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Original Research

Risk Factors and Clinical Outcome Status Of Patients with Refractory Status Epilepticus undergoing Treatment with Lacosimide

Amit Sharma[1], Parampreet Singh[2], Manoj K Goyal[3], Vivek Lal[4]

[1]Senior Resident, [2,4]Professor, [3]Associate professor

Department of Neurology, Post Graduate Institute of Medical Education & Research, Chandigarh, India

***ABSTRACT*:**

Introduction: Neurologic emergencies such as status epilepticus (SE) and seizure cluster (SC) require urgent and consequent treatment with antiepileptic drugs (AEDs). Status epilepticus (SE) is the most severe manifestation of epilepsy, which requires intensive care. **Aim**: The purpose of this study was to evaluate the risk factors and clinical outcome of LCM in RSE patients in hospital setting. **Material and methods:** This retrospective analysis of patients with RSE was conducted 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). RSE was diagnosed if a first line (either lorazepam or diazepam) and a second line drug (either of the following: phenytoin or levetiracetam). Demographic information, history of epilepsy and precipitating causes, primary and secondary outcomes were also recorded and compared within the study groups. **Results**: When demographic profile of patients in two groups was compared, no significant difference was observed in parameters. Primary outcome of study was control of RSE within 30 minutes of start of infusion of the study drugs, which was seen in 16 (30.77%) patients. Various secondary outcomes were recurrence of SE within 24 hrs after control of seizures, need for ventilatory assistance, final neurological outcome at discharge as assessed by mRS and adverse drug reactions. Overall there were no differences in primary and secondary outcomes in the case and control groups. Thus, either of the drug combinations was equally effective in terms of all primary and secondary outcome measures. **Conclusion**: Although our observations are limited as its a retrospective design, and the short-term follow-up as well as the small cohort. Therefore further large studies and randomized control trials is needed to establish the therapeutic effect of IV LCM in treatment of RSE.

Key words: Lacosimide, Refractory Status Epilepticus.

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Corresponding author: Dr. Amit Sharma, Senior Resident, Department of Neurology, Post Graduate Institute of Medical Education & Research, Chandigarh, India

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INTRODUCTION:

Neurologic emergencies such as status epilepticus (SE) and seizure cluster (SC) require urgent and consequent treatment with antiepileptic drugs (AEDs). Status epilepticus (SE) is the most severe manifestation of epilepsy, which requires intensive care. Its incidence ranges from 15 to 20 per 100,000 per year.[1,2] Several treatment guidelines for SE suggest a four-step algorithm depending on the persistence of SE.[3-5] Briefly, benzodiazepines are recommended as first-line antiepileptic drugs (AEDs), followed by one further intravenous (i.v.) second-line AED if SE persists, such as phenytoin, valproic acid, a combination of both, or levetiracetam. For further ongoing seizure activity non-sedating third-line AEDs are often used, followed by anesthetic drugs to induce a deep coma titrated at least to burst-suppression or even flat-line electroencephalography (EEG).

Lacosamide (LCM) became recently available as an IV solution based on bioequivalence to the oral formulation.[6,7] LCM is a functionalized amino acid with anticonvulsant properties. It acts by enhancing the slow inactivation of sodium channels. LCM was effective in different rodent seizure models for generalized and complex partial seizures as well as for SE.[8,9] Recently, there have been single case reports as well as small case series that have evaluated the efficacy of LCM in patients with RSE. Although some of these case series yielded promising results, others found no benefit to the addition of LCM for RSE.[10-15]

The largest published data on use of LCM reported that the Efficacy was highest when used as either first, second or third line drug (57–60% seizure cessation)

but only 20% seizure cessation when used as fourth line or later. In addition, many patients with initial response to LCM required addition of subsequent AEDs.[16]
The purpose of this study was to evaluate the risk factors and clinical outcome of LCM in RSE patients in hospital setting.

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. 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. 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 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.

STATISTICAL ANALYSIS:

All the data was recorded and 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:

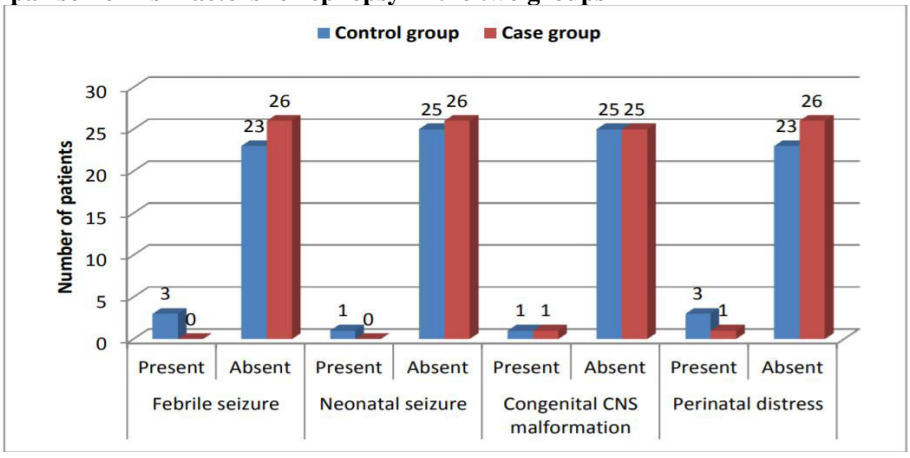
When demographic profile of patients in two groups was compared, no significant difference was observed in parameters like mean age of patients, gender, mean age of onset of seizure, mean period of seizure, past history of seizure, mean duration of status epilepticus and past history of status epilepticus.
Risk factors for epilepsy like febrile seizure, neonatal seizure, congenital CNS malformation and perinatal distress were compared in both the groups and the difference between the two groups was found to be not significant. (Table 1, graph 1

Table 1: Comparison of risk factors for epilepsy in the two groups

Risk factors for epilepsy		Control group (n=26) No. (%)	Case group (n=26) No. (%)	p-value
Febrile seizure	Present	3 (11.54)	0	.23*
	Absent	23 (88.46)	26 (100.00)	
Neonatal seizure	Present	1 (3.85)	0	1.00*
	Absent	25 (96.15)	26 (100.00)	
Congenital CNS malformation	Present	1 (3.85)	1 (3.85)	1.00*
	Absent	25 (96.15)	25 (96.15)	
Perintal distress	Present	3 (11.54)	1 (3.85)	.61*
	Absent	23 (88.46)	25 (96.15)	

*Not significant (p>0.05)

GRAPH 1: Comparison of risk factors for epilepsy in the two groups

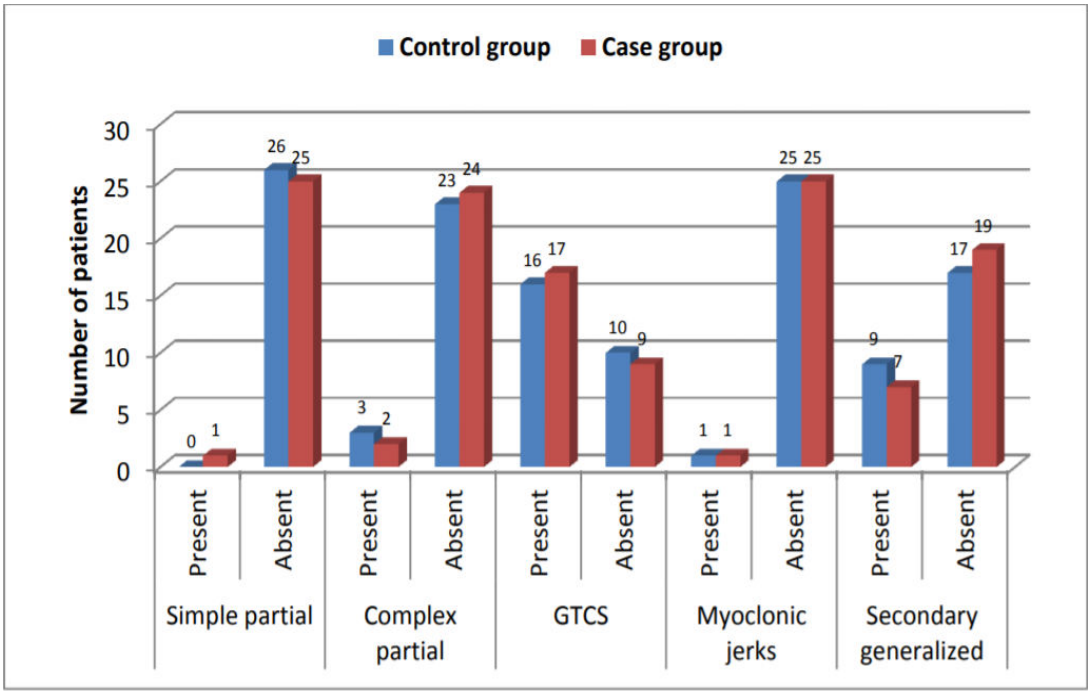


Type of seizures observed in the present study were simple partial, complex partial, GTCS, myoclonic jerks and secondary generalized. GTCS was observed in 33 (63.46%) patients, secondary generalized in 16 (30.77%), complex partial in 5 (9.62%), myoclonic jerks in 2 (3.85%) and simple partial in 1 (1.92%) patient. Five (9.62%) patients presented with multiple seizures. When respective seizures were compared in both the groups, the difference between the two groups was found to be not significant (Table 2, graph 2).

Table 2: Comparison of type of seizures in the two groups

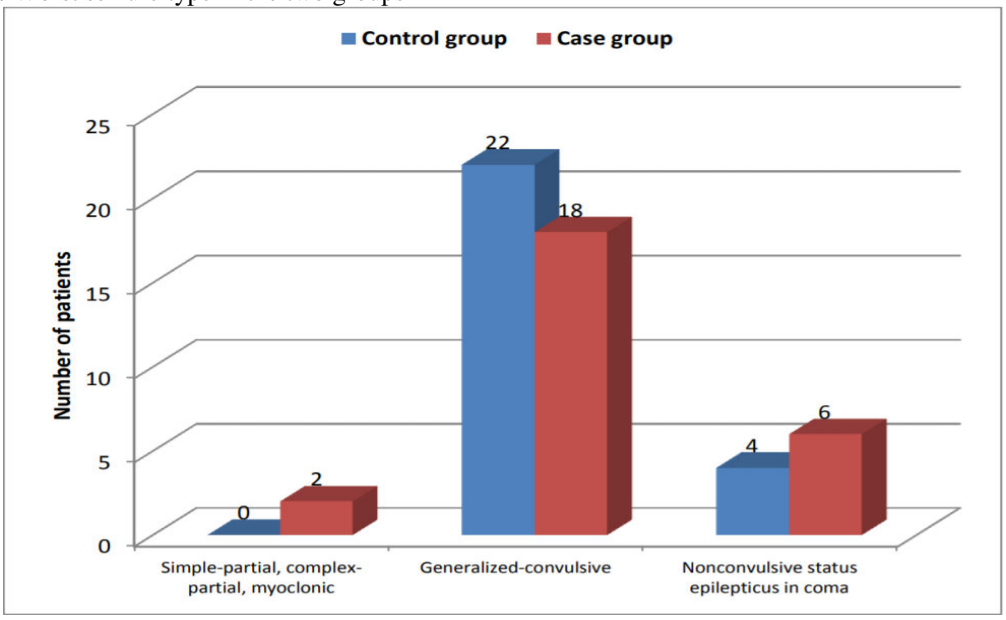
Type of seizure		Control group (n=26) No. (%)	Case group (n=26) No. (%)	p-value
Simple partial	Present	0	1 (3.85)	1.00*
	Absent	26 (100.00)	25 (96.15)	
Complex partial	Present	3 (11.54)	2 (7.69)	1.00*
	Absent	23 (88.46)	24 (92.31)	
Generalized tonic clonic seizure (GTCS)	Present	16 (61.54)	17 (65.38)	1.00*
	Absent	10 (38.46)	9 (34.62)	
Myoclonic jerks	Present	1 (3.85)	1 (3.85)	1.00*
	Absent	25 (96.15)	25 (96.15)	
Secondary generalized	Present	9 (34.62)	7 (26.92)	.76*
	Absent	17 (65.38)	19 (73.08)	

Graph 2: Comparison of type of seizures in the two groups



Under worst seizure type, generalized-convulsive was present in 40 (76.92%), nonconvulsive status epilepticus in coma in 10 (19.23%) and simple-partial/complex-partial/ myoclonic jerks in 2 (3.85%) patients. The difference in number of worst seizure type between the two groups was statistically not significant.(graph 3).

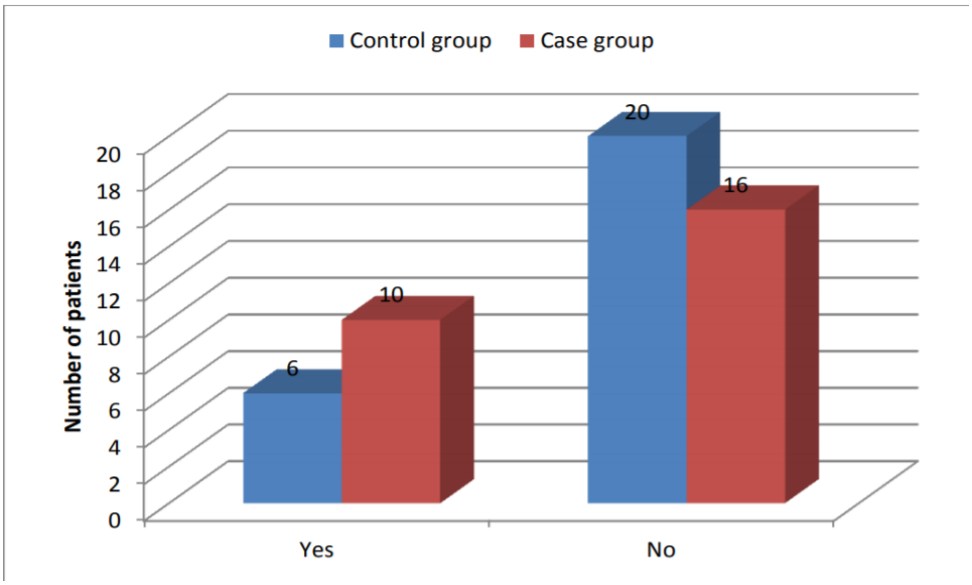
Graph 3: Worst seizure type in the two groups



Out of 52 patients in the study, 25 (48.08%) expired during the course of the study, while 27 (51.92%) recovered. Comparing the two groups with respect to the outcome of treatment, the study observed no significant difference between the two groups.

Primary outcome: Primary outcome measure in this study was control of RSE within 30 minutes of start of infusion of the study drug. Seizures were controlled in 16 (30.77%) patients, while 36 (69.23%) patients required additional treatment. Primary outcome measures were compared between the two study groups. 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. (graph 4)

Graph 4: Comparison of primary outcome measures in the two groups



Secondary outcome: Secondary outcomes analysed in current study were: (1) Recurrence of seizures within 24 hours; (2) need for ventilator assistance; (3) final neurological outcome at discharge, as assessed by mRS (modified Rankin Scale); and (4) adverse drug effects related to study drugs in question.

In the study group, 36 (69.23%) had a recurrence of seizures within 24 hours, 42 (80.77%) patients showed poor neurological outcome at discharge as determined by mRS (scale 4 or 5) and 40 (76.92%) required ventilatory assistance. None of patients in lacosamide group had adverse effects, while one female patient in phenytoin group developed hypotension, from which she recovered.

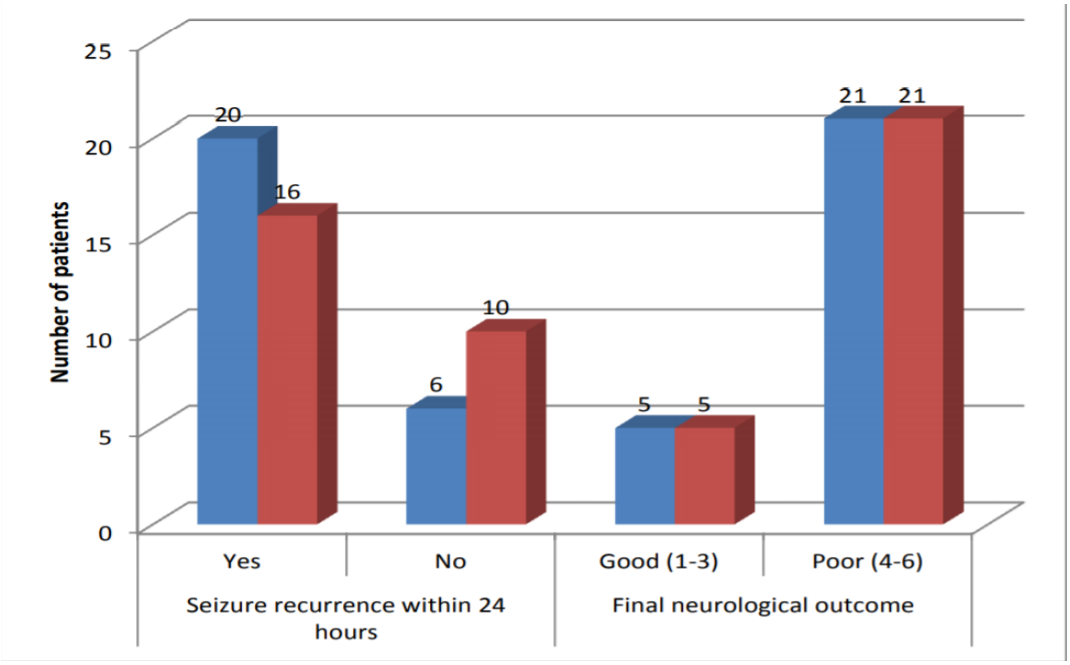
The rate of recurrence of seizures within 24 hours of control of RSE was compared between the two groups. Seizure recurrence was higher in phenytoin plus levetiracetam group (20, 76.92%) than in phenytoin or levetiracetam plus lacosamide group (16, 61.54%). However, there was no statistically significant difference between the two groups, indicating that both the drugs were equally effective, in preventing recurrence of seizures within 24 hours of control of RSE.

Similarly, final neurological outcome was compared between the two groups. Poor outcome was similar in both the groups (21, 80.77%). There was statistically no significant difference between the two groups. The results of the final neurological outcome indicate, that both lacosamide and phenytoin/levetiracetam, were associated with poor neurological outcome as determined by mRS scores, in patients of RSE. (table 3)

Table 3: Comparison of secondary outcome measures in the two groups

Secondary outcome measures		**Control group (n=26) No. (%)**	**Case group (n=26) No. (%)**	**p-value**
Seizure recurrence within 24 hours	Yes	20 (76.92)	16 (61.54)	.36*
	No	6 (23.08)	10 (38.46)	
Final neurological outcome	Good (1-3)	5 (19.23)	5 (19.23)	1.00*
	Poor (4-6)	21 (80.77)	21 (80.77)	

Graph 5: Comparison of secondary outcome measures in the two groups



DISCUSSION:

This prospective study was carried out on 52 patients of refractory status epilepticus (RSE). Among the patients with refractory status epilepticus, 33(63.46%) had primary generalized tonic clonic seizures, 16 (30.77%) had secondary GTCS, 5 (9.62%) complex partial, 2 (3.85%) myoclonic jerks and 1 (1.92%) had simple partial seizures.

Primary outcome measure in this study was control of RSE within 30 minutes of start of infusion of the study drug. Seizures were controlled in 16 (30.77%) patients, while 36 (69.23%) patients required additional treatment. Primary outcome measures were compared between the two study groups. 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 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. [17]

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.[18] However, Goodwin et al observed no evidence that lacosamide is effective in RSE in their small sample size of nine patients.[19]

Secondary outcome: Secondary outcomes analysed in current study were: (1) Recurrence of seizures within 24 hours; (2) need for ventilator assistance; (3) final neurological outcome at discharge as assessed by mRS (modified Rankin Scale); and (4) adverse drug effects related to study drugs in question. In the study group, 36 (69.23%) had a recurrence of seizures within 24 hours, 42 (80.77%) patients showed poor neurological outcome at discharge as determined by mRS (scale 4 or 5) and 40 (76.92%) required ventilatory assistance.

None of patients in lacosamide group had adverse effects, while one female patient in phenytoin group developed hypotension from which she recovered. The rate of recurrence of seizures within 24 hours of control of RSE was compared between the two groups. Seizure recurrence was higher in phenytoin/levetiracetam group (20, 76.92%) than in lacosamide group (16, 61.54%). However, there was statistically no significant difference between the two groups, indicating that both the drugs were equally effective in preventing recurrence of seizures within 24 hours of control of RSE.[20]

Similarly, final neurological outcome was compared between the two groups. Poor outcome was similar in both the groups (21, 80.77%). There was statistically no significant difference between the two groups. The results of the final neurological outcome indicate that both lacosamide and phenytoin/levetiracetam were associated with poor neurological outcome as determined by mRS scores in patients of RSE. 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. However, phenytoin was associated with relevant side effects that were not seen with lacosamide, which is similar to our study.[16]

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.[21] 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.[18] In contrast, Goodwin et al, reported a complete lack of response to lacosamide in 9 cases.[19]

Over all there were no differences in prmary and secondary outcomes in the case and control groups. Thus, either of the drug combinations was equally effective in terms of all primary and secondary outcome measures.

CONCLUSION:

Although our observations are limited as its a retrospective design, and the short-term follow-up as well as the small cohort. Therefore further large studies and randomized control trials is needed to establish the therapeutic effect of IV LCM in treatment of RSE.

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