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Original Article

Intranasal versus intravenous midazolam in control of generalized tonic–clonic seizures in children

M Veerendra Kumar[1], K V Sumi[2]

From Departments of Pediatrics, [1]Government Medical College, Kollam, [2]Government Medical College, Kottayam, Kerala, India

Correspondence to: M Veerendra Kumar, Lekshminivas, Shasthamkavu, Karapuzha, Kottayam - 686 003, Kerala, India. Phone: +91-9447959077. E-mail: vkumarbabu@gmail.com

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ABSTRACT

Background: Seizures are very common in pediatric patients. As the duration of seizures impacts morbidity and mortality to child's life, control of seizures should be achieved as early as possible, preferably at home. Intranasal (IN) midazolam is a simple method for control of seizures and can be administered by the parents. **Objectives:** To study the effectiveness of IN versus intravenous (IV) midazolam in control of generalized tonic–clonic seizures in children between 2 months and 12 years. **Materials and Methods:** We assessed the efficacy of IN midazolam in comparison with the same drug given by IV route. Neonates, children having partial seizures, and children who got prior medication for the present seizure and seizures that settled spontaneously were excluded from the study. 100 children were enrolled with 50 in each group. The two groups were analyzed for the time taken to control seizures from the time of drug administration. The number of treatment failures, recurrences, and treatment failure of recurrence were noted and compared. **Results:** The mean time for seizure control, treatment failures, number of recurrences, and treatment failure of recurrences were similar in both groups statistically. **Conclusion:** IN midazolam and IV midazolam are comparable in efficacy, however, IN midazolam is an easy route of drug delivery to control seizures.

Key words: *Benzodiazepines, Intranasal route, Midazolam, Seizures*

Seizures in children are a frightening experience for families and care providers. Because the duration of seizure activity impacts on morbidity and mortality, effective methods for its control should be instituted as soon as possible, preferably before arrival at hospital. Approximately, 4-10% of the children experience at least one seizure in the first 16 years of life. The cumulative lifetime incidence of epilepsy is 3%, and more than half of the cases start in childhood. The annual prevalence is 0.5-1% [1]. Febrile seizures are the most common type of seizures in childhood, with an incidence of 3-4% [1].

The rapidity by which medication can be delivered to the systemic circulation and then to the brain plays a significant role in reducing the time needed to control seizures and to reduce opportunity for damage to the central nervous system. Speed and ease of delivery, particularly outside the hospital, is enhanced when transmucosal routes of delivery are used in place of an intravenous (IV) injection [2].

The emergency medicine is striving to improve the seizure management by improving the drug delivery techniques to reduce the time of seizure control. Rectal diazepam emerged first in this context. However, it is not as effective as IV diazepam in seizure control. Rectally administered diazepam results in variable plasma concentrations and fails to terminate 30% of the seizures. The tendency for diazepam to accumulate in adipose tissue when given in repeated doses can cause respiratory depression. Other disadvantage is the lower social acceptability of the rectal route.

Buccal and intranasal (IN) midazolam are preferable alternatives in the community setting. However, buccal administration has been found to provoke gagging, coughing, aspiration, and delivery is difficult when the teeth are clenched during a tonic–clonic seizure. IN midazolam, given as a sedative agent, has been shown to be safe and effective in children undergoing various diagnostic studies and minor surgical procedures [3]. IN midazolam also suppresses the seizure activity and improves the background electroencephalogram (EEG) in children with epilepsy [4,5].

MATERIALS AND METHODS

This study was conducted at the Department of Pediatrics in a tertiary care teaching hospital in South India. This prospective, randomized controlled interventional study was conducted after getting approval from the Institutional Ethics Committee. Objectives of the study were (1) to study IN versus IV midazolam to control generalized tonic–clonic seizures (GTCS) in children between 2 months and 12 years, (2) to compare the incidence of seizure recurrence after IN and IV midazolam, and (3) to compare the efficacy of both routes in control of recurrent seizures. Neonates, children having partial seizures, children who got

prior medication for the present seizure and seizures that settled spontaneously were excluded from the study. The sample size was calculated as 100, 50 in each group by applying n Master 1.0, using the data from a previous study [6].

Before starting the treatment, informed written consent was obtained from parents. In case of refusal, a complete care was provided following the routine protocols of the hospital. A total of 100 children were recruited for the study. All the patients were stabilized initially for airway, breathing, and circulation. Enrolled even number children were given IV midazolam, and odd number children were given commercially available preparation of IN midazolam as atomizer (0.5 mg/puff) as per recommended methods [4]. Dose was 0.2 mg/kg body weight, in both the routes [1,4]. Drugs were administered, and responses were monitored by the resident.

Time of the onset of seizure was noted in history. Time of seizure control after each drug was precisely calculated using electronic stopwatch, deducting drug administration time. Patients were monitored for the cessation of seizures, heart rate, respiratory rate, SpO_2, and adverse effects of drugs. Treatment was considered successful if the seizures ceased within 10 min. Seizure that did not stop after this time was defined as treatment failure and other treatment was given as per the protocol of international league against epilepsy.

The time from the onset to seizure control and from drug administration to seizure control, as well as, treatment failures were taken for analysis. Seizures that were controlled by the drugs but recurred within 60 min were defined as recurrent seizures [7]. Recurrence was treated in the same initial line, but any further recurrence was treated with other medications and was taken as treatment failure of the recurrence. After initial control of seizures, all patients were investigated and further managed according to the diagnosis. The data recorded was tabulated and statistically analyzed by SPSS17 for the independent t-test and MINITAB16 for the proportion tests.

RESULTS

Children who received IN midazolam were included in Group 1 and who received IV midazolam in Group 2 with 50 participants in each group. Both groups were statistically identical in gender, etiology, long-term seizure medications, and age distribution. Etiology of seizures was seizure disorders (53%), febrile seizures (36%), ketotic hypoglycemia (3%), and others (8%) which included 2 cases of meningitis, 2 cases of brain tumor, one case of acute disseminated encephalomyelitis, and one case of diarrhea with hypocalcemia. Table 1 compares the two groups in 2 parameters, time from seizure onset to seizure control and time of drug administration to seizure control. The duration of seizures (from onset to seizure control) ranged from 2 to 35 min in IN group and 2 min to 30 min in IV group with a mean of 8.54 and 7.98, respectively (p=0.330). Table 2 compares the two groups in three parameters such as treatment failure, recurrences, and treatment failure of recurrences. On comparing the treatment failures in both groups, no significant difference was found (p=0.0137) suggesting that both routes were equally effective. Recurrences and treatment failure of recurrences were also similar in both groups.

Table 1: Group statistics

Variable	Study group	Numbers	Mean±standard deviation (minutes)
Time of seizure control from onset	Group 1 (IN)	50	8.5400±6.86966
	Group 2 (IV)	50	7.9800±5.75872
			p=0.330
Time of seizure control from drug administration*	Group 1 (IN)	50	3.7684±1.4722
	Group 2 (IV)	50	2.9428±0.9811
			p<0.05

*Excluding administration time. IN: Intranasal, IV: Intravenous

Table 2: Group statistics

Variable	Group*	Number	Total number children	Proportion of failure
Treatment failure	Group 1	4	50	0.08
	Group 2	9	50	0.18
				p=0.1371
Recurrence of seizure	Group 1	6	50	0.12
	Group 2	9	50	0.18
				p=0.401
Treatment failure of recurrence	Group 1	2	50	0.04
	Group 2	2	50	0.04
				p=1.0

*Group 1 - IN and Group 2 - IV midazolam. IN: Intranasal, IV: Intravenous

DISCUSSION

We conducted this study as most of the previous studies compared IN midazolam with IV or rectal diazepam, and there were only very few studies comparing IN and IV midazolam in childhood seizures. Our study suggests that IN midazolam is an effective and easy alternative to IV midazolam. In our study, there was no significant difference in the duration of seizures (from onset to seizure control) between the two groups. IN midazolam was as effective as IV midazolam in the control of GTCS based on the time of onset to seizure control. Study by Lahat et al. in children with febrile seizures had yielded similar results [8]. The interval from drug administration to seizure control was better in IV group than the IN group (p<0.05). However, Sharma and Harish found that intranasal midazolam was superior in seizure control from the time of drug administration [6].

In our study, both the routes were equally effective as no difference was found in treatment failures. Similarly, recurrences and treatment failure of recurrences were also similar in both groups. Therefore, the two routes of administration of midazolam were comparable in time taken to control seizures, treatment failure, recurrences, and treatment failure of recurrences. Several other studies also support these results [9-11].

Intranasal sprays of medication, intended for systemic drug absorption, are generally designed to target the turbinates on the lateral wall of nasal cavity. This region of nasal cavity is covered by a thin monolayer ciliated epithelium with abundant blood supply and large surface area of 180 cm^2. These conditions are ideal to permit passive transcellular and paracellular diffusion of medications [2]. This bypasses the gut metabolism, so adequate blood levels are achieved faster. Use of IN midazolam has been reported since 1988 [12]. Midazolam, a water-soluble benzodiazepine, becomes fat soluble at physiological pH, allowing it to cross the nasal mucosa into adjacent tissues including CSF, resulting in rapid onset of action. Intranasal route obviates the need for IV access, rapid in effect, and avoids the pain of IM administration. The safety margin of midazolam and easiness of administration allows prehospital use of this medication even by parents [13,14] so that the seizure control and outcome will be good.

Limitations of this study were that we conducted the study in GTCS only and excluded focal seizures with the assumption that the most focal seizures are symptomatic and difficult to control. Second, we have not assessed the EEG control of seizures. Therefore, more studies are required to compare these two routes of administration of midazolam.

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