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Comparison of lacosamide versus sodium valproate in status epilepticus: A pilot study

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ABSTRACT

Purpose: The purpose of this study was to compare the efficacy and safety of lacosamide (LCM) and sodium valproate (SVA) in lorazepam (LOR)-resistant SE.
Methods: Patients with LOR-resistant SE were randomized to intravenous LCM 400mg at the rate of 60 mg/kg/min or SVA 30 mg/kg at the rate of 100 mg/min. The SE severity score (STESS), duration of SE and its etiology, and MRI findings were noted. Primary outcome was seizure cessation for 1 h, and secondary outcomes were 24 h seizure remission, in-hospital death, and severe adverse events (SAE).
Results: Sixty-six patients were included, and their median age was 40 (range 18–90) years. Thirty-three patients each received LCM and SVA. Their demographic, clinical, STESS, etiology, and MRI findings were not significantly different. One-hour seizure remission was not significantly different between LCM and SVA groups (66.7% vs 69.7%; P = 0.79). Twenty-four-hour seizure freedom was insignificantly higher in SVA (20, 66.6%) compared with LCM group (15, 45.5%). Death (10 vs 12) and composite side effects (4 vs 6) were also not significantly different in LCM and SVA groups. LCM was associated with hypotension and bradycardia (1 patient), and SVA with liver dysfunction (6).
Conclusion: In patients with LOR-resistant SE, both LCM and SVA have comparable efficacy and safety.

1. Introduction

Status epilepticus (SE) is a life-threatening neurological emergency. About 60% patients with generalized convulsive SE (GCSE) are controlled by first-line antiepileptic drugs (AEDs) such as lorazepam (LOR), diazepam, or midazolam [1–3]. The remaining patients need additional AEDs. Phenytoin or phosphenytoin is used for controlling seizures as second-line AED [4,5].The other drugs such as sodium valproate (SVA) and levetiracetam have been used with some advantage [6–10]. The side effects of AEDs, especially cardiovascular and respiratory depression, are the limiting factors. These side effects necessitate the management of patients with SE in intensive care unit with facilities for mechanical ventilation and cardiac monitoring. In the developing countries, there is shortage of ICU beds and ventilators. It is therefore important to explore AEDs which are effective and at the same time have low respiratory and cardiovascular side effects. We have reported higher safety and efficacy of SVA compared with phenytoin [6]. In another study, patients with SE receiving levetiracetam required mechanical ventilation less frequently compared with LOR [7].

Intravenous formulation of lacosamide (LCM) has been available since 2009 and is bioequivalent to the oral formulation [11,12]. Lacosamide is a fractionalized amino acid, which acts by selective enhancement of slow sodium channel inactivation [13]. There is limited experience of LCM in SE. A meta-analysis based on 136 episodes of refractory SE revealed overall success rate of 56% (76/136) and adverse events in 25% [9,14]. Moreover, the available literature on the efficacy of LCM in SE is based on case series and retrospective case analysis. In this communication, we report our preliminary experience on the efficacy and safety of LCM and compare it with SVA as a second-line AED in the patients with LOR-resistant SE.

2. Subjects and methods

This is a single-center, investigator-initiated, randomized open-labeled trial carried out in a tertiary care teaching hospital in India. The protocol was duly approved by the Institute Ethics Committee (2013–110-IP-73). Legally authorized representatives of the patients gave informed consent.

2.1. Sample size calculation

The sample size was calculated using one-sided *Z* test of proportion keeping the type 1 error $\alpha = 0.05$ and type II error $\beta = 0.1$. A 20% difference in the response between the two study drugs was considered significant. Considering the efficacy of SVA as 65% [6], the sample size was calculated to be 116 in each arm with the power of 90%. During

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the study period, we could recruit 73 patients only; therefore, the study is being presented as a preliminary experience.

2.2. Inclusion criteria

Consecutive patients with convulsive SE or subtle convulsive SE during September 2013 to January 2016 were recruited. Convulsive SE was defined as 2 or more convulsive seizures without full recovery or continuous convulsions lasting for more than 5 min [15]. The patients were classified as subtle SE if coma and ictal discharges on electroencephalography (EEG) were associated with subtle convulsive movements [16].

2.3. Exclusion criteria

Patients with history of drug allergy, children (<18 years), pregnancy, nonconvulsive SE, primary renal or hepatic failure, malignancy, and those having received LCM or SVA were excluded.

2.4. Evaluation

A detailed history including demographic information, duration of SE, history of seizures in the past, fever, headache, vomiting and focal neurological deficit was inquired. History of head injury, stroke, delayed milestones, perinatal hypoxia, or any other medical illness was noted. Consciousness was assessed using the Glasgow Coma Scale (GCS). Status Epilepticus Severity Score (STESS) was administered, which included level of consciousness (stupor or coma = 1, alert = 0), seizure type (generalized = 1, nonconvulsive = 2, others = 0), age (<65 y = 0, ≥65 y = 1), and history of previous seizure (present = 0, absent or unknown = 1). STESS was categorized into favorable (0–2) or unfavorable (3–6) [17]. Presence of focal deficit (hemiplegia, quadriplegia, or monoplegia), cranial nerve palsy, tendon reflex, and plantar response was noted.

2.5. Investigations

Blood counts, hemoglobin, blood sugar, serum bilirubin, transaminase, creatinine, sodium, potassium, calcium, protein, and albumin were measured. Arterial blood gas analysis was also done. Electroencephalography was carried out 1 h after cessation of GCSE or to diagnose subtle SE. Cranial MRI or CT scan was done. Cerebrospinal fluid examination was done to diagnose central nervous system (CNS) infection. Chest radiograph and electrocardiogram were also done. The etiology of SE was categorized into acute CNS pathology, acute non-CNS pathology, chronic CNS pathology, congenital CNS pathology, and others [18].

2.6. Interventions

The patients received 4 mg lorazepam IV in 10 ml saline in 2–4 min, which was repeated after 10 min if seizures were not controlled. The patients who did not respond to second dose of lorazepam were randomized to SVA or LCM using computer-generated random numbers. Sodium valproate 30 mg/kg was administered intravenously at a rate of 100 mg/min. LCM 400 mg intravenously was administered at a rate of 60 mg/min. If the seizures were not controlled in 10 min, the patients were treated with midazolam, levetiracetam, phenytoin, propofol, or phenobarbitone at the discretion of treating physician. Heart rate, blood pressure, and oxygen saturation were monitored for at least 24 h or longer as indicated. The patients were given supportive treatment such as antibiotic for infection, acyclovir for herpes simplex encephalitis, artesunate for malaria, doxycycline or azithromycin for scrub typhus, and ampicillin for leptospira. Fever was treated by cold sponging and paracetamol. Fluid, calories and electrolytes were provided. The patients developing hypotension were treated with fluid challenge and vasopressors. The patients with respiratory failure and those with ABG evidence of hypoxia (PO_2 < 60 cm H_2O), hypercarbia (PCO_2 > 50 cm H_2O) or acidosis (pH < 7.3) were intubated and mechanically ventilated [19].

Adverse events such as hypotension; respiratory failure; heart block on ECG; and rise in serum transaminase, bilirubin, and creatinine were noted.

2.7. Outcome measures

The primary outcome was seizure cessation for 1 h after the infusion of study drug. In subtle convulsive SE, the seizure cessation was confirmed by EEG. Secondary outcomes were 24 h seizure freedom, hospital mortality and severe adverse events. The functional outcome at the time of discharge was evaluated using modified Rankin Scale (mRS) and categorized as good (mRS ≤ 2) or poor (mRS > 2).

2.8. Statistical analysis

The baseline characteristics between LCM and SVA groups were compared using independent *t* test for continuous variable and chi-square test for categorical variables. The primary outcome was compared between the two groups using chi-square test. The secondary outcome parameters were also tested using nonparametric tests. A variable was considered significant if 2-tailed *P* value was <0.05. The statistical analysis was done using SPSS version 16 software.

3. Results

During the study period, 126 patients with SE were admitted; 73 of whom were resistant to lorazepam and have been included in the present study. Seven patients were excluded because of kidney failure in 3, hepatic failure in 2, and psychogenic seizure in 2. The results are therefore based on 66 patients. The median age of the patients was 40(18–90) years, and20(31.3%)were females. The etiology of SE was CNS infection in 22 (33.3%), stroke in 16 (24.2%), metabolic disorders in 10 (15.2%), drug default in 1 (1.5%), and others in 17 (25.8%) patients. The patient with drug default SE was on phenytoin 300 mg for focal epilepsy. Cranial imaging was done in 63 patients and was abnormal in 34 (51.5%). The abnormalities included cerebral infarction in 10, hemorrhage in 3, venous infarct in 3, granuloma in 3, congenital anomalies in 3, meningeal enhancement in 4, and thalamic involvement in 3 patients.

The median duration of SE before the treatment was 2 (0.08–160) hours. Thirty-three patients each received LCM or SVA. There was no significant difference in the baseline clinical, laboratory and MRI findings between the two groups (Table 1). Mechanical ventilation was needed in 32 (48.5%) patients.

3.1. Outcome

Seizure cessation for 1 h was achieved in 44 (66.7%) patients; 21(63.6%) in LCM and 23 (69.7%) in SVA groups (P = 0.79). The time for SE cessation after starting study drug was not significantly different between LCM and SVA groups (8.13 ± 2.34 vs 7.52 + 2.64 min). Secondary endpoints were also not significantly different in the two groups. Twenty-four-hour seizure freedom was achieved in 15 (45.5%) in LCM and 20 (60.6%) in SVA group (P = 0.20). Twenty-two (33.3%) patients died in the hospital after a median duration of 4 (1–57) days; 10 (30.3%) in LCM and 12 (36.4%) in SVA group (P = 0.60). Death was attributed to SE in 1 patient only. In the remaining patients, the death was attributed to sepsis in 13 (61.9%) and brain herniation in 5 (23.8%) patients. The primary and secondary outcome measures are presented in Table 2.At the time of discharge, 18 patients in LCM and 15 in SVA group had good outcome (P = 0.46).

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