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Original Research

Efficacy of Intravenous Lacosamide in Refractory Status Epilepticus Patients

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***ABSTRACT*:**

Introduction: Refractory status epilepticus (RSE) establishes in 23-43% section of the patients with SE. Lacosamide (LCM) is one of the newer antiepileptic drugs used for the treatment of such patents. Since its introduction, use of this drug is steadily increasing and it has achieved rapid spread in clinical practice.It has been shown to have a low rate of hemodynamic changes, elevated liver function tests, cardiac arrhythmias, renal dysfunction, and hypersensitivity. **Aim**: The purpose of this study was to evaluate the effectiveness of lacosamide in terms of laborartory and EEG findings in critically ill patients of refactory status epilepticus. **Material and methods:** The present study was carried out on 52 patients of RSE. The safety of lacosamide was evaluated in patients by reviewing blood pressure pre-lacosamide and again at 1, 4, and 24 h after lacosamide administration. Liver enzymes and creatinine were evaluated prelacosamide and 1 and 7 days post-lacosamide. **Results**: The mean age of patients at time of evaluation was 39.73 ± 15.29 (range: 13-70) years and most common identifiable cause of status epilepticus was ischemic stroke. On day 1 post-lacosamide, 6 patients developed an elevation in liver function testing and by day 7 post-lacosamide, 9 patients had transaminitis. On evaluation of kidney function similarly, Creatinine was found to be not significantly different on both day 1 and day 7 post-lacosamide. EEG was done in 43 (82.69%) patients. Abnormal EEG recordings were in the form of diffuse slowing in 22 (51.16%. After receiving lacosamide, the length of status epilepticus was 31.1 ± 4.6 h. When comparing medication responses at 4, 12, 24, and 48 h in the patients, at 4 h, 17.3 % of lacosamide patients responded while the number increased to 78.8% by 48 h. **Conclusion**: Lacosamide seems to be an ideal antiepileptic for use in the critically ill. there is a need for a large, prospective study evaluating lacosamide in status epilepticus and comparing the effectiveness to traditional antiepileptics, such as phenytoin.

Key words: Status epilepticus, Refractory status epilepticus, Lacosamide, liver function.

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INTRODUCTION:

Status epilepticus (SE) has traditionally been defined as more than 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness in between for a total of more than 30 minutes.[1,2] In the year 1999, Lowenstein et al, stated some fresh working definition which lowered the said threshold to greater than five minutes of any persistent seizure activity.[3] This stated definition is more relevant when seen clinically, given that the majority of self-aborting seizures are very brief, that last less than 2 minutes and response to therapy decreases with increase in duration of the seizure.[4]

Refractory status epilepticus establishes (RSE) 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. In view of the danger of RSE and duration determining the outcome, there is need for timely, appropriate and effective pharmacologic treatment.[5-8]

Lacosamide (LCM) is one of the newer antiepileptic drugs introduced in the year 2009.[9] 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.[10] It also influences collaps in response mediator protein 2 (CRMP-2), thereby not allowing the formation of abnormal neuronal connections in brain.[11]

It has been shown to have a low rate of hemodynamic changes, elevated liver function tests, cardiac arrhythmias, renal dysfunction, and hypersensitivity.[12]. The purpose of this study was to evaluate the effectiveness of lacosamide in terms of laborartory and EEG findings in critically ill patients of refactory status epilepticus.

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). 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. Patients were noted for lacosamide effectiveness analysis.

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. Further continuous EEG prior to administration of lacosamide and at least 48 h after administration were specifically recorded. Patients were also reviewed for demographic data, seizure risk factors, seizure history including prior status and AEDs, and current and subsequent status epilepticus treatment.

The safety of lacosamide was evaluated in patients by reviewing blood pressure pre-lacosamide and again at 1, 4, and 24 h after lacosamide administration. Liver enzymes and creatinine were evaluated prelacosamide and 1 and 7 days post-lacosamide. Increase in liver function tests was defined as a twofold increase from the upper limit of normal (>120 U/L for AST and >100 U/L for ALT), and an elevation of creatinine was defined as an elevation of greater than 2.0 mg/dL.[12] The PR intervals on electrocardiogram (EKG) were reviewed prelacosamide and post-lacosamide and were considered increased if there was a >20 ms change.

Lacosamide has been previously shown to have a time to peak of 4 h after oral administration Anesthetics were weaned prior to the administration of lacosamide. The cEEG reports and raw EEG data were then reviewed for onset and cessation of status epilepticus Cessation of status epilepticus was defined as the end of convulsive activity or resolution of previously documented electrographic seizure activity (i.e., evolution in field, morphology, and/or frequency of spikes, sharp waves, or rhythmic waveforms) for a minimum of 24 h.[13]

RESULTS:

The present prospective study included 52 patients with refractory status epilepticus (RSE). The mean age of patients at time of evaluation was 39.73 ± 15.29 (range: 13-70) years. Study group included 35 men and 17 women. All details of demographic profile of patients are given in table 1.

Table 1: Demographic profile of patients

Parameters	Study group(n=52)
Mean age of patients in years ± SD	39.73 ± 15.29
Gender, no. (%)	Male: 35 (67.3%) Female: 17 (32.6%)
Mean age of onset of seizure in years ± SD	36.69 ± 17.28
Mean period of seizure in months ± SD	39.76 ± 100.12
Past history of seizure, no. (%)	Yes: 17 (65.38%) No: 9 (34.62%)
Mean duration of status epilepticus in minutes ± SD	29.58 ± 22.48
Past history of status epilepticus	Yes: nil No: 26 (100%)
Requirement of additional AEDs	16 (30.76%)
Discharged home, n (%)	28 (53.84%)
Expired, n (%)	26 (46.1%)

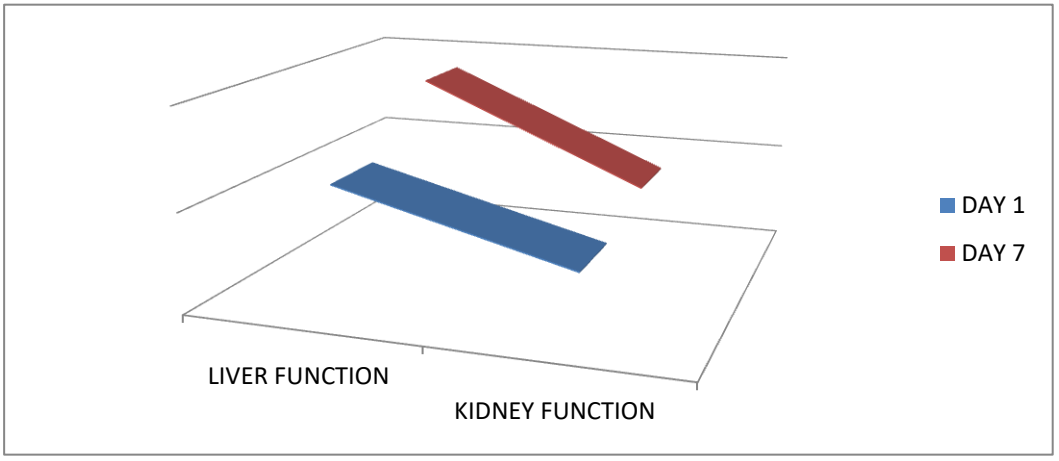
The most common identifiable cause of status epilepticus was ischemic stroke (remote or acute (16.7 %). Other causes included hemorrhagic strokes, brain injury, infections, neurodegenerative injuries and reperfusion injury. The majority (61.5 %) of seizures had no clinical signs.

Further mean values of laboratory parameters on day 1were evaluated and are tabulated in table 2. On comparision of day 1 and day 7 it was observed that at day 1 post-lacosamide, 6 patients developed an elevation in liver function testing (i.e., transaminitis) and by day 7 post-lacosamide, 9 patients had transaminitis. On evaluation of kidney function similarly, Creatinine was found to be not significantly different on both day 1 and day 7 post-lacosamide. Overall only 1 patient developed acute renal failure at day 7 post-lacosamide.

Table 2: Laboratory parameters of patients our study.

Parameters	**Study group (n=52) Mean ± SD**
Haemoglobin (gm%)	11.11 ± 2.02
TLC (per mm^3)	12819.23± 5538.88
Blood sugar (mg/dL)	160.08 ± 75.14
Serum sodium (mg/dL)	143.11 ± 10.74
Serum calcium (mg/dL)	8.55 ± 1.12
Serum magnesium (mg/dL)	2.02 ± 0.33
Serum urea (mg/dL)	48.46 ± 47.88
Serum creatinine (mg/dL)	1.28 ± 1.13
Serum bilirubin (mg/dL)	1.09 ± 1.35
SGOT (IU/L)	65.19 ± 32.07
SGPT (IU/L)	52.92 ± 25.86
ALP (IU/L)	212.58 ± 97.34
CSF – TLC (mg/dL)	110.00 ± 216.262
CSF – sugar (mg/dL)	75.43 ± 50.74
CSF – protein (mg/dL)	103.00 ± 128.57

GRAPH 1: COMPARISION OF DAY 1 AND DAY 7 FOR LIVER FUNCTION AND KIDNEY FUNCTION



Laboratory abnormalities on day 1 noted were leukocytosis in 28 (53.85%) patients, hypocalcemia in 24 (46.15%) patients and hypomagnesaemia in 4 (7.69%) patients.

TABLE 3: LEUCOCYTOSIS, HYPOCALCEMIA AND HYPOMAGNESAEMIA IN THE STUDY GROUP.

Parameters		**Case group (n=26) No. (%)**
Leucocystosis (TLC >11000/mm^3)	Present	28 (53.85%)
	Absent	24 (46.15%)
Hypocalcemia (Serum Ca <8.5 mg/dL)	Present	24 (46.15%)
	Absent	12 (46.15%)
Hypomagnesaemia (Serum Mg <1.7 mg/dL)	Present	4 (7.69%)
	Absent	48 (92.30%)

EEG was done in 43 (82.69%) patients. Abnormal EEG recordings were in the form of diffuse slowing in 22 (51.16%; slowing – 7, delta – 3, theta – 10, theta to delta – 2), focal epileptiform discharges in 8 (18.60%) and generalized discharges in 4 (9.30%). Normal/beta activity without any epileptiform discharges were observed in 9 (20.93%) patients.

After receiving lacosamide, the length of status epilepticus was 31.1 ± 4.6 h. Seizures were controlled in 16 (30.77%) patients, while 36 (69.23%) patients required additional treatment. Therefore Requirement of AEDs in addition to Phenytoin, Levetiracetam or Lacosamide to control RSE was needed for 36 (69.23%) patients.

When comparing medication responses at 4, 12, 24, and 48 h in the patients, at 4 h, 17.3 % of lacosamide patients responded while the number increased to 78.8% by 48 h.

DISCUSSION:

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.[14-16] 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 reccomend a time duration of the status epilepticus of greater than one hour.[14] 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"). [15] 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.

Early abortion of the SE, achieved with the rapid treatment hike, can prevent the development of RSE. Despite poor outcome of RSE, in maximum number of the patients, there have been no randomized controlled trials as such. Majority of the experience comes from management with the coma-inducing drugs such as pentobarbital, midazolam and drug propofol. [17-18] In early Veteran Administrative Cooperative Study, patients who are refractory to the 1st line anti epileptic drugs (AEDs), had a cumulative response rate of approximately 7% to 2nd line agents and only 2% to that of the 3rd line agents.[19] Only 5% of SE patients do not respond to drugs like lorazepam and phenytoin, but showed response to phenobarbital administration.

Intravenous lacosamide in a dose of 200 mg appears to be safe dose safe in our study. 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. These patients were given IV LCM over 30, 15, and 10 min for 2-5 days. 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. 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.[20]

In another trial on safety and tolerability, with twenty five subjects, intravenous lacosamide was given in 3 increasing doses (200, 300, and 400 mg). Tolerance was optimal with intravenous doses of 200 and 300 mg given over 15 minutes; a high frequency of dose-related adverse events (sleepiness, nausea, dizziness and double vision) was seen with dose of 400 mg.[21]When comparing medication responses at 4, 12, 24, and 48 h in the patients, at 4 h, 17.3 % of lacosamide patients responded while the number increased to 78.8% by 48 h. This highlights that the response of lacosamide seems promising in those patients who have failed prior anticonvulsant.

In a small case series, RSE terminated after the administration of lacosamide in all 7 cases in the first 24 hours, while in a separate study RSE could be terminated after lacosamide in 17 patients, while 22 patients required further escalation of treatment.[22]

In the small, retrospective study, thirteen episodes of refractory status epilepticus were identified of which 5 (38 %) had cessation (average time of 11.2 h) of seizures after lacosamide and an additional 7 (54 %) had at least a 50 % reduction in seizures.[12] Miro et al, reported recurrence of seizures in 12 (35.29%) out of 34 patients with refractory status epilepticus. They needed further AED therapy or required anaesthesia. Sutter et al, conducted a study involving 111 adult RSE patients, in which intravenous lacosamide was evaluated, as an add-on treatment in RSE. Intravenous lacosamide was used in 53% of patients. Lacosamide use was associated with better seizure control, decreased need for coma induction and a decreased mortality. There were no serious, lacosamide-related adverse events. In contrast, Goodwin et al, reported a complete lack of response to lacosamide in 9 cases.[23]

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]. Early responses (occurring within 3 hr of initiation of LCM) were significantly more frequent in the 400 mg group [4/14 (28%) 57 vs. 0/11 (0%)]. Overall, 9/25 patients (36%) responded to LCM and seizures were terminated in eight more patients (32%), by adding other anticonvulsants. 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.[24]

Lacosamide has a favorable side effect profile with the most common side effects in clinical trials being drowsiness, nausea, headache, visual disturbance, and dizziness.[25] Many of these side effects can be tolerated in the critically ill. In addition to the favorable side effect profile, the low plasma protein binding and low drug–drug interaction of lacosamide make it an ideal antiepileptic for treating status epilepticus. The rarer side effects of PR prolongation (4.4–6.1 ms in the initial clinical trials), hypotension, transaminitis, and perhaps renal failure are of greater concern.[26]

CONCLUSION:

Lacosamide seems to be an ideal antiepileptic for use in the critically ill. It has qualities like it does not bind to any other binding sites of anticonvulsants or analgesics, has minimal adverse effects and protein binding and reaches maximum plasma concentration within 1–4 h after. In Our study number of patients was relatively small and further large RCTs are required to confirm above findings. Thus we can conclude saying that there is a need for a large, prospective study evaluating

lacosamide in status epilepticus and comparing the effectiveness to traditional antiepileptics, such as phenytoin.

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