtually all the patients receive 2nd line treatment.⁵ The agents which are available for 2nd line treatment include phenytoin, fosphenytoin, valproate and levetiracetam.

Once a patient fails to get controlled with first and second line drugs, he is labelled as a case of refractory SE (RSE) and is planned for coma induction with IV midazolam or propofol or thiopentone. However, induction of coma is

associated with significant treatment related side effects and requires continuous respiratory and blood pressure (BP) monitoring in intensive care unit (ICU), which is not always available in resource poor countries. Hence from a practical point of view, a significant proportion of patients with SE, who fail first line and one of the second line agents, receive another second line agent before induction of coma is considered.

Refractory status epilepticus establishes in 23-43% section of the patients with SE. It is stated that occurrence of RSE is found to be mostly associated with severe, acute and potentially fatal etiologies such as, infections like encephalitis, a massive CVA, or progressive primary CNS tumors, with severe impairment of consciousness, 16 to 39% is the estimated short term fatality rate for RSE; as compared to the non-refractory SE, and the mortality rate after RSE is estimated to be about 3 times higher.^{14,15} In view of the danger of RSE and duration determining the outcome, there is need for timely, appropriate and effective pharmacologic treatment.^{6,7}

Lacosamide (LCM) is one of the newer antiepileptic drugs introduced in the year 2009.⁸ Since its introduction, use of this drug is steadily increasing and it has achieved rapid spread in clinical practice, due in large part to its properties related to pharmacology (e.g. minimal binding to protein and its minimal drug-drug interactions) and also to its favourable profile related to side effects.

It is a functional amino acid that acts through voltage gated sodium (Na⁺) channels, resulting in inhibition of the repetitive neuronal firing, stabilization of hyperexcitable neuronal membranes and the reduction of long term channel availability.¹⁹ It also influences collapsin response mediator protein 2 (CRMP-2), thereby not allowing the formation of abnormal neuronal connections in brain.²⁰ LCM has a 100% bioavailability and does not have any pharmacokinetic interaction with other anti epileptic drugs (AEDs) that act on sodium channels. All these factors make it an interesting option for use in treatment of SE, especially in refractory SE (RSE), where coma induction cannot be carried out. LCM has the evidence to support efficacy in RSE.⁹⁻¹¹

The use of LCM in RSE has been described in some case reports and smaller case series.¹²⁻¹⁴ Randomized controlled trials on the efficacy of LCM in RSE are lacking and not registered in the National Institutes of Health (NIH)-sponsored database (clinicaltrials.org), possibly because of ethical restrictions in these critically ill patients.¹⁵

Therefore the present study was planned to evaluate the role of LCM in RSE, compared to other conventional 2nd line agents. If LCM is found useful, this study will provide evidence for efficacy and will add an additional novel agent to the repertoire of drugs for use in RSE

MATERIAL AND METHODS:

Study design: The present study was carried out on 52 patients of RSE, who were admitted in the Emergency Medical Department or Neurology ward, of our tertiary care hospital (Postgraduate Institute of Medical Education and Research, Chandigarh). The study period was from

January 2015 to June 2016. Consecutive patients presenting with RSE were enrolled in the study, after obtaining an informed consent. They were chosen irrespective of etiology or duration of SE, age, sex, ethnic origin and occupation. Status epilepticus was defined as continuous, generalized, convulsive seizures lasting >5 min, or two or more seizures during which the patient did not regain normal sensorium. RSE was diagnosed if a first line (either lorazepam or diazepam) and a second line drug (either of the following: phenytoin or levetiracetam) administered in proper dosages, failed to control the SE.

Inclusion and exclusion criteria: Patients who fulfilled the definition of RSE and Patients who gave written consent for participation in the study were included in the study. whereas those patients who refused to give informed consent, Patients who were already taking the study drug in question and those who had history of allergy to the study drugs were excluded from the study.

Study protocol: All the patients with SE received first line treatment in form of IV lorazepam 0.1mg/kg at rate of 1mg/min. All the 34 patients also receive a second line agent, which was either phenytoin 20mg/kg, at 50mg/min or IV levetiracetam 20mg/kg, at 150mg/min. In case SE was not controlled, additional 10mg/kg dose of earlier used agent was administered. All the patients with SE, received the above said treatment. The patients whose SE was controlled at this stage were not enrolled for further study. A total of 52 patients, whose SE still persisted and coma induction was not feasible for lack of resources, were enrolled in the study.

The patients were randomly divided into two equal groups – Cases and Controls. Patients in Cases group (n=26) received IV LCM in a dosage of a 200mg IV bolus, while patients in Controls group (n=26) received a second conventional AED (either phenytoin or levetiracetam depending upon the first used agent *i.e* levetiracetam was administered if phenytoin was used initially and phenytoin was administered if levetiracetam was the initial agent). The maintenance doses of the drugs were administered as per protocol.

A thorough history was taken and meticulous general physical, systemic and neurological examinations were performed in all the patients. Details were noted down as per the proforma attached. All the patients underwent detailed investigations for determination of underlying etiology, as per the proforma attached.

STATISTICAL ANALYSIS:

All the data was recorded manually in the proforma as well as entered in Windows compatible SPSS version 22. The data was analysed using SPSS software and descriptive statistical methods were used, wherever appropriate. The p value of less than 0.05 was considered statistically significant.

RESULTS:

The present prospective study included 52 patients with refractory status epilepticus (RSE). The patients were randomly divided into two equal groups—Case and Control. Patients in Case group (n=26) received IV

phenytoin or levetiracetam plus LCM in a dosage of 200 mg IV bolus, while patients in Control group (n=26) received a second conventional AED (phenytoin plus levetiracetam).

DEMOGRAPHIC PROFILE:

The mean age of patients at time of evaluation was 36.53± 15.81 (range: 13-70) years. Study group included 35 men and 17 women. Male gender dominated in both the groups with 21 (80.77%) in the Control group and 14 (53.85%) in

the Case group. All studied parameters are tabulated below

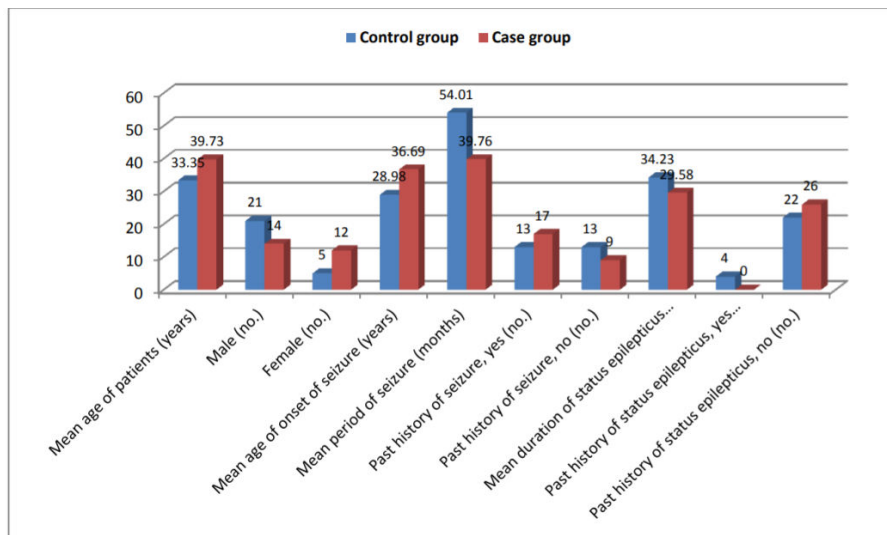
(Table 1 and graph 1). On comparison within the study groups, no significant difference was observed in parameters like mean age of patients, gender, mean age of onset of seizure, mean period of seizure, past history of seizure, mean duration of status epilepticus and past history of status epilepticus.

Table 1: Comparison of demographic profile of patients in the two groups

Parameters	Control group (n=26)	Case group (n=26)	p-value
Mean age of patients in years ± SD	33.35 ± 15.97	39.73 ± 15.29	.14
Gender, no. (%)	Male: 21 (80.77%) Female: 5 (19.23%)	Male: 14 (53.85%) Female: 12 (46.15%)	.07
Mean age of onset of seizure in years ± SD	28.98 ± 20.14	36.69 ± 17.28	.14
Mean period of seizure in months ± SD	54.01 ± 94.52	39.76 ± 100.12	.60
Past history of seizure, no. (%)	Yes: 13 (50%) No: 13 (50%)	Yes: 17 (65.38%) No: 9 (34.62%)	.40
Mean duration of status epilepticus in minutes ± SD	34.23 ± 22.23	29.58 ± 22.48	.45
Past history of status epilepticus	Yes: 4 (15.38%) No: 22 (84.62%)	Yes: nil No: 26 (100%)	.11

*Not significant (p>.05)

Graph 1: Comparison of demographic profile of patients in the two groups



On Comparisons of clinical characteristics including SE severity gradation by STESS and categorization of SE etiology according to the ILAE guidelines of patients in both the study groups was done. Overall, there were no significant differences in SE severity and etiology or critical medical conditions between both groups. Presumed RSE etiologies categorized according to the ILAE guidelines and SE severity graded by STESS did not differ significantly between both groups. Requirement of AEDs in addition to Phenytoin, Levetiracetam or Lacosamide to control RSE was needed for 36 (69.23%) patients, 20 (76.92%) in the Control group and 16 (61.54%) patients in the Case group. However, requirement of add on AEDs was comparable in both the groups (Table 2).

Table 2: Comparison of requirement of other AEDs in the two groups

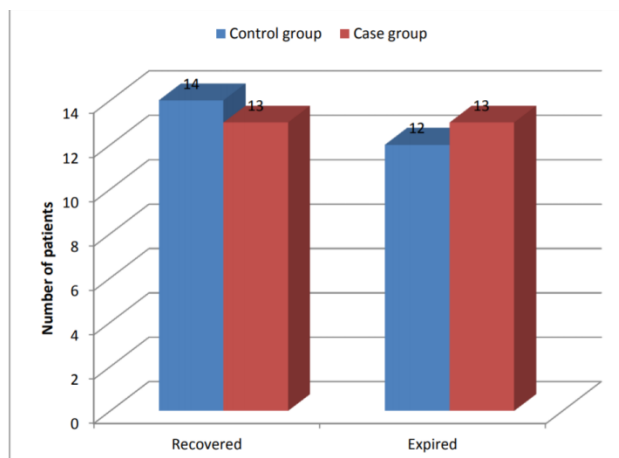
Parameter		Control group (n=26) No. (%)	Case group (n=26) No. (%)	p-value
Requirement of additional AEDs	Yes	20 (76.92)	16 (61.54)	.36
	No	6 (23.08)	10 (38.46)	

*Not significant (p>.05)

The duration of hospital stay was calculated as <7 days and ≥7 days. It was observed that more patients with RSE 29 (55.77%) had hospital stay <7 days, while 23 (44.23%) patients had hospital stay ≥7 days. Mean hospital stay of study group was 10.36 ± 12.96 (range: 1-60) days. Mean hospital stay was more in Control group as compared to Case group. However, the difference between the two was statistically not significant.

It was observed that Phenytoin plus levetiracetam (Control group) achieved control of RSE in 6 (23.08%) patients compared to 10 (38.46%) patients who were infused phenytoin or levetiracetam plus lacosamide (Case group). When the two groups were compared, it was found that RSE was controlled more in patients of case group as compared to control group. However, the difference was statistically not significant, indicating that phenytoin or levetiracetam plus lacosamide and phenytoin plus levetiracetam were equally effective in controlling RSE within 30 minutes. None of patients in lacosamide group had adverse effects, while one female patient in phenytoin group developed hypotension, from which she recovered.

Further, Out of 52 patients in the study, 25 (48.08%) expired during the course of the study, while 27 (51.92%) recovered. (Graph 2) Comparing the two groups with respect to the outcome of treatment, the study observed no significant difference between the two groups. A total of 39 (75%) patients required ventilatory support in the study, though there was no statistically significant difference in number of patients in the two groups.



GRAPH 2: Comparison of outcome of RSE in the two groups

DISCUSSION:

This study explored the efficacy and safety of LCM on treatment for critically ill adult patients suffering from RSE in the hospital. The present prospective study was conducted on 52 patients, whose status epilepticus persisted after first line treatment in form of IV lorazepam 0.1 mg/kg at rate of 1 mg/min and second line agent which was either phenytoin 20 mg/kg at 50 mg/min or IV levetiracetam 20 mg/kg at 150 mg/min. These patients were also administered, additional 10 mg/kg dose of earlier used agent, as SE was not controlled.

When the two groups were compared, it was found that RSE was controlled, more in patients of case group as compared to control group. However, the difference was not statistically significant, indicating that phenytoin or levetiracetam plus lacosamide (Case group) and phenytoin plus levetiracetam (Control group), were equally effective in controlling RSE within 30 minutes. Thakur et al found that status epilepticus was controlled on addition of lacosamide in 11 (31%) cases and remained uncontrolled in 18 (49%) cases, which is similar to our study. In their study, 7 (19%) patients were infused with other AED's in addition to lacosamide for resolving status epilepticus. Where as Sutter et al, reported that seizure control was achieved in 91% of their 34 RSE patients, who were treated with lacosamide, which is in contrast to our study. The study did not mention time period of seizure control.¹⁵

None of patients in lacosamide group had adverse effects, while one female patient in phenytoin group developed hypotension from which she recovered. According to Kellinghaus et al, lacosamide and phenytoin showed similar success rates for treatment of status epilepticus when used after failure of benzodiazepines and levetiracetam.¹⁶ However, phenytoin was associated with relevant side effects that were not seen with lacosamide, which is similar to our study.

The experience of LCM for SE treatment in adults is limited to a few reports on LCM ^{16,17} and even more restricted for the treatment of patients with RSE to a few case reports and recent case series.¹²⁻¹⁴

In a small case series, RSE terminated after the administration of lacosamide in all 7 cases in the first 24 hours,¹⁸ while in a separate study RSE could be terminated after lacosamide in 17 patients, while 22 patients required further escalation of treatment.¹³ Legros et al, observed trend in favor of a higher response rate to lacosamide in the 400 mg group [7/14 (50%) vs. 2/11 (18%), respectively].

The following adverse events were attributed to LCM: myoclonus and confusion, increase in seizure frequency, vertigo, ataxia and an asymptomatic increase in liver enzymes level. All occurred in the 200 mg group. No skin rash, renal, cardiac, or hemodynamic side effects were observed in any group. In contrast to prior reports on the use of i.v. LCM in SE, LCM was not administered with a 'loading bolus' of 400 mg, an important difference that might have reduced its efficacy.

In the present study Side effect of hypotension was noted in one patient treated with phenytoin. In accordance to ours, Cherry S et al reported Hypotension was noted 1 h after LCM load in five patient episodes (19%).¹⁹ Though, this has not been reported in previous studies, and investigation in larger studies is needed to further evaluate for a possible association.

Overall Patients demographics, clinical characteristics, and presumed etiologies of RSE were similar to those in previous studies on the treatment of RSE. Decreased mortality in patients with i.v. LCM might still be the result of multiple effects, such as improvement of critical care in general, which is difficult to address.

CONCLUSION:

Phenytoin plus levetiracetam (Control group) and phenytoin or levetiracetam plus lacosamide (Case group), both were equally effective and safe in management of RSE. To conclude, our results suggest that LCM appears to be a safe and effective alternative for treatment of seizures in critically ill patients. The low rate of response may be due to LCM being used as a 3rd line drug and dose used of LCM was 200 mg only. However, number of patients was relatively small and further large RCTs are required to confirm above findings.

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