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Original Research

A Dose Dependent Comparison of Intravenous Lacosamide in Refractory Status Epilepticus

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***ABSTRACT*:**

Introduction: RSE is life threatening and quite common emergency in neurology, in the intensive care units (ICUs), with high morbidity and mortality. The treatment of refractory status epilepticus (RSE), defined as status epilepticus (SE) persisting despite use of two lines of anticonvulsant drug, remains challenging. Lacosamide (LCM) is a new AED which has been shown to significantly reduce seizure frequency in patients. with uncontrolled partial-onset seizures. **Aim**: Aim of this prospective study was to evaluate the efficacy and safety of two initial loading doses, 200 and 400 mg of iv Lacosamide. **Material and methods**: The present study was carried out on 31 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). A first group received an IV load of 200 mg of LCM. After the initial part of the study, a second group received a loading dose of 400 mg. Outcome measures included efficacy as response rate, and adverse effects. **Results**: Our results showed that Patients in the group 2 were found to be more ill than in the group 2. In 11 of 31 patients (35.8 %) showed control of seizures and thus responded to treatment with LCM. It was observed that greater response rate to LCM was observed in the 400 mg group [7/16 (43.7 %) in group 2 in comparison to vs. 4/15 (26.6 %)] within 24 hr after LCM introduction. **Conclusion:** We conclude that loading dose of 400 mg of LCM proved to be better and was associated with early termination of RSE and with no significant increase in toxicity in patients. LCM proves to a promising drug with better efficacy even in higher dosage. More such dosage related studies are required to validate our results, as this study has its own limitations due to small sample size.

Key words: Intravenous Lacosamide, Refractory Status Epilepticus

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INTRODUCTION:

RSE is life threatening and quite common emergency in neurology, in the intensive care units (ICUs), with high morbidity and mortality. RSE leads to in hospital admission for long time and bad outcome than the status epilepticus (SE) which is responsive to drugs.[1,2] RSE is defined to be continuous epileptic activity after the start of a 1st line drug (intravenous benzodiazepines) and one 2nd line anti epileptic drug (phenobarbitol, phenytoin, valproate, or levetiracetam), while others recommend a time duration of the status epilepticus of greater than one hour.[2,3] In its severest form, refractory status epilepticus (RSE) was defined by Holtkamp et al, as continuous epileptic activity after a high dose of intravenous anesthetics (i.e. "malignant SE").[4] Inspite of the demographic impact of refractory status epilepticus (RSE), diagnosis and the management depends chiefly on the opinion of experts, some small case series, and few retrospective studies.[2,3,4]

The treatment of refractory status epilepticus (RSE), defined as status epilepticus (SE) persisting despite use of two lines of anticonvulsant drug, remains challenging. The choice of IV anticonvulsants is currently limited to phenytoin (PHT) (and its pro-drug fosphenytoin), valproate (VPA), levetiracetam (LEV), and lacosamide (LCM). PHT and VPA can potentially cause serious adverse events and have a poor pharmacokinetic profile, with significant protein

binding, metabolism and interactions with other drugs.

Lacosamide (LCM) is a new AED which has been shown to significantly reduce seizure frequency in patients. with uncontrolled partial-onset seizures.[5] It received FDA approval for adjunctive therapy of partial-onset seizures in 2009. LEV has a better safety and pharmacokinetic profile but may be inferior in terms of efficacy.[6]

There is currently a lack of consensus regarding the optimal dosage of LCM in this setting. Loading doses of 200–400 mg are suggested. Therefore we compared in this prospective study the efficacy and safety of two initial loading doses, 200 and 400 mg.

MATERIAL AND METHODS:

The present study was carried out on 31 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 June2016. All patients with RSE were examined by the study investigator, in person. They were given treatment as per the protocol being followed in our institute. All the patients with SE received first line treatment in form of IV lorazepam 0.1mg/kg at rate of 1mg/min. Second line agent, which was either phenytoin 20mg/kg, at 50mg/min or IV levetiracetam 20mg/kg, at 150mg/min. In cases refractory to these first two lines, patients receive either general anesthesia (with midazolam, propofol or thiopental) and/or additional trials of another IV anticonvulsant.

A total of 31 patients, enrolled in the study were randomly divided into two equal groups. GROUP 1 patients (N = 15) received an IV load of 200 mg of LCM administered over 15 min (infusion rate of 13.33 mg/ min), as per a treatment protocol. GROUP 2 had a loading dose of 400 mg of LCM over 15 min in a second group (N = 16). The maintenance dose was similar in both groups (200 mg every 12 h, given orally).

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. All the patients underwent neuroimaging and scalp EEG, wherever needed.

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. Fisher's exact tests and Mann–Whitney U-tests (also known as Wilcoxon rank sum tests) were used to assess group differences in numeric variables. The p value of less than 0.05 was considered statistically significant.

RESULTS:

Demographic variables were recorded for the patients of the study group. (Table:1)

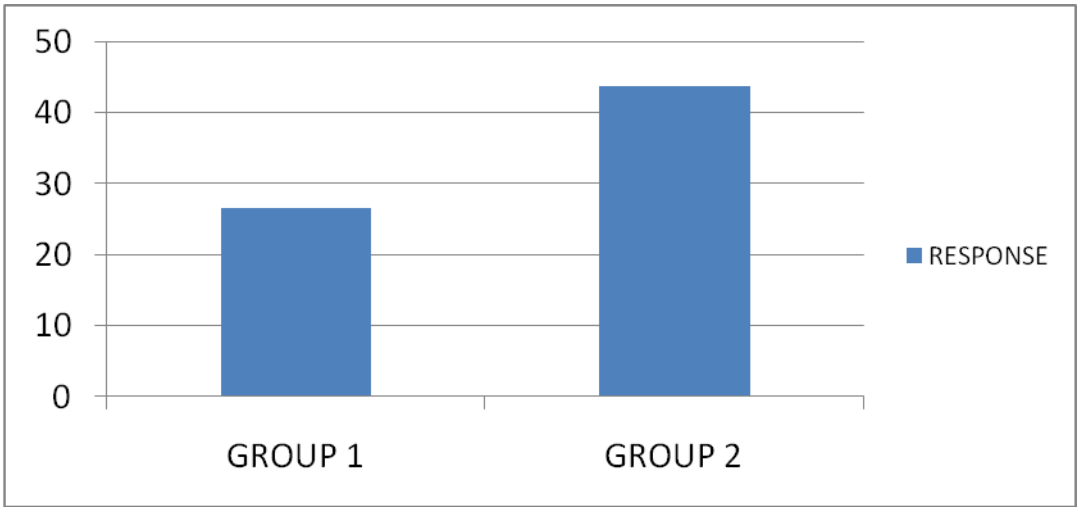
Table 1Comparison of demographic profile of patients in the two groups

Parameters	**Group 1 (n=15)**	**Group 2 (n=16)**
Mean age of patients in years ± SD	32.35 ± 10.2	34.14 ± 12.31
Gender, no. (%)	Male: 21 (78.7%) Female: 5 (22.2%)	Male: 64.8% Female: 36.2%
Mean age of onset of seizure in years ± SD	29.98 ± 20.15	32.62 ± 11.91
Mean period of seizure in months ± SD	54.01 ± 94.52	39.76 ± 100.12
Past history of status epilepticus	Yes: 25.3% No:74.7	Yes: 22.4% No: 77.6%

Our results showed that Patients in the group 2(400 mg group) were found to be more ill than in the 200 mg group, as more number of patients of group 2 were admitted to an ICU at the time of RSE, but this was not significant.

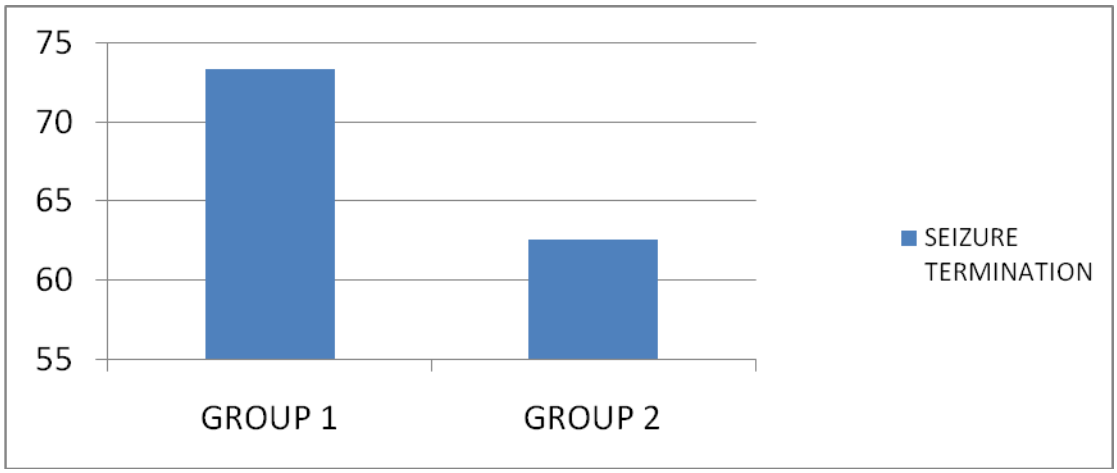
Primary outcome:
In 11 of 31 patients (35.8 %) showed control of seizures and thus responded to treatment with LCM. It was observed that greater response rate to LCM was observed in the 400 mg group [7/16 (43.7 %) in group 2 in comparison to vs. 4/15 (26.6 %)] within 24 hr after LCM introduction.

GRAPH 1: COMPARISION OF STUDY GROUPS IN RESPONSE TO TREATMENT



In group 1: 2 patients had generalized tonic–clonic seizure followed by a cluster of partial seizures. In comparison, group 2: 4 patients had NCSE and one had a cluster of partial seizures. Overall, seizures were terminated in 21/31 patients [11/15 (73.3 %) vs. 10/16 (62.5%), in the 200 and 400 mg groups respectively]. (graph 2)

GRAPH 2: COMPARISION OF STUDY GROUPS IN RESPONSE TO TREATMENT



We observed a significant increase in ALT in one patient in the 200 mg group and one patient in developed hypotension but recovered. and none such events were seen in 400 mg group. Over all clinical adverse events attributed to LCM occurred in the 200 mg group only while such events were absent in 400 mg group.

DISCUSSION:
RSE is defined as continuous or repetitive seizures which do not show response to 1st and 2nd line therapy. There is lack of consensus regarding its definition. Proposed criteria for RSE vary with respect to number of antiepileptic drugs failed (2 drugs or 3 drugs) and a minimum duration of persistent seizure activity (range: none to 1 hour or 2 hours).[7] A study focused on RSE revealed, that it occurred in an approximate 30% of the patients with SE and median duration of RSE is approximately 20 hours. Focal motor seizures and subtle/ non convulsive SE are risk factors for RSE.[1]
In the present study, we observed that a loading dose of 400 mg of LCM proved to be better in terms of earlier termination of RSE and tended to be associated with a higher rate of termination of RSE/SC overall than a loading dose of 200 mg. Drug tolerance was

also observed to be better in 400mg loading dose in comparision to 200mg dosage as less side effects were obsereved in this group.

Krauss et al, published multicenter, open-label, dose-escalation trial with some 160 in patients from ongoing open-label, long-term trials who were taking stable doses of oral drug LCM and about 3 concurrent AEDs. Majority of the cases were given IV LCM 200–600 mg/day; around 4% (7/160) received 700–800 mg/day in fifteen minutes. The adverse effect (AE) rate was less, with the commonest being (10% or less) pain in head, double vision, giddiness and somnolence. The incidence of AEs correlates with the higher doses of LCM, but not with shorter infusion time. Two cases developed cardiac AEs: one case being treated with the βblockers developed reversible bradycardia of 26 beats per minute, during a fifteen minute infusion on 2nd day of therapy with 300 mg/day intravenous lacosamide; the 2nd case developed nonrecurring prolonged QTc interval, without any clinical manifestations on 4th day of management with 100 mg/day IV LCM by a fifteen minute infusion. It should however be mentioned that all cases were long-term responders to LCM in open-label extension trials, meaning that LCM was well tolerated by the study population.[8]

Kellinghaus et al, described the combined experience of 4 centers in Germany, Austria, and Switzerland. In total, thirty nine cases receiving intravenous levetiracetam for the therapy of status epilepticus (6 convulsive status epilepticus [CSE], 17 non convulsive status epilepticus(NCSE) and 16 focal status epilepticus) not responding to benzodiazepines were included. Lacosamide (LCM) was used with success, as 1st or 2nd drug in three of five cases, as 3rd drug in eleven of nineteen cases and as 4th or later drug in three of the 15 cases. Median bolus dose of 400mg was given (dose range from 200–400mg). In about 28 44% of cases (17/39), SE resolved with the drug LCM; only few AEs were seen (one allergic dermatitis, 25 hypersomnolence, 4 low BP). Amongst 39 cases, 37 were given benzodiazepines as 1st line therapy. The drug lacosamide was given early (as 1st, 2nd or 3rd drug) it was found to be useful in 60%, while only 20% benefitted when used in later stages of status epilepticus.[9]

In previous series, by Hofler J the loading doses varied from 50 to 600 mg, but mostly between 50 and 400 mg but No clear dose-efficacy relationship was found. The lack of uniformity in diagnostic criteria, therapeutic algorithm and outcome measures, and the absence of individual information in some studies preclude a pooled analysis. Similar to ours, B. Legros et al also reported that a loading dose of 400 mg of LCM tended to be associated with a better response rate.[11]

In few case series, RSE terminated after infusing lacosamide, in all the seven patients in first twenty four hours,[12]while in an another study RSE could be terminated after administration of lacosamide in seventeen cases, while twenty two cases required further escalation of therapy. However, Goodwin et al, found no 20 response to lacosamide drug in nine patients.109 Recently few of the promising therapeutic regimens for RSE, such as inhaled anesthetics (use with caution), electroconvulsive therapy, surgery, hypothermia, stimulation of vagus nerve, and the ketogenic diets have been reasessed.[13]

With its limitations like small sample size and lack of standardization of dose of LCM this study investigated the dose dependent efficacy of LCM in RSE. We observed that a loading dose of 400 mg of LCM in comparision to dose of 200 mg, proved to be better and was associated with early termination of RSE and with no significant increase in toxicity in patients.

CONCLUSION:

We conclude that loading dose of 400 mg of LCM proved to be better and was associated with early termination of RSE and with no significant increase in toxicity in patients. LCM proves to a promising drug with better efficacy even in higher dosage. More such dosage related studies are required to validate our results, as this study has its own limitations due to small sample size.

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