Ketamine use for super-refractory status epilepticus in children

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Ketamine is a potent N-methyl-D-aspartate (NMDA) receptor antagonist. It has been used for short anaesthesia and sedation since 1985, with good safety profile. However, ketamine is also well known for its abuse potential; it is especially popular in Asia, and is known as a post-clubbing drug.[1] Use of ketamine for controlling seizures was first reported in the 1990s.[2] Ketamine is now an emerging treatment option for status epilepticus (SE), particularly refractory SE (RSE), defined as ongoing seizures that have not responded one benzodiazepine and another antiepileptic drug, or super-refractory SE (SRSE), defined as SE that continues or recurs ≥24 hours after the onset of anaesthesia, including those cases in which SE recurs on the reduction or withdrawal of anaesthesia.[3] Midazolam, thiopentone/pentobarbital and/or propofol are commonly used anaesthetics in these conditions.[4] A recent review of ketamine use in RSE in 244 patients (adults and children) suggested an overall efficacy up to 73% to 74%. However, very heterogenous dosage have been used, ranging from 0.04 to 10 mg/kg/hour, which makes direct comparison among studies difficult. Higher efficacy has been noted in earlier use of ketamine, up to 64% when used in RSE <3 days versus 32% in RSE with mean duration of 26.5 days.[5]

We have reported our experience of using ketamine in children with SRSE in our hospital over a 7-year period.[6] Among 15 patients with de novo onset of SRSE, only three patients had received ketamine as the third anaesthetic ranging from day 7 to 15 of anaesthesia for 1 to 29 days. Exact efficacy of ketamine might also be difficult to elucidate, as there were often concomitant interventions, such as ketogenic diet and/or immunomodulatory therapies. In our report, its utility in SRSE and acceptance among intensivists is still variable.

Recent studies have suggested that with prolonged seizures, the number of activated γ-aminobutyric acid type A ($GABA_A$) receptors on the postsynaptic membrane gradually decreases while the number of inactive $GABA_A$ receptors increases.[7] This might explain the loss of efficacy of anticonvulsants in prolonged seizures that act on GABAergic system, such as benzodiazepines. This problem may be overcome by using higher doses of anticonvulsants with similar mechanisms, such as valproic acid, midazolam, or phenobarbitone. However, higher doses are also associated with more significant adverse effects. It was observed that while GABA receptors decreased, number and activities of NMDA receptors increased, perpetuating neuronal hyperexcitability. The utility of ketamine in this scenario becomes clear, as it works on an alternative mechanism. Animal studies support the efficacy of ketamine in stopping seizures in earlier stages of SE.[8] Early use of polytherapy and use of NMDA receptor antagonists such as ketamine have also been advocated.[9] Moreover, ketamine is also potentially neuroprotective, as documented in animal models.[10]

In children, midazolam and thiopentone are commonly used in RSE and SRSE. Propofol use is limited by concerns in increased risk of potentially fatal propofol infusion syndrome. Midazolam is associated with high recurrence rate and problem of tolerance, while thiopentone is associated with significant hypotension, respiratory depression, immunosuppression, and prolonged stay in intensive care unit. It also tends to accumulate in the body with long half-life.[3,4] In our unit, ketamine is frequently used as a third anaesthetic agent, usually after failure to stop anaesthetic agent, commonly after >1 week of anaesthesia use.

In addition to the advantages in mechanism of action, ketamine also causes less respiratory and cardiovascular depression. This is in contrast to the use of thiopentone which causes significant cardiovascular suppression. Ketamine has also been shown to shorten stay in intensive care unit for patients with acute worsening of RSE, such as in seizure clusters.[11] There is also a report of ketamine use in neonatal RSE.[12]

The lack of standard dosing is a potential barrier to ketamine use. Currently two ongoing clinical trials are studying the efficacy and safety of ketamine in RSE (NCT02431663 and NCT03115489), which will hopefully provide objective evidence. In one of the studies (NCT03115489) involving adults, the intervention includes a loading dose of 2.5 mg/kg, followed by continuous infusion starting from 3 mg/kg/hr with titration in 1 mg/kg/hr increments until burst suppression is achieved or a maximum dose of 10 mg/kg/hr is reached. After 48 hours of burst suppression the ketamine dosage will be reduced by 2 mg/kg/hr in a stepwise fashion to evaluate for electroencephalogram or clinical evidence of seizure recurrence.[13]

Although ketamine has a good safety profile,

it is associated with increased intracranial pressure, hypertension, and potential cerebellar toxicity. However, in recent studies on ketamine use in nontraumatic neurological diseases, no increase in intracranial pressure was reported.[14] Gaspard et al[15] noted only mild elevation of intracranial pressure in two out of 58 patients using ketamine in SRSE, but these two patients both had brain oedema secondary to hypoxic brain damage.

Other adverse effects of ketamine may include psychiatric symptoms like hallucinations, delirium, and blurred vision, but these are reportedly less common in children.[16] Concomitant use of midazolam may decrease the occurrence of these adverse effects.[17] The United States Food and Drug Administration has suggested against use of ketamine in severe hypertension and patients with allergy to ketamine. Ketamine should also be used with caution for patients with coronary heart disease, heart failure, glaucoma, atherosclerosis, pulmonary heart disease, pulmonary hypertension, severe intracranial hypertension, pregnancy, a history of mental illness, hyperthyroidism, tachyarrhythmia, adrenal pheochromocytoma, or alcoholism.[18] Despite its good safety profile, rare fatality has also been reported.[19] As long-term ketamine abuse is also associated with various urological, hepatobiliary, and other complications,[1] the maximum safe duration of ketamine use remains uncertain.

Despite the lack of robust evidence, ketamine is increasingly accepted and used in United States centres for SRSE, most commonly after pentobarbitone.[20] It is also increasingly included in SE treatment protocols/algorithms, which are still largely based on expert opinion.[4]

Ketamine is generally well tolerated and efficacious in children with SRSE. The potential of early use in RSE/SRSE makes ketamine an attractive alternative. Although ketamine has been included in algorithms for SRSE, its role and utility in controlling seizures remains to be defined.

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Analysis or interpretation of data: ELW Fung.
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Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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