IJMS
Vol 32, No 2, June 2007

Original Article

The Efficacy of Propofol and Midazolam in Treatment of Refractory Status Epilepticus in Children

F. Mahvelati, H. Tonekaboni, M. Javadzade[1], M. Ghofrani

Abstract

Background: In this study, we compared the efficacy and safety of propofol and midazolam in treatment of children's refractory status epilepticus.

Methods: We recruited 32 patients with refractory status epilepticus. Of those, 16 were treated primarily with midazolam and 16 received propofol.

Results: We achieved complete seizure control in 6 (38%) patients treated by midazolam, and in 10 (63%) of 16 patients receiving propofol. After drug withdrawal, seizure recurred in 2 of 6 children who had complete seizure control with midazolam and in 2 of 10 patients who were successfully treated with propofol. Overall treatment with propofol failed in 4 (25%) patients, while in the midazolam group, the failure was 50%. Complications in the midazolam group consisted of bradycardia which led to cardiac arrest in one patient who fortunately recovered following cardiopulmonary resuscitation, and rise in serum creatine phosphokinase in another. Untoward reactions seen in the propofol group included elevated serum creatine phosphokinase in 5 patients and dyslipidemia in another 5. Untoward reactions in children who received propofol consisted of rise in serum creatine phosphokinase in 5 and increase in serum triglyceride and cholesterol in 5 patients. No significant change was observed in the frequencies of apnea, hypotension, sepsis, electrolyte imbalance and median duration of stay in intensive care unit between the two treatment groups.

Conclusion: Propofol, if used appropriately, can quickly and effectively terminate episodes of refractory status epilepticus in children.

Iran J Med Sci 2007; 32(2): 74-79.

Keywords ● Status epilepticus ● midazolam ● propofol ● seizure ● epilepsy ● convulsion ● Child

Department of Child Neurology, Mofid Children's Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, Iran.
[1]Department Child Neurologist Zahedan University of Medical Sciences, Zahedan, Iran.

Correspondence:
Farhad Mahvelati MD,
Department of Child Neurology, Mofid Children's Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, Iran.
Tel: +98 912 109 9758
Fax: +98 21 2290559
Email: fmshamsa@yahoo.com

Introduction

Status epilepticus is a medical emergency which necessitates prompt and aggressive treatment [1]. Stabilization of airway, breathing, circulation and expeditious termination of seizures are immediate goals.[2,3] Intravenous administration of benzodiazepines, phenytoin and phenobarbital is the first line of treatment recommended for cessation of seizures.[4-6] In children, the mortality from status epilepticus

ranges from 3%–10%; the morbidity is twice as high.[7,8] The outcomes depend on the underlying etiology, patient's age, duration of status epilepticus and adequacy of treatment.[9-11]

The classical definition of refractory status epilepticus is a kind of seizure which does not cease in spite of sequential treatment with benzodiazepines, phenytoin and phenobarbital; the condition is also referred to a seizure continuing more than 60 min in spite of aggressive treatment.[2,12,13] Often, intravenous anesthetic agents must be administered and intense monitoring should be carried out in a Pediatric Intensive Care Unit (ICU) with a multidisciplinary approach.[14,15] New antiepileptic drugs have provided alternatives to traditional treatment paradigms for refractory status epilepticus.[16] A potent antiepileptic drug with a shorter duration of action and rapid elimination may thus result in reduced complications of the treatment.[17]

Propofol (2, 6, di-isopropylphenol) is an intravenous anesthetic agent with a short duration of action which has barbiturate- and benzodiazepine-like effects on the γ-amino butyric acid (GABA) receptors and thus, can suppress the central nervous system metabolic activities.[17,18] We conducted the present study to determine the effectiveness of propofol in treatment of refractory status epilepticus in children and compare it with midazolam.

Patients and Methods

Treatment protocol

In a clinical trial, 32 patients were admitted and treated for refractory status epilepticus in the Pediatric ICU of Mofid Children's Hospital, Tehran, Iran between January, 2000 and December, 2002. All patients were under the care of a child neurologist when refractory status epilepticus was diagnosed. Patients and their relatives were advised about the drugs and their side-effects and that propofol was used for treating refractory status epilepticus, but wasn't approved yet, and asked to give informed consent. Our patients were randomized to either the midazolam (n=16) or propofol (n=16) group. The treatment was not given blind. The study was reviewed and approved by the Research and Ethnics Committee of Shaheed Beheshti University of Medical Sciences.

Our criteria for refractory status epilepticus were 1) acute seizures persisting more than 60 min despite being treated with first-line antiepileptic drugs including intravenous diazepam, phenytoin and phenobarbital; and 2) seizures recurring at a rate of at least two times per hour without any recovery of the consciousness between attacks.

All patients included in this study had generalized tonic-clonic seizures and were admitted to the Pediatric ICU. Treatment of patients by conventional antiepileptic drugs consisted of the standard loading dose of 0.3 mg/kg diazepam, 20 mg/kg phenytoin and 10 mg/kg phenobarbital intravenously. Patients receiving other maintenance antiepileptic drugs, such as valproic acid and carbamazepine, continued their medications.

Sixteen of these children with refractory status epilepticus received midazolam and the other 16 were given propofol. Our goal was elimination of clinical seizures as quickly as possible while minimizing the possibility of significant drug side-effects such as hypotension. The suspected etiology of refractory status epilepticus was determined by all available clinical, radiologic or laboratory data including serum electrolytes, blood sugar, liver function tests, blood gas, serum amino acids, serum lactate and ammonia, brain CT scan, EEG and if necessary brain MRI.. We were vigilant to detect any hemodynamic compromise and infectious complications by close observing of patients and doing necessary laboratory studies including Complete Blood Count, ESR, C-reactive Protein and blood cultures.

Midazolam treatment protocol

Although the details of treatment were individualized, our general principle was to begin with a loading dose of 0.15 mg/kg midazolam intravenously. Then, a continuous infusion of midazolam was initiated at a rate of one μg/kg/min. If this could not control the seizure, the rate of infusion was increased every 15 min up to six μg/kg/min; if the seizure was not stopped with six μg/kg/min midazolam within two hours, the drug was discontinued and pentobarbital was started. However, if seizure was controlled, midazolam infusion was continued for another 24 hours and then tapered off over the next 24 hours. The rate of decrement was one μg/kg/min every two hours.[13,20]

Propofol treatment protocol

An initial bolus dose of one mg/kg propofol was administered over a five-min period. If cessation of clinical seizure activity was not evident after infusion of the first bolus, an additional one mg/kg bolus of propofol was administered. Maintenance infusion was started at two mg/kg/h and titrated up to eight mg/kg/h; if seizure was not controlled by this protocol within 40 min, the drug was discontinued and pentobarbital was started. However, if seizure control was achieved, we continued propofol infusion for 24 hours and then tapered it off over the next 24 hours. The rate of decrement was 5%

of the maintenance infusion rate.[13,20,21] A standard infusion pump controlled the drug delivery.

Cessation of seizure was defined as complete suppression of motor manifestations. Clinical seizure occurring during maintenance and 24 hours after withdrawal of the drug was considered "treatment failure." Vital signs including pulse rate, respiratory rate and blood pressure were measured during treatment. Occurrence of sepsis and other evidence of infectious process were under surveillance by close observing of patients and doing necessary laboratory studies including Complete Blood Count, ESR, C-reactive Protein and blood cultures.

Laboratory studies including arterial blood gas, serum creatine phosphokinase, triglycerides and cholesterol, lactic dehydrogenase, electrolytes and urinalysis were performed before and after the treatment.

Data analyses were performed using SPSS, ver. 10. *Student's t* test was used to compare means of age and duration of stay in the Pediatric ICU between the two treatment groups. Fisher's exact two was used to analyze contingency tables.

Results

Demographics

Sixteen (seven female, nine males) patients had a mean±SD age of 3.83±3.79 years and received midazolam. Another 16 (seven female, nine male) patients with a mean±SD age of 5.08±4.82 years were treated with propofol (p=0.42).

Initiation of treatment

Complete seizure control was achieved in six (38%) of 16 patients of the midazolam treated group and 10 (63%) of the 16 receiving propofol. After successful seizure control, following drug discontinuation, seizures recurred in two (33%) of six patients on midazolam and in two (20%) of 10 treated with propofol. Eight (50%) patients in the midazolam group and four (25%) in the propofol group did not respond to the treatment. The difference in response to treatment, though marked, was not statistically significant (p=0.28) (table 1).

Side-effects in the midazolam group consisted of bradycardia followed by cardiac arrest in one patient who was successfully resuscitated, and elevated serum creatine phosphokinase in another. Untoward reactions in children who received propofol consisted of rise in serum creatine phosphokinase (three to five times of normal ranges) in five (31%) and increase in serum triglyceride and cholesterol (two to three times of normal ranges) in five patients (31%). These elevations were significantly different in the two groups (p=0.04). The median duration of stay in the Pediatric ICU for the midazolam group was 5.37 (range: 2–11) days and for propofol treated group was 7.56 (range: 2–22) days (p=0.19). Also, the incidence of apnea and intubations were similar in both treatment groups (p=0.71) (table 2). The clinical characteristics of the patients, dosage of drugs and other information are given in tables 3 and 4.

Table 1: Clinical response to treatment in the midazolam and propofol groups

Response / Groups		Complete control	Recur after drug discontinuation	No response
Midazolam	No.	6	2	8
	(%)	37.5	12.5	50
Propofol	No.	10	2	4
	(%)	62.5	12.5	25
total	No.	16	4	12
	(%)	50	12.5	37.5

P=0.28 (Difference is not significant)

Table 2: Drug side effects in the midazolam and propofol groups

Complication / Groups		Apnea[1]	Bradycardia[2]	Hypotension	Acidosis	CPK rising[3]	Serum TG and cholesterol rising[4]
Midazolam	No.	9	1	0	0	1	0
	(%)	56.25	6.25	0	0	6.25	0
Propofol	No.	11	0	0	0	5	5
	(%)	68.75	0	0	0	31.25	31.25

1- p=0.71 (Difference is not significant)
2- p=1 (Difference is not significant)
3- p=0.17 (Difference is not significant)
4- p=0.04 (Difference is significant)

Table 3: Characteristics of the midazolam-treated group

number	Age (yr.)	sex	etiology	Neuroimaging	stay in ICU (days)	intubation	Midazolam (µg/kg/min)
1	4.5	female	encephalitis	NL	2	yes	1
2	0.5	male	congenital CMV	Calcification	9	yes	5
3	0.33	male	Symptomatic epilepsy	Atrophy	2	no	2
4	0.33	female	HIE	Atrophy	6	yes	3
5	0.41	female	congenital CMV	Microcephaly	3	no	3
6	6	male	PME	NL	2	no	2
7	2.5	female	Symptomatic epilepsy	atrophy	4	no	2
8	1.5	male	Symptomatic epilepsy	atrophy	6	yes	2
9	6	female	LGS	pachygyria	2	no	1
10	6	female	PME	PVL	11	yes	5
11	10	male	hydrocephaly	ventriculomegaly	2	no	1
12	0.16	male	HIE	NL	3	no	1
13	12	female	CP	NL	11	yes	5
14	1.1	female	encephalitis	diffuse hypodensity	5	yes	4
15	0.91	female	organic aciduria	atrophy	10	yes	4
16	9	male	NCL	atrophy	8	yes	5

LGS: Lennox-Gastaut syndrome, CP: cerebral palsy, PME: progressive myoclonus epilepsy, NCL: neuronal ceroid lipofuscinosis, NL: normal, HIE: hypoxic ischemic encephalopathy, PVL: periventricular leukomalacia, CMV: cytomegalovirus, CPK: Creatin phosphokinase, **±**: recurrence after drug withdrawal

Table 4: Characteristics of the propofol-treated group

number	Age (yr.)	sex	etiology	Neuroimaging	stay in ICU (days)	intubation	Propofol (mg/kg/h)
1	9	male	LGS	NL	16	yes	7
2	0.75	male	encephalitis	encephalomalacia	6	no	2
3	6.5	female	Symptomatic epilepsy	cerebellar hypoplasia	4	yes	6
4	0.16	female	Symptomatic epilepsy	migrational anomaly	4	yes	6
5	13	female	Idiopathic epi-lepsy	NL	2	no	2
6	7	male	CP	brain edema	6	yes	2
7	11	female	PME	NL	9	yes	3
8	0.33	female	Leiner Syn.	atrophy	4	yes	2
9	0.75	female	organic aciduria	atrophy	4	yes	2
10	0.58	female	organic aciduria	atrophy	5	no	4
11	0.33	male	Symptomatic epilepsy	atrophy	2	no	6
12	1.25	male	Idiopathic epi-lepsy	NL	7	no	6
13	8.5	female	Idiopathic epi-lepsy	NL	8	yes	2
14	0.5	male	meningitis	atrophy	22	yes	6
15	9	male	NCL	atrophy	4	yes	6
16	13	female	CRF	brain edema	18	yes	6

LGS: Lennox-Gastaut syndrome, CP: cerebral palsy, ME: progressive myoclonus epilepsy, NCL: neuronal ceroid lipofuscinosis, NL: normal, CRF: chronic renal failure, CPK: Creatin phosphokinase, TG: Triglycerides, **±**: recurrence after drug withdrawal

Discussion

Status epilepticus is a serious life-threatening emergency characterized by prolonged seizure activity. The prognosis of status epilepticus, most importantly, depends on its etiology; however, duration of convulsions is also important. Early termination of seizures is critical for recovery.[19] Refractory status epilepticus is defined as status epilepticus that fails to respond to first-line therapies.

Treatment for refractory status epilepticus is difficult, usually requiring intensive support of vital functions. Three agents—pentobarbital, midazolam and propofol—have emerged as treatments of choice for refractory status epilepticus, but success rates vary.[20] Propofol is a rapidly-acting, highly lipid-soluble anesthetic agent currently used in induction of general anesthesia.[21]

Stecker, *et al*, compared propofol with high dose barbiturates in the treatment of refractory status epilepticus in 16 adult patients and found that propofol can control refractory status epilepticus much more quickly than high dose barbiturates.[17] Prasad, *et al*, compared 14 adult patients treated primarily with propofol and six with midazolam. In their study, propofol

and midazolam showed no differences in clinical and electrographic seizure control.[20] Claassen, *et al*, performed a literature search of studies published between January 1970 and September 2001, describing the use of midazolam, propofol or pentobarbital for the treatment of refractory status epilepticus. The results suggested that treatment with new continuous infusion antiepileptic drugs may be more effective than other strategies used for treating refractory status epilepticus.[21] To the best of our knowledge, the present study included the largest number of patients suffering from refractory status epilepticus in the pediatric age group.

In the present study, we reported 32 patients suffering from refractory status epilepticus who, in two separate groups of 16, received propofol and midazolam. The results of our investigation revealed that a higher number of propofol-treated patients had complete seizure control as compared to the midazolam group. Our results were in agreement with those obtained by Prasad, *et al*, and Van Gestel, et al.[20,22]

There were no significant differences between the two drugs as far as complications were concerned except serum creatine phosphokinase, triglyceride and cholesterol elevations that became higher in the propofol-treated group; nevertheless, the rise had no clinical significance. An increased mortality rate in high dose, long-term treatment with propofol was published recently.[23,24,25] Propofol infusion syndrome is a rare and often fatal condition seen in patients after a high dose or long-term infusion of propofol.[26,27] We had no sepsis, metabolic acidosis, rhabdomyolysis or acute renal failure due to propofol use, contrary to the findings reported earlier.[27-29] This may be due to short-term infusion of low dose propofol in our study (maximum 36 hours). There was no mortality in our patients.

Our study has nonetheless, some limitations. This study was limited by small numbers of cases. Moreover, in view of the lack of electroencephalographic (EEG) monitoring in our Pediatric ICU, we evaluated the efficacy of midazolam and propofol based upon clinical judgments and cessation of seizure. Literature searches showed that higher doses of propofol than we used were necessary to achieve EEG burst-suppression pattern.[12,16,17] Subsequently, it appears that the reason why we had no significant side effects was probably due to the lower doses of propofol used here as compared to those used in other studies.

We believe that propofol, if administered at proper doses for short durations, can control refractory status epilepticus without any significant side-effects and can therefore be a superior or an alternative drug for patients who showed no response to other drugs.

Further multi-institutional randomized clinical trials on more children suffering from refractory status epilepticus by EEG monitoring, are needed to evaluate the safety, efficacy and untoward reactions originating from propofol therapy in the management of refractory status epilepticus.

Acknowledgments

The authors are indebted to Mrs. Nilufir Shiva for her critical editing and assistance in the preparation of this manuscript.

References

1 Bleck TP. Management approaches to prolonged seizures and status epilepticus. *Epilepsia* 1999; 40: S59-63.
2 Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med* 1998; 338: 970-6.
3 Misra S, Singh NN. Management of status epilepticus. *J Indian Med Assoc* 2002; 100: 299-303.
4 Ramsay RE. Treatment of status epilepticus. *Epilepsia* 1993; 34: S71-81.
5 Roberts MR, Eng-Bourquin J. Status epilepticus in children. *Emerg Med Clin North Am* 1995; 13: 489-507.
6 Shorvon S. Status epilepticus-Its clinical features and treatment in children and adults. Cambridge, Cambridge University Press; 1994.
7 Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. *Epilepsia* 1994; 35: 27-34.
8 Sahin M, Menache CC, Holmes GL, Riviello JJ. Outcome of sever refractory status epilepticus in children. *Epilepsia* 2001; 42: 1461-7.
9 Rosenow F, Arzimanoglou A, Baulac M. Recent development in treatment of status epilepticus: a review. *Epileptic disord* 2002; 4: S41-51.
10 DeLorenzo RJ, Towne AR, Pellock JM, Ko D. Status epilepticus in children, adults, and elderly. *Epilepsia* 1992; 33: S15-25.
11 Walsh GO, Delgado-Escueta AV. Status epilepticus. *Neurol Clin* 1993; 11: 835-56.
12 Gregory L Holmes, James J, Riviello Jr. Consequence and treatment of refractory status epilepticus. *International Pediatrics* 1999; 14: 208-12.
13 Hanhan U, Fiallos M, Orlowski J. Status epilepticus. *Pediatr Clin North Am* 48: 683-94.
14 Singhi S, Singhi P, Dass R. Status epilep-

ticus: emergency management. *Indian J Pediatr* 2003; 70: S17-22.
15 Pourrat X, Serekian JM, Antier D, Grassin J. Generalized tonic-. clonic status epilepticus: therapeutic. strategy. *Presse Med* 2001; 30: 1031–6.
16 Hirsch LJ, Claassen J. The current state of treatment of status epilepticus. *Curr Neurol Neurosci Rep* 2002; 2: 345-56.
17 Stecker MM, Kramer TH, Raps EC, et al. Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. *Epilepsia* 1998; 39: 18-26.
18 Fragen RJ. Diprivan (Propofol) A historical perspective. *Semin Anesthesia* 1988; 7: 1.
19 Kuisma M, Roine RO. Propofol in prehospital treatment of convulsive status epilepticus. *Epilepsia* 1995; 36: 1241-3.
20 Prasad A, Worrall BB, Bertram EH, Bleck TP. Propofol and midazolam in the treatment of refractory status epilepticus. *Epilepsia* 2001; 42: 380-6.
21 Claassen J, Hirsch LJ, Emerson RG, et al. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2002; 43: 146-53.
22 Van Gestel JPJ, Blussé van Oud-Alblas HJ, Malingré M, et al. Propofol and thiopental for refractory status epilepticus in children. *Neurology* 2005; 65: 506-7.
23 Eriksen J, Povey HM. A case of suspected non-neurosurgical adult fatal propofol infusion syndrome. *Acta Anaesthesiol Scand* 2006; 50: 117-9.
24 Kumar MA, Urrutia VC, Thomas CE, et al. The syndrome of irreversible acidosis after prolonged propofol infusion. *Neurocrit Care* 2005; 3: 257-9.
25 Liolios A, Guérit JM, Scholtes JL, et al. Propofol infusion syndrome associated with short-term large-dose infusion during surgical anesthesia in an adult. *Anesth Analg* 2005; 100: 1804-6.
26 Hansen TG. Propofol infusion syndrome in children. *Ugeskr Laeger* 2005; 167: 3672-5.
27 Niermeijer JM, Uiterwaal CS, Van Donselaar CA. Propofol in status epilepticus: little evidence, many dangers? *J Neurol* 2003; 250: 1237-40.
28 Hanna JP, Ramundo ML. Rhabdomyolysis and hypoxia associated with prolonged propofol infusion in children. *Neurology* 1998; 50: 301-3.
29 Bray RJ. The propofol infusion syndrome in infants and children: can we predict the risk? *Curr Opin Anaesthesiol* 2002; 15: 339-42.