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Efficacy of lacosamide in the treatment of non-convulsive seizure and non-convulsive status epilepticus in septic patients: a narrative review

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Abstract: Non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE) are of the acute complications of patients admitted to the intensive care unit (ICU), which lead to increased mortality and morbidity. In these cases, immediate treatment with antiepileptic drugs (AEDs) is important to prevent further damage to the brain. AEDs are the first line of treatment, however, most of these medications have many side effects. In the recent years, significant advances have been made in this area and lacosamide is one of the therapeutic options. The intravenous formulation of this drug is most popular due to the lack of drug-drug interaction and properly designed studies which have been conducted in this field. In this review, the latest findings on the effect of lacosamide on acute non-convulsive and generalized-convulsive seizures (G-CS) are evaluated in critically ill patients admitted to the ICU.

Keywords: Critically Ill, Intensive Care Unit, Lacosamide, Non-convulsive Seizures, Non-convulsive Status Epilepticus, Sepsis

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1. Introduction

One main reason for loss of consciousness and coma in a high percentage of patients admitted to the intensive care unit (ICU) is non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE) (1). These patients have adverse consequences and worse outcome with prolonged ICU stay and high treatment cost. Furthermore, the frequency of recurrent seizures is as high as 60% after discharge (2). These patients demand prompt adoption of therapeutic interventions, and if the treatment is not given early, there will be a severe reduction in the treatment efficiency. Another cause of seizures in patients admitted to the ICU is sepsis-related seizures, better known as sepsis-associated encephalopathy (SAE), which can affect more than 20% of acute septic patients. It occurs in both convulsive (focal or generalized) or NCS forms (3). In the absence of prompt treatment, the increase in mortality or morbidity may be seen (4). The administration of antiepileptic drugs (AEDs) is the cornerstone of treatment. In about 70% of patients, seizures are completely or almost completely controlled with medication, while the frequency and severity of seizures are significantly reduced in around 20-25% of patients (5). Despite the variety of AEDs, a high percentage of patients do not respond to these drugs and their seizures are not controlled effectively (6). Many AEDs have side effects and complications (7). Therefore, exploring for new drugs for the management of epilepsy is an inevitable necessity. Lacosamide (LCM) is a relatively new AED prescribed for partial onset seizures in adults and for the management of neuropathic pain in diabetic patients (8). This medication is approved by FDA and also prescribed for epileptic patients in the Europe. The mechanism of action of the drug is to inactivate sodium channels and consequently inhibit excessive firing of the nerves. Figure 1 represents a schematic presentation of LCM mechanism of action in affected neurons. It has far fewer side effects than other AEDs, as the occurrence of dizziness, headache, and nausea following the administration of LCM has been rarely reported (9). LCM has 100% oral bioavailability and reaches the maximal plasma concentration within 1-4 hours. Lacosamide is eliminated largely by the liver and to some extent by the kidneys and has a half-life of 13 hours in adults (10). In this review, we aimed to evaluate the latest findings on the effect of lacosamide on acute non-convulsive and generalized-convulsive seizures (G-CS) in critically ill patients admitted to the ICU.

2. Sepsis-related seizure pathophysiology

Following sepsis, the interaction between the infectious agent and the host immune responses leads to a cytokine storm and the release of proinflammatory cytokines. Subsequently, they affect the central nervous system (CNS) via N-methyl-D-aspartate (NMDA) and γ-aminobutyric acid (GABA) (11,12). Meanwhile, the interaction between proinflammatory and anti-inflammatory cytokines seems to play an important role in sepsis-related seizures (12). One of the underlying mechanisms of sepsis-related seizures is activation of the neuronal interleukin 1 receptor type 1 (IL-1R1) and phosphorylation of the NMDA receptor NR2B subunit. This is due to increasing the concentration of interleukin 1β (IL-1β) which leads to an increase in the concentration of calcium ions in the nerves (13). Another possible mechanism of sepsis-related seizures is an increase in extracellular glutamate concentration (12,14). In patients with sepsis-related seizures, it appears that there is an increase in the permeability of the blood-brain barrier (BBB) and consequent increase in seizure sensitivity.

3. Clinical consequences of sepsis-related seizures

The risk of seizure recurrence after discharge in a septic patient is 5 times higher than in the general population (15). Among these, inflammation of the brain, increased BBB permeability, impaired respiration and metabolism of brain cells, and increased cell apoptosis are among the pathophysiological mechanisms of long-term brain injury following seizures (16,17). Therefore, in patients admitted to the ICU, it is essential to diagnose seizures early, initiate effective treatment, and prevent long-term effects after discharge.

4. Treatment

A review of the literature demonstrates that management of seizure in septic patients admitted to the ICU has received less attention. As mentioned, proper and rapid management of seizures in these patients is vital. Among the treatment options, the rapid administration of benzodiazepines such as midazolam and lorazepam seems to be the first line of pharmacotherapy in such patients (18,19). These drugs act through increasing the activity of the GABA neurotransmitters. The effects of midazolam and lorazepam last for 1-6 hours and 8-12 hours after administration, respectively (20). However, these drugs cause depression, insomnia, and drop in blood pressure as side effects. For those patients who still seize despite receiving the first line of treatment and for prevention of seizure recurrence after discharge, the second line of treatment is recommended, including anticonvulsants with blockade of sodium channels (21). Phenytoin is one of the second-line AEDs with a relatively long-lasting effect of 24 hours after administration. Since this drug is not soluble in water, its hydrolyzed form, fosphenytoin, was introduced. Fosphenytoin needs conversion to its active form in the plasma. Drop in the blood pressure and irregular heartbeat are two important side effects of this drug, which itself can cause additional complication in septic patients who are usually hypotensive (22). Valproic acid is another drug used to treat seizures in septic patients. The underlying mechanism of action is via inhibition of voltage-gated ion channels as well as histone deacetylase (23). It rapidly enters the BBB and inhibits seizures at non-sedative concentrations. The profile of side effects includes tremor and coma (22). Another widely used AEDs in intensive care setting is levetiracetam. This drug has low protein binding properties (24). One recently introduced anti-epileptic medication which selectively reduces the activity of sodium channels and increases neuronal depolarization thresholds is lacosamide (25). This drug has been suggested as an alternative to fosphenytoin in NSCs (26).

5. Lacosamide chemistry

Lacosamide, or Vimpat®, the analog of D-serine amino acid, has amphiphilic properties with the ability to dissolve in water for rapid absorption from the intestine and high solubility in fat, to rapidly cross the BBB (27). Lacosamide has a high permeability and low plasma protein binding with a molecular weight of 250.3 g/mol (28).

6. Lacosamide pharmacokinetics and pharmacodynamics

Lacosamide is rapidly absorbed and peaks 4 to 5 hours after administration (29). Meal does not affect the absorption of this drug or the maximal plasma concentration (30). It seems that administering a loading dose of 200 mg and then 100 mg twice daily results in the constant concentration-time profile (31).

As mentioned, this drug has the ability to bind to a small amount of protein in healthy volunteers or patients. Therefore, this drug is dialyzable. The results of a study showed that half the concentration of lacosamide was cleared and removed during standard hemodialysis (32). The elimination of this drug is through renal removal of intact drug and also its metabolic breakdown. It is stated that about 40% of the drug is excreted by the kidneys in the form of intact drug. Decomposition of the drug includes demethylation, deacetylation and hydroxylation in the initial phase and glucuronidation in the second phase. Cytochrome P450 (CYP) enzymes are involved in drug breakdown (33,34). The underlying mechanism of action of lacosamide appears to be different from that of other anticonvulsant drugs. It is stated that LCM does not affect the targets of other anticonvulsant drugs and does not have a high affinity for receptors affected by AEDs (9). The action mechanism of this drug is thought to be related to sodium channel inactivation (35) and its reaction with collapsing-response mediator protein-2 (CRMP-2)

(36).

7. Therapeutic effects of lacosamide

7.1. Animal study

The maximal electroshock (MES) test, the hippocampal kindling test, and the 6-Hz psychomotor seizure model have been used to evaluate the therapeutic effects of this drug in seizure in animal models (37,38). LCM was found to be effective in the MES model of mice and rats (39,40). It was also found to be effective in reducing the frequency of seizures in rats in the hippocampal kindling test with ED50 of 13.5 mg/kg intraperitoneal (IP) injection (41). When the efficacy of this drug, at the dose of 25 mg/kg was compared with phenytoin, carbamazepine, and valporic acid in the seizure model of rat, this drug significantly reduced the frequency of seizures in rats compared to other drugs (39).

However, this drug has shown conflicting results in chemoconvulsant models. It was not effective against clonic seizures induced by subcutaneous injection of pentylenetetrazole. Notably, as an intravenous infusion, it increased the threshold for the first twitch and clonus in pentylenetetrazole induced seizure (41). While the drug was not effective against bicuculline or picrotoxin-induced seizures (27), LCM was able to reduce NMDA-induced seizures in mice and prevent death (41). The protective role of LMC at a dose of 100 mg/kg has been shown in the status epilepticus-induced rat model with direct application of cobalt to the frontal cortex and administration of homocysteine (41). In amygdala model in rats, LCM was effective at doses of 10 and 30 mg/kg.

7.2. Lacosamide in partial-onset seizures

The results of clinical trials indicated the effectiveness of LCM as an adjunctive treatment in patients with partial-onset seizures. In this trial, various doses of LCM, 200, 400 and 600 mg per day, were compared in the management of partial-onset seizures (42). The results of this study showed that LCM was not effective at the dose of 200 mg/day in creating a significant effect in some endpoints, but had the best retention rate. LCM at the dose of 600 mg/day had the lowest retention rate with similar efficiency to the dose of 400 mg/day. Therefore, the recommended dose of LCM for the management of partial-onset seizures is 400 mg/day, which is best tolerable and has the optimal efficiency.

7.3. LCM in the form of intravenous solution

Due to the high solubility of LCM, its intravenous (IV) solution form was developed. It contains 10 mg/L of isotonic solution which is stable at room temperature and resistant to light (43). In a trial conducted to evaluate tolerability of LCM and its possible adverse effects, no differences were observed between the oral and IV formulation of LCM at dose range of 200 to 600 mg/day in terms of adverse effects as well as pharmacokinetic parameters (44). In another trial (45), 15 minutes of bradycardia on the second day of injection was reported as the adverse event associated with IV LCM. However, the infusion on the first day of the drug was not reported to cause any adverse events. In 5% to 8% of patients, headache and dizziness were reported, while in 80% of these cases, it was not related to infusion. Therefore, intravenous LCM is considered safe and a therapeutic option for the management of seizure.

8. Lacosamide in treatment of NCSs

As mentioned, seizure is a common complication in critically ill patients admitted to the ICU. A high percentage of them are NCSs, which are detected by only electroencephalography (EEG) (46). A significant relationship exists between NCSs and increased mortality and the subsequent development of epilepsy (47). Until now, there is no standard and generally accepted treatment for NCSs. Nevertheless, there have been reports of the effectiveness of IV LCM in the management and controlling NCSs and NCSE in critically ill patients (46,48).

The Treatment of Recurrent Electrographic Nonconvulsive Seizures (TRENdS) trial was conducted to evaluate the efficacy of intravenous LCM (IV LCM bolus of 400mg) versus IV fosphenytoin (fPHT 20mg phenytoin equivalents (PE) / kg) as the gold standard for the treatment of NCSs. In this clinical trial, the primary endpoint was the cessation of electrographic NCSs on EEG. Two hours after administration of the intervention medications, patients were followed for six hours for the progression of seizure. The results of this trial demonstrated that the occurrence of seizure was halted in 63.3 % of patients receiving IV LCM and 50% in the fPHT arm. The authors of this trial concluded that LCM is non-inferior to fPHT for the management of NCSs (49).

CNS damage in sepsis, is called sepsis-associated encephalopathy, in which neuroinflammation, oxidative stress, and apoptosis play a very critical role. The protective role of LCM in preventing lipopolysaccharide (LPS)-induced neuroinflammation has recently been studied. Savran et al. (2019) studied the effect of LCM on LPS-induced inflammation in older rats (50). The results of their study suggested that LCM could reduce inflammatory cytokines, oxidative stress, lipid peroxidation of membranes, and the activity of caspase-3, exerting the anti-inflammatory, antioxidant, and apoptotic properties of LCM in the cortex and cerebellum.

Intravenous LCM was studied at loading doses of 200 and 400 mg in refractory seizure clusters and status epilepticus (51). They performed a prospective observational study in patients receiving doses of 200 and 400 mg IV LCM over a two-year period. The outcomes assessed in this study were response rate, response time, and the prevalence of adverse events. The results of their study showed a high response rate to 400 mg IV LCM. A total of 36% of patients responded to lacosamide and seizures resolved in 32% of them. Hence, a loading dose of 400 mg IV LCM was considered as the optimal dose for LCM loading.

One main cause of high mortality in septic patients admitted

Table 1 Recent studies on the administration of intravenous lacosamide in status epilepticus

Ref	Patient attributes	Seizure types	Dose	Time from IV LCM to SE cessation	LCM efficacy
(54)	age: (18-90) male: 46 % female: 54 %	Convulsive generalized, complex partial, simple focal	Mean: 328mg (200-600mg)	18% patient: 7.39h 26%: 10.39h	44%
(55)	age: (33-88) male: 96 % female: 14 %	Focal SE	400 mg	100% patients: <24h	100%
(56)	age: (47-89) male: 22 % female: 78 %	NCSE: 67% CSE: 33%	200mg-400mg	-	22%
(57)	age: (22-95) male: 55 % female: 45 %	NCSE: 32% CSE: 36% FSE: 32%	200-400mg	-	NCSE: 70% CSE: 91% FSE: 80%
(58)	age: (53-79) male: 0 % female:100 %	NCSE: 100%	50-100mg	15-120min mean: 71min	100%
(59)	age: (52-84) male: 33 % female: 67 %	NCSE: 80% EPC: 20%	100mg	-	20%
(60)	age: (52-84) male: 33 % female: 67 %	NCSE: 54% FMSE: 31% G-CSE: 15%	100-400mg	11.2h	38%
(61)	age: (16-90) male: 40 % female: 60 %	NCSE: 100%	200-300mg	-	70%
(62)	age: (70-84) male: 44 % female: 56 %	NCSE: 100% 400mg	45-60min	50%	
(63)	age: (52-80) male: 33 % female: 66 %	FMSE: 82% NCSE: 15% G-CSE: 3%	100-400mg	70% patients <12h	64.7%
(64)	age: (21-85) male: 60 % female: 40 %	FMSE: 55% NCSE: 32% G-CSE: 13%	200-600mg	20h	84.6%

LCM: Lacosamide; SE: Status epilepticus; NCSE: Non-convulsive status epilepticus; CSE: Convulsive status epilepticus; FSE: Focal status epilepticus; FMSE: Focal motor status epilepticus; EPC: Epilepsia partialis continua; G-CSE: Generalized convulsive status epilepticus

to ICU is status epilepticus (SE). Prompt treatment of these patients with first-line AEDs is achieved in only 50% of them, and most patients need treatment with second-line AEDs to terminate seizures. Infusion of LCM has been a promising choice in the treatment of SE. In an observational study by Moreno Morales et al. (2015), the efficacy of IV LCM was investigated in patients with convulsive versus non-convulsive status epilepticus (52). These patients received IV LCM treatment at a dose of 400 mg/day for 8 days and were evaluated for EEG response and seizure termination. In this study, 69.8% of patients were treated with IV LCM for convulsive (43.4%) and non-convulsive (56.6%) SE. The results showed an increase in paroxysmal activity in patients treated with IV LCM in EEG recordings in 56.6% of patients. The authors concluded that IV LCM has similar effects in convulsive or non-convulsive SE patients. IV infusion of LCM with its high safety profile and good tolerability is a suitable option in the management of SE. The efficacy of lacosamide injection in status epilepticus was assessed in a systematic review by Strzelczyk et al. (2017). They included 486 adults and 36 children and adolescents (53) in their study. The results showed that the efficacy of IV lacosamide is 57% in status epilepticus. Moreover, IV LMC injection was efficient 57% in non-convulsive, 61% in generalized-convulsive and overall effi-

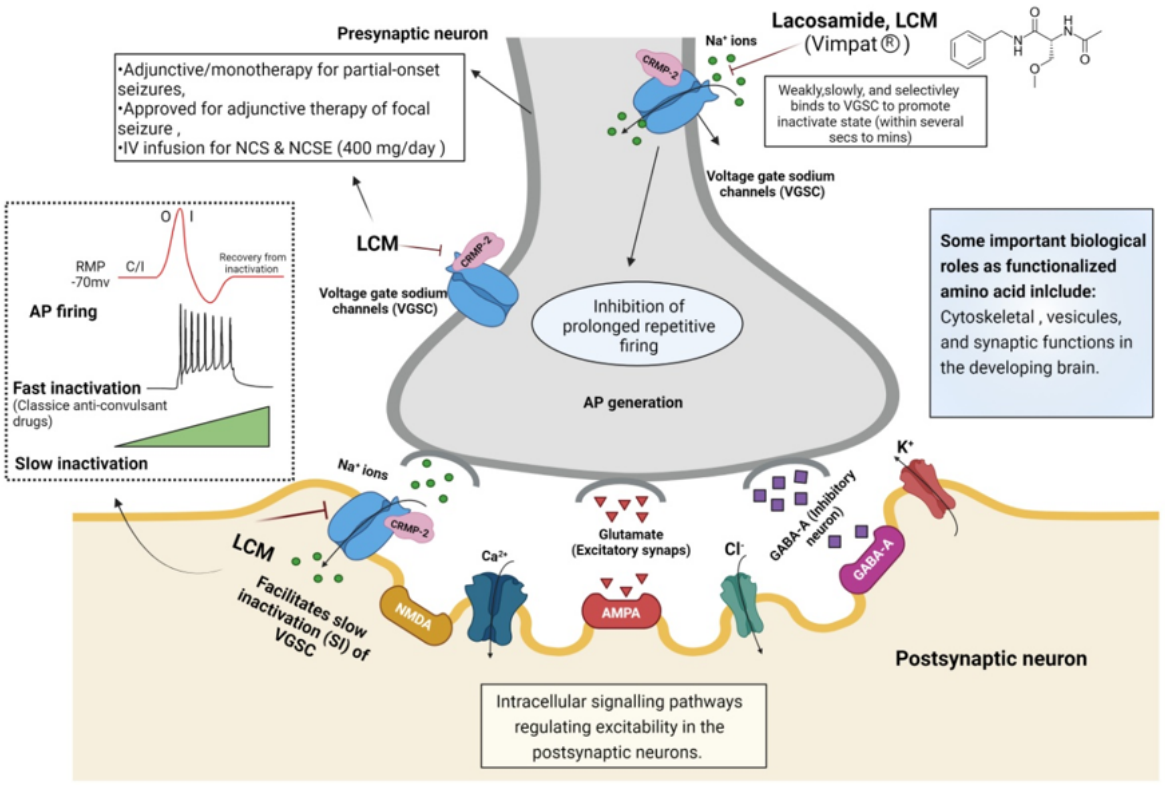

Figure 1 A schematic presentation of lacosamide (LCM) mechanism of action in affected neurons. This drug selectively promotes slow inactivation (SI) of voltage gate sodium channels (VGSCs), which play an important role to initiate action potential (AP), and also binds to collapsin response mediator protein-2 (CRMP-2) under the neuronal firing over a timescale of several seconds to minutes. AP is defined as a physiological process mediating signal provocation and synaptic transmission. During the neural resting membrane potential (RMP) (~ -70mV), VGSC is presented in the closed and inactivated (C/I) channels state. Under pathological conditions, the VGSC enters into the slow inactivated state during persistent AP firing when neurons are in a depolarized state with high-frequency firing. In this regard, LCM by enhancing VGSCs maintenance in SI state contributes to the reduction as well as blocking of AP firing process and consequently interrupts Na+ ions flow

ciency was reported as high as 92% in focal motor SE (FMSE). The most troublesome side effects were dizziness, abnormal vision, diplopia, and ataxia. However, the drug was tolerated well and do not follow a drug-drug response. They concluded that intravenous formulation of LCM can be used in emergency situations in critically ill patients with SE. The studies evaluating the efficacy of IV lacosamide in SE condition are summarized in table 1.

9. Conclusion

Intravenous infusion of lacosamide is a potential therapeutic option in the treatment of SE in acute patients admitted to the ICU. This medication has reduced mortality and morbidity. The high safety profile, promising efficacy, no drug-drug interaction and the intravenous formulation of lacosamide are main advantages of this anti-epileptic medication. Lacosamide can rapidly be administered in acute medical emergencies with promising effectiveness in reducing seizures in various clinical studies.

10. Declarations

10.1. Acknowledgment

None.

10.2. Authors' contribution

All the authors met the criteria for authorship in accordance with the recommendations of international committee of medical journal editors.

10.3. Conflict of interest

There is no conflict of interest with regard to the current study.

10.4. Funding

None declared.

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