

RESEARCH ARTICLE

Efficacy of Continuous High Dose Midazolam Infusion in Childhood Refractory Generalized Convulsive Status Epilepticus

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Abstract

Objective

Prolonged and uncontrolled refractory status epilepticus (SE) is a life-threatening medical emergency in children (1,2,3). There is no consensus on the optimal therapy for refractory status epilepticus (1). The aim of this study was to develop a new method for treating patients with refractory status epilepticus.

Materials & Methods

Ten children with refractory status epilepticus in Mofid Hospital, who did not respond to 10 µg/kg per min of intravenous midazolam, had their dose of midazolam increased to 30 µg/kg per min. All children were monitored for the development of side effects.

Results

Ten children with no response to low-dose midazolam were given a higher dose of midazolam, and 5 (50%) children had a good response. These patients had significantly different response to high-dose midazolam.

One patient in the high-dose midazolam group was intubated and required mechanical ventilation. The duration of stay in the hospital and PICU and on mechanical ventilation in patients with no response to low-dose midazolam following with other drugs was longer than in the high-dose midazolam group. No death occurred in high dose midazolam group.

Conclusion

High-midazolam dose drip infusion is a safe and effective protocol for refractory status epilepticus in children.

Keywords: Refractory status epilepticus; midazolam; mortality; childhood.

Introduction

Status epilepticus (SE) is a life-threatening medical emergency that consists of persistent or recurring seizures that require prompt intervention in children. Prolonged and uncontrolled refractory status epilepticus is associated with high mortality and morbidity, and its prognosis is dependent on the management of the underlying condition and on the treatment of seizures (1,2,3,4,5).

Care involves the termination of seizures and the identification and management of any underlying conditions.

There is no consensus on the optimal therapy for refractory status epilepticus, but there is increasing published experience with multiple medications and treatment strategies, such as high-dose phenobarbital ketamine, midazolam, thiopental, and

propofol (1). Midazolam has remarkable anticonvulsant activity, and several clinical reports have described the successful use of midazolam for refractory SE in children using different doses and methods (1,4-11). The mechanism of midazolam involves the modulation of GABA type A receptors, which suppresses neuronal excitability (12). The conventional midazolam dose in most studies and in Mofid Children Hospital is an initial bolus of 0.1-0.2 mg/kg, followed by an infusion of 1-2 µg/kg/min that is increased as needed to 7-10 µg/kg/min. In some studies, midazolam was increased as needed to 20-30 µg/kg/min (1, 4, 10). These studies suggest that a greater increase is associated with more prompt seizure control.

The aim of this study was to develop a new method for treating patients with refractory status epilepticus and investigate the efficacy and side effects of a high-dose (to 30 µg/kg/min) midazolam infusion in childhood refractory status epilepticus compared with low-dose midazolam.

Materials & Methods

This study included children with refractory status epilepticus who were admitted to Mofid Hospital, aged 1 month to less than 16 years, from October 2008 to May 2010.

In patients with status epilepticus, if seizures persisted despite treatment with adequate doses of 2 or 3 anticonvulsant medications, the condition was considered refractory status epilepticus.

All patients were transferred to the PICU, and midazolam was administered as an intravenous bolus dose (0.2 mg/kg), followed by low-dose continuous intravenous infusion (1-10 µg/kg per min). In 10 children with no response to 10 µg/kg per min of intravenous midazolam, the dose of midazolam was increased by 1 µg/kg per min every 15 min until complete control of seizures or up to 30 µg/kg per min.

All children were monitored for the development of side effects of midazolam, such as hypotension and respiratory depression. Routine laboratory examinations and EEGs were performed for all patients. Brain CT or MRI was performed if needed.

Clinical data, including age, sex, seizure history, underlying etiology, and outcome, were carefully

recorded for each patient.

We compared the 2 groups by independent sample t test, Fisher's exact test, or Mann-Whitney U test. A value of $P < 0.05$ was regarded as significant.

Results

Our refractory status epilepticus groups comprised 24 patients-11 boys and 13 girls (age range 7 months to 12 years). Fourteen patients had neurodevelopmental disabilities, and 15 cases had a background of symptomatic or cryptogenic epilepsy.

Low-dose intravenous midazolam was given to 24 patients. Eight (33, 3%) children had a good response to this dose of midazolam. Ten of 16 patients with no response to low-dose midazolam were treated with a higher dose of midazolam, and 6 patients were treated with other drugs, such as propofol and thiopental. In the high-dose midazolam group, 5 (50%) children had a good response. Patients with no response to low-dose midazolam had a significantly different response from those who were given high-dose midazolam ($P = 0/010$). In the high-dose group, of the 5 patients with no response to midazolam, 4 children's seizure were controlled by other anticonvulsant drugs.

During admission to the hospital, 1 patient in the high-dose midazolam group and 6 patients in the low-dose diazepam group (2 with good response and 4 who were treated with other medications, such as thiopental and propofol) were intubated and required mechanical ventilation ($P = 0/081$).

Fourteen children had symptomatic epilepsy (5 patients in the high-dose group), and 1 child in the high-dose group had cryptogenic epilepsy.

Bradycardia was seen in 1 child who was treated with high-dose midazolam, which resolved with a decrease in dose.

The duration of stay in the hospital and PICU and on mechanical ventilation in patients with no response to low-dose midazolam following with other drugs was longer than in the high-dose midazolam group ($P = NS$) (Table 1).

Five deaths occurred during treatment in patients with no response to low-dose midazolam that following with other medications, but it was difficult to judge the causal relationship between the mortalities and drugs. No

deaths occurred in the high-dose midazolam group. In the high-dose midazolam group, 6 patients were discharged with complete control of their seizures, and 4 patients had partial control.

Discussion

The safety and efficacy of midazolam have been demonstrated in several clinical studies for acute seizures and status epilepticus in adult and children (1,4-11).

In refractory status epilepticus, we found that if seizures failed to cease with continuous low-dose intravenous midazolam (10 µg/kg per/min), increasing the dose up to 30 µg/kg per/min was effective in half of the cases; further, this protocol is a safe method with a low side effect into other medications.

We recently showed that the adverse effects of high-dose midazolam do not exceed those of low-dose midazolam, nor do the duration of admission to the PICU and hospitalization and need for mechanical ventilation.

Early termination of status epilepticus is important in preventing adverse consequences and reducing the risk of developing brain sequels (1-4).

A high midazolam dose drip infusion is a safe and effective protocol for refractory status epilepticus and does not require specific specialty to administration such as propofol and thiopental.

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