ORIGINAL ARTICLE

COMPARATIVE STUDY OF INTRANASAL MIDAZOLAM AND INTRAVENOUS BENZODIAZEPINES IN CONTROL OF SEIZURES IN CHILDREN

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ABSTRACT

Background: Seizures are very common in pediatric patients. As duration of seizures impacts morbidity and mortality to child's life, control of seizures should be achieved as early as possible, preferably at home. Rectal diazepam and intranasal midazolam are available methods for control of seizures and can be learnt by parents.

Methods: We assessed safety and efficacy of intranasal midazolam for control of seizures and also compared its effect with other benzodiazepines given by intravenous route.

Results: Among 84 patients, success rate of treatment with Midazolam (intranasal) was 45.5% and success rate with Benzodiazepines (intravenous) was 90%. The difference is statistically significant. In present study, average time recorded to give drug after arrival at hospital in IN Midazolam group was 0.379 min, where as it was 1.598 min in IV Benzodiazepine group. Average time for cessation of seizures after giving drug was 3.001 min in IN Midazolam group, where as it was 1.009 min in IV Benzodiazepine group.

Conclusion: Intra-venous route for control of seizures is most effective compare to Inta-nasal Midazolam. However intranasal Midazolam can be use full when IV access is not available at home or during transport of patient to health care centre.

Keywords: Intra nasal route, Midazolam, benzodiazepines, seizures

INTRODUCTION

A seizure in a child is a frightening experience for parents as well as care providers. Because duration of seizure activity impacts morbidity and mortality[1], effective methods for seizure control should be instituted as soon as possible, preferably at home.

The cumulative lifetime incidence of epilepsy is 3%, with onset during childhood in more than half the cases[2]. Current evidence suggests that prolonged seizures are best stopped with early treatment.[3]

Benzodiazepines are the most widely used drug for the acute management of all types of seizures in children. Outside the hospital, where intravenous and intramuscular therapy may be difficult or impossible to administer, rectal diazepam has emerged as the primary treatment option for breakthrough seizures. However, rectal diazepam has a slower onset of action than the intravenously delivered drug[4]. Other disadvantages include the lower social acceptability of the rectal route[5]. The oral or intranasal route offers a potential alternative means of delivery of benzodiazepine treatment. However, buccal administration is more amenable to a small volume of drugs. It has been found to provoke gagging, coughing and aspiration[1,4]. Sublingual delivery is difficult to use when the teeth are clenched during a tonic-clonic seizure. Other alternative route is intranasal administration.

According to ayurveda - "the nose is the door to the brain" and that treatment with nasal drops (nasya) improves voice, vision, and mental clarity[6]. The nasal mucosa provides a large (180 cm2), highly vascular absorptive surface adjacent to the brain[7]. Together with the neighboring olfactory mucosa, it offers a direct pathway for drug absorption into the bloodstream and cerebrospinal fluid. Therefore, the nasal route is a good option for drugs those undergo extensive first-pass hepatic metabolism and drugs with erratic absorption patterns, thereby increasing their bioavailability. It is also advantageous when drugs with a short latency of action -- such as benzodiazepines -- are required.

Midazolam, a water-soluble benzodiazepine, is usually given intravenously in convulsion, is widely accepted as a parenteral anxiolytic and premedicant.

Midazolam given intranasally as an anesthetic agent has been shown to be safe and effective in children undergoing various diagnostic studies and minor surgical procedures[8]. Intranasal midazolam also suppresses epileptic activity and improves the background of electroencephalograms in children with epilepsy.

The aim of this study is to determine whether intranasal midazolam is as safe and effective as intravenous benzodiazepines in the treatment of acute childhood seizures.

MATERIALS AND METHODS

This was an intervention study conducted at a tertiary care hospital after obtaining clearance from Institutional Ethical Committee.

More than one month to 12 years of age child presented at pediatric ward with active convulsion were included in the study. Child weighted less than 5 kg or had taken any anticonvulsant were excluded from the study.

Prior to start treatment intervention, informed written consent was obtained from parents. In case of refusal a complete care is provided following the routine protocols of the hospital. Total 84 children were recruited for the study. All the patients were stabilized initially for airway, breathing and circulation. After that they are randomly divided in to two groups, 44 were were given IN midazolam and 40 were given IV benzodiazepines. Patients were informed about the drug and it's route of administration before recruitment so blinding was not possibel. As four patients in IV benzodiazepines had taken discharge against medical advice after control of seizures, they were dropped out from the group. Commercially available preparation of Intranasal Midazolam as atomizer (0.5 mg/puff) is given in a dose of 0.2 mg/kg, divided half in each nostril in to patients, by using recommended method.

Procedure

Using your free hand to hold the crown of the head stable, place the tip of the atomizer snugly against the nostril aiming slightly up and outward (towards the top of the ear on same side as nostril ear).

Briskly compress the plunger to deliver half of the medication into the nostril.

Move the device over to the opposite nostril and administer the remaining medication into that nostril.

In others IV Benzodiazepines- IV Lorazepam (0.1 mg/kg) or IV Diazepam (0.2 mg/kg) were given after inserting appropriate size of cannula.

Resuscitation kit (AMBU bag, laryngoscope, ET tube, suction catheter, oxygen source and emergency drugs) were kept ready by side of patient. Patients were moniterd for cessation of seizures, HR, RR, Spo2 and adverse effects of drugs. Treatment was considered, successful if the seizures ceased within five minutes. Seizures that did not stop after treatment, it was defined as treatment failure and other treatment was given as per protocol of AIIMS for management of convulsions.

HR, RR and oxygen saturation were noted, after 1 minute, 5 minute and 10 minute of insertion of drugs. Duration from arrival of patient in hospital to starting treatment and cessation of seizures were recorded.

Seizures that were controlled by drugs, but recurred within 60 minutes were defined as recurrent seizures.

Treatment of underlying cause & treatment of fever had given when required. Side effects of the drugs were recorded. All the patients were monitored until score one or two of sedation reached at recovery.

After initial control of seizures, all patients were investigated and managed accordingly, but that is beyond this study design. The data recorded was tabulated and statistically analyzed by SPSS Software.

OBSERVATION AND DISCUSSION

Present study was conducted for period from June 2009 to November 2011. In this study, total 84 patients were included.

Table 1: Distribution of patients according to Cause of seizures

Groups	Febrile		Unprovoked seizures	Known case of epilepsy	Total
	1st attack	Recurrent			
IN Midazolam	26	5	4	9	44
IV Benzodiazepine	24	1	5	10	40
Total	**50**	**6**	**9**	**19**	**84**

In present study, out of total 84 patients, 50(59.5%) patients had presented with 1st attack of febrile seizures. In which 26 had received IN Midazolam as treatment, while 24 had received IV benzodiazepine as first treatment.

There were 6(7%) patients with recurrent (past history of) febrile seizures, in them 5 had received IN midazolam and 1 had received IV benzodiazepine.

Total 9 (11%) patients were presented with unprovoked convulsion, in which 4 were in IN midazolam group and 5 were in IV benzodiazepine group.

And 19(23%) patients of known case of epilepsy, in which 9 had received IN midazolam and 10 had received IV benzodiazepine.

Table 2: Response observed by IN Midazolam and IV Benzodiazepine as primary treatment

Control of seizures	IN Midazolam Patients (%)	IV Benzodiazepine Patients (%)
Yes	20 (45.5)	36 (90)
No	24 (54.5)	4 (10)
Total	44 (100)	40 (100)

$\chi 2$ test $P<0.001$

In present study, 44 patients who had received IN midazolam as primary treatment at emergency room of our ward, 20(45.5%) patients had responded to treatment in form of cessation of seizures. And 24(54.5%) patients had not responded to IN midazolam and received other treatment for cessation of seizures as per protocol.

Table 3: Patients who had not responded to IN Midazolam

Control of seizures achieved by	Cause of seizures			
	Febrile seizures		Unprovoked seizures	K/C/O epilepsy
	1st attack	Recurrent		
IV Benzodiazepine	12	1	2	3
IV Phenytoin	2	--	--	2
IV phenobarbitone	1	--	1	1

Of total 44 patients in IN Midazolam group, 24 had not responded to IN Midazolam as primary treatment, all had received IV Benzodiazepine as second treatment of seizures.

Among them 17(70%) patients had responded to IV benzodiazepam. Other 7 patients eventually developed status epilepticus, and required further management. Out of them 4 had responded to IV phenytoin. 3 had responded to add on drug IV phenobarbitone.

During study, we had observed that, patients who had not responded to IN Midazolam may be due to, excessive nasal secretions; improper position of head while inserting drug; excessive dose may run off in patients with more weight as they require large doses; and dead space within the delivery device.

In 40 patients who had received IV Benzodiazepines as first treatment at emergency room of our ward, 36 patients had responded to it. Only 4 patients had not responded to IV drugs. So success of IV benzodiazepine group is 90% as a first line treatment.

The 4 patients who had not responded to IV Benzodiazepine were of, atypical febrile seizure, pyogenic meningitis - responded to IV Phenytoin and other two of, status epilepticus with febrile seizures; and unprovoked convulsion - responded to IV phenobarbitone.

Table 4: Average duration of Time intervals (in minutes) with [standard deviation]; for starting treatment and seizure control in study groups

Duration (in minutes)	IN Midazolam Mean[SD]	IV Benzodiazepine Mean[SD]
Time to give drug after arrival at hospital	0.379[0.47]	1.598[0.82]
Time to cessation of seizures after giving drug	3.001[0.99]	1.009[0.83]
Total Time to cessation of seizures after arrival at hospital	3.380[1.19]	2.608[1.27]

Unpaired 't' test $P = 0.03$

In present study, average time recorded to give drug after arrival at hospital in IN Midazolam group was 0.379 min, where as it was 1.598 min in IV Benzodiazepine group. Average time for cessation of seizures after giving drug was 3.001 min in IN Midazolam group, where as it was 1.009 min in IV Benzodiazepine group.

It was observed that average time required to initiate treatment in IV Benzodiazepine group after arrival in hospital is more than IN Midazolam due to some time required to take IV access, but average time required for IV Benzodiazepine to control seizure after arrival in hospital is far less than IN Midazolam because IV benzodiazepine take less time to control seizure as compared to IN midazolam once given.

Total time required for control of seizures (from arrival at hospital to cessation of seizures) is much less in IV Benzodiazepine group (2.608 min) than in IN midazolam group (3.380 min).

Table 5: Comparison of various studies for time duration (in minutes)

Time duration from arrival at hospital to cessation of seizures	Punkaj mittal et al (2006)[9]	Lahat et al (2000)[10]	Mahmoudian T. et al (2004)[11]	**Present study**
IN midazolam group (min)	5.25	6.1	3.68	**3.380**
IV benzodiazepine group (min)	6.51	8.0	2.94	**2.608**

For this data we had applied unpaired 't' test. In which '**t' test value** is 2.18 and **P value** is 0.03. Statistical analysis had showed a significant difference between two groups for the Total time for cessation of seizures.

In present study, it was observed that average time required to control seizures after arrival at hospital in IN midazolam group (3.380 min) and IV benzodiazepine group (2.608 min) was comparable to Mahmoudian et al study; in which time required to control seizures was 3.68 min in IN midazolam group and 2.94 min in IV benzodiazepine group.

However, it was also observed that time required for cessation of seizures after arrival at hospital in Pankaj mittal et al study and Lahat et al study, in IV benzodiazepine group (6.51 min and 8 min in both studies respectively) was more than in IN Midazolam group (5.25 min and 6.1 min respectively). In both study, they had noted that, more time required in IV benzodiazepine group was due to some time required to take IV access.

Side effects observed in both groups:

In our study, during treatment and monitoring, patients were observed for known side effects of both drugs. In IN Midazolam received patients only 4 (9%) patients had irritation of nasal mucosa, but major side effects like; urticaria, rashes, hypertension or bradycardia were not occurred to any patients.

In IV Benzodiazepine group no major side effects were observed. Both drugs are relatively safe for control of seizures in pediatric patients.

CONCLUSION

Time duration for starting treatment is less in IN Midazolam compare to IV Benzodiazepines as As insertion of IV cannula takes some time, for IV benzodiazepine drugs.

IV drugs are faster acting to control seizures than intranasal route. , IV benzodiazepine is more effective in control of seizures than IN midazolam. However, IN midazolam is also an effective drug for control of seizures when IV access is not available for control of seizures at home or during transport to the health care centre. Both drugs are relatively safe in control of convulsions.

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