Leveratiracetam in Status Epilepticus

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I. INTRODUCTION

Status Epilepticus is a medical emergency with significant morbidity and mortality. Refractory status epilepticus is a prolonged status epilepticus with a grave prognosis until treated timely and wisely. Various agents are used for Status Epilepticus but fewer studies are there for control of refractory status epilepticus. This review highlights the use of levetiracetam in refractory status epilepticus.

Refractory status epilepticus is defined as seizures which last longer than sixty minutes despite treatment with a benzodiazepine and an adequate loading dose of intra venous antiepileptic drug[(1)] It has high mortality (32-77%) and requires prompt management. Refractory status epilepticus is also associated with co-morbidities and multiple organ dysfunction in patients in intensive care unit (ICU). [(2)]

Refractory status epilepticus may cause irreversible brain injury [(3).] Currently recommended drugs are midazolam, pentobarbital and propofol but these drugs often necessitates ionotropic and ventilatory support. [(4)] There arises a need for much safer drug which are effective as intravenous agent and does not result in prolonged sedation and respiration compromise. Refractory status epilepticus is more prevelant in incidence than recurrent status epilepticus. Risk factors predisposing to refractory status epilepticus include delay in receiving treatment, infections of central nervous system, metabolic encephalopathy and hypoxia and much more[(5,6,7).] Encephalitis is a predictor for refractory status epilepticus, which is associated with markedly poor outcome, in particular, the development of post status epilepticus symptomatic epilepsy. [(8)] Pathophysiology of refractory status epilepticus includes failure of normal factors that serve to terminate a typical seizure and it is ϒ-amino butyric acid (GABA) receptor mediated inhibition. In addition, there is activation of N-methyl-D aspartate (NMDA) receptor by glutamate leading to propagation of seizure activity. In experimental models, resistance to both benzodiazepenes (BZP) and GABA leads to prolonged seizure. Continuous EEG monitoring is required in diagnosis and management especially in non convulsive status epilepticus and electrographic seizures.

To date, no randomised controlled trials are done for status epilepticus refractory to first and second line therapy. Most experience exists with continuous IV infusion of pentobarbital, Midazolam and propofol. [(9,10)] Traditional drugs like barbiturates such as pentobarbital or thiopental which are used to terminate status epilepticus has side effects like coma and EEG suppression. Propofol treated 21 episodes (67%) of refractory status epilepticus but reported to have 23% deaths. Propofol causes metabolic acidosis and cardiovascular collapse with prolonged used leading to death [(11)] called as propofol infusion syndromes. Intravenous Midazolam has failed in 14-18% of refractory status epilepticus [(12).]

First clinical trial for IV levetiracetam in status epilepticus was reported by moddelat et all [(13)]. In 2006, levetiracetam was approved as first newer anticonvulsant formulation for patients with epileptic seizure unable to take oral medication. IV Valproate has shown significant promise in this regard [(14)] and now IV levetiracetam is demonstrating similar promise. USA Food and Drug administration in 2006 approved IV formaulation of levetiracetam for instances in which oral medication cannot be used.

Lawrence J Hersch [(14)] has reported experience with use of IV levetiracetam for treatment of 18 episodes of benzodiazepine refractory focal status epilepticus and in 16 patients including 4 patients with secondary generalized status epilepticus. They noted no severe side effects and further suggested that IV levetiracetam may be an alternative for treatment of refractory status epilepticus in future even in patients that did not respond to benzodiazepines.

Initially IV levetiracetam was not approved for higher doses or for use in status epilepticus. However, studies showed that upto 2500 mg over 5 minutes and upto 4000 mg over 15 minutes could be administered safely to normal volunteers [(15).] Knake et all reported use of levetiracetam mean loading dose of 944 mg/d. there was no serious adverse effect and intubation was avoided in 17 out of 18 episodes. Efficacy was impressive with clinical seizure activity stopping in all patients. **Five** patients had failed IV valproate prior to receiving IV levetiracetam, only one had failed IV phenytoin first. All patients were discharged on oral levetiracetam with mean dose of 2000 mg/day [(16).] Limitation of the study, it was highly selective (i.e. those patients with hepatic failure and to avoid interaction with anticoagulant or chemotherapy). Nonetheless, Knake et all report is quite encouraging and provide justification for further prospective clinical trials.

Levetiracetam stops seizure activity mainly be desynchronizing neuronal network without affecting normal neuronal transmission thereby preventing burst firing. Levetiracetam binds to synaptic vesicle **protease** 2A, a regulator of vesicular traffic and prevent early changes in gene expression during kindling and modulates effect of calcium and GABA.

IV Levetiracetam is required mainly in critically ill patients who can not take the drug orally. Leveteracetam bio-availability is 95% ([16).] There are several studies that have found oral leveteracetam (via naso-gastric tube) to be effective in acute refractory seizures including **NCSE** [(17, 18, 19)]. Another study reported use of IV Levetiracetam in 50 critically ill patients including 24 with status epilepticus. Status epilepticus ceased in 2/3rd of cases at a mean dose of 1780 mg, typically given over 15-30 minutes and seizure ceasation was confirmed by EEG. 20

of 50 patients given IV Levetiracetam developed transient thrombocytopenia. No serious adverse effects were noted except agitation and infection which were more frequent in individuals on Levetiracetam than on placebo in clinical trials [20]. So this needs more comparative, prospective trials. Nonetheless IV Levetiracetam has many attractive features that will ensure its common use in the in patients settings including most by renal clearance, virtually no interaction, rare allergic reactions, minimal respiratory and cardiovascular effect with IV loading, broad spectrum and ease of use. No other IV medication for seizures shares these features. Lawrence Hirsch report provides justification for continued use of IV Levetiracetam for critically ill patients with seizures especially refractory status epilepticus.

P. Bhargava also reported IV leveteracetam use in refractory status epilepticus in 3 cases where IV leveteracetam has been successful in abating refractory status epilepticus [21].

Pastalas showed that leveteracetum has many favourable drug profile like no protein binging, no hepatic or renal metabolism, no autoinduction and no accumulation on multiple dosing. Successful oral leveteracetam use for refractory status epilepticus also been reported [22]. Ramel et all have demonstrated the safety and tolerability of IV Levetiracetum at doses higher than proposed [23].

II. Conclusion

Levetiracetum can be use to control status epitepticus and refractory status epilepticus effectively in ICU setting.Its use in NCSE has been showed in one pilot study.
While waiting for large, controlled studies, IV Levetiracetum might be an alteranative for treatment of refractory status epilepticus especially in elderly patients with vascular status epilepticus and concomitant medical conditions.

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