A Comparative Study between Intranasal Midazolam and Intravenous Midazolam In Control Of Seizure In Children

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Abstract

Introduction: Seizures are one of the important reasons for children visiting the hospital. Febrile seizures are the most common type of seizures found in childhood. Earlier Diazepam was widely used for treating all types of seizures but due to short duration of action, newer drugs were tried and found better than diazepam.

Aims: To compare midazolam given intranasally with midazolam given intravenously for the treatment of febrile seizures in children.

Methods: This prospective study was conducted in children suffering from seizures at the Paediatric Emergency Department of Teerthanker Mahaveer Medical over a period of 12 months. 84 children between the ages of one month to fourteen years with febrile seizures lasting for at least 10 minutes were eligible for inclusion in our study. Treatment was considered successful if the seizure ceased within one hundred twenty seconds.

Results: In group A out of 44 patients, 20(45.5%) patients were responded to Intranasal Midazolam, whereas in group B 40 patients who were treated with IV Midazolam as first line treatment, 36 patients (90%) had responded to it. Time recorded for the commencement was more in IV Midazolam group (1.598 min) than IN Midazolam group (0.379 min), but average response time was lesser in group B (1.009 min) than group A (3.001 min).

Conclusion: Midazolam given intranasally is a safe and effective treatment for prolonged febrile seizures in children and may be used in general practice and, with appropriate instructions, by the parents of children with recurrent febrile seizures at home.

Keywords: Midazolam, Seizures, Anti-epileptics.

Introduction

Convulsions triggered by fever (febrile seizures) are the most common type of seizures in childhood, with a prevalence of 3-4%. Acute onset of febrile seizures requires prompt medical attention, ventilation support, and appropriate oxygenation until they either stop spontaneously or are controlled by drugs. Diazepam is the most widely used drug for the acute management of all types of seizures in both adults and children. However, it has a short duration of action, should be given intravenously or rectally (since its absorption is slow if given intramuscularly), and tends to accumulate if repeated doses are given, with the possible rare complication of brain stem depression leading to bradypnoea or even respiratory arrest. The introduction of an intravenous line may be difficult, particularly in children with generalised tonic-clonic febrile seizures. Diazepam may also be given rectally to control seizures, which is as effective as intra- venous diazepam. However, rectal diazepam has a slower onset of action than the intravenously delivered drug.

Other disadvantages include the lower social acceptability of the rectal route.

Midazolam, the first water soluble benzodiazepine, is widely accepted as a parenteral anxiolytic and premedicant. Its safety and efficacy as an anticonvulsant drug given intramuscularly have been shown in several studies in humans (adults and children). Midazolam given intranasally as an anaesthetic agent has proved successful in treating all types of seizures such as status epilepticus. Long-
term use for the management of epilepsy is not recommended, however, due to the significant risk of tolerance (which renders midazolam and other benzodiazepines ineffective) and the significant side effect of sedation.

A benefit of midazolam is that in children it can be administered buccally or intranasally at home or at school for emergency control of acute seizures, including status epilepticus. Midazolam is effective for refractory status epilepticus, and has advantages of being water-soluble, having a rapid onset of action and not causing metabolic acidosis from the propylene glycol vehicle, which occurs with other benzodiazepines. Drawbacks include a high degree of breakthrough seizures—due to the short half-life of midazolam—in over 50% of people treated, as well as treatment failure in 14–18% of people with refractory status epilepticus. Tolerance develops rapidly to the anticonvulsant effect, and the dose may need to be increased by several times to maintain anticonvulsant therapeutic effects. With prolonged use, tolerance and tachyphylaxis can occur and the elimination half-life may increase, up to days.

We recently showed that intranasal midazolam is safe and effective for the management of acute seizures in children. In the present study, we aimed to compare midazolam given intranasally with midazolam given intravenously for the treatment of febrile seizures in children.

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. Sublingual delivery is difficult to use when the teeth are clenched during a tonic-clonic seizure. Other alternative route is intranasal administration.

The nasal mucosa provides a large (180 cm²), highly vascular absorptive surface adjacent to the brain. Together with the neighbouring 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. Intranasal midazolam also suppresses epileptic activity.

Method

The prospective study was done in children suffering from seizures at the Paediatric Emergency Department of Teerthanker Mahaveer Medical College in Moradabad, UP India, over a period of 12 months, i.e. March 2014 to February 2015. All children between the ages of one months to fourteen years who presented with febrile seizures (tonic, clonic, or tonic-clonic) lasting for at least 10 minutes were eligible for inclusion in our study. We excluded children with established intravenous lines or those who had received anticonvulsants before admission or who has major trauma as the precipitant of the seizure or If there is immediate need of endotracheal intubation or the patient is known allergy to benzodiazepine or child is in bradycardia. We chose 10 minutes of ongoing motor seizure as the entry criterion, as most emergency physicians would initiate anticonvulsive treatment after that time.

After seizures were controlled in the children, their parents were asked to sign a consent form giving permission to enrol them in our study. The hospital's ethics committee approved the study on the understanding that, because midazolam is rapidly taken up by the intranasal route, there would be no significant delay in treating patients. Patients were randomized to receive this drug, and if this treatment failed an intravenous line would immediately be introduced. We randomly assigned 84 episodes of febrile seizure to treatment with either intranasal midazolam 0.2 mg/kg or intravenous midazolam 0.1 mg/kg, the maximum dose being 10 mg. Randomization was performed in advance with a random number table by a hospital nursing staff not involved in the study.

Midazolam solution (5 mg/ml) was puffed by atomizer into both nostrils in equal doses, and an intravenous line was immediately introduced.

We recorded the following time duration:

1. Arrival at hospital
2. Treatment with intranasal midazolam,
3. Intravenous access, cessation of seizures, and recurrence of seizure, hypotension bradycardia/tachycardia, apnea, hypoglycaemia, hypothermia.

Treatment Outcomes

Treatment was considered successful if the seizure ceased within one hundred twenty seconds.

Seizures that stopped between one hundred twenty to three hundred seconds after treatment were defined as successful but delayed control of seizure.

Seizures that did not stop within 5 minutes after treatment were defined as treatment failures, and intravenous midazolam 0.1 mg/kg was given.

Seizures that were controlled with midazolam or diazepam but recurred within 60 minutes were defined as recurrent seizures.

During seizure activity and for 60 minutes after control, the children were followed by continuous cardiorespiratory and pulse oximetry monitors. Vital signs were recorded every 15 minutes. During seizure activity, high flow oxygen was
provided through a mask. All the children were admitted to the paediatric ward for 24 hour observation after cessation of seizures.

**Dose Calculation**

To calculate it manually, use the below formula:

Assess weight: children weight in kg = 10 + 2(Age in years)

Calculate appropriate dose of midazolam using the following formula:

Children: Total kg wt X 0.2 mg = total mg dose of midazolam

Total volume in millilitres of midazolam (5mg/ml concentration) = (Total mg dose divided by 5mg/ml) + 0.1 ml for dead space of device.

**Ethical approval**

Ethical approval for the study was obtained through the Medical research and Ethics Committee at the Teerthanker Mahaveer Medical Collage and Research Centre (TMMC & RC).

**Statistical Analysis**

For this data we had applied unpaired ‘t’ test. In which 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.

**Results**

84 patients enrolled with predominance of male patients n=48 than female patients n=36 [Table 1]. Enrolled patients were divided into two groups i.e. group A (n=44) treated with Intra Nasal Midazolam and group B (n=40) treated with Intravenous Midazolam.

In group A out of 44 patients at paediatric ICU, 20(45.5%) patients were responded to Intranasal Midazolam as primary treatment in the form of cessation of seizures. And 24(54.5%) patients were not responded to primary treatment (i.e. seizures were not controlled) were treated as per protocol [Table 2, Fig. 1].

<table>
<thead>
<tr>
<th>Groups</th>
<th>Total(n)</th>
<th>Responded to treatment</th>
<th>Not responded to treatment</th>
<th>Success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>44</td>
<td>20</td>
<td>24</td>
<td>45.5%</td>
</tr>
<tr>
<td>B</td>
<td>40</td>
<td>36</td>
<td>4</td>
<td>90%</td>
</tr>
</tbody>
</table>

In our study, average frequency of time recorded for the commencement of treatment in IN Midazolam group was 0.379 min, where as it was 1.598 min in IV Midazolam group. Average response time for cessation of seizures after giving drug was 3.001 min in group A, where it was 1.009 min in group B (Table 3). It was observed that average time required to initiate treatment was found to be more in IV Midazolam group in comparison to IN Midazolam group due to some time required to take IV access, but average response time required for IV Midazolam to control seizure after commencement of treatment is far less than IN Midazolam as IV route had 100% bioavailability. Total time required for control of seizures (from commencement of treatment to cessation of seizures) is much less in IV midazolam group (2.608min) than in IN Midazolam group (3.380min) [Table 3].

**Table 2: Treatment table for group A: Patients treated with IN Midazolam: group B: Patients treated with IV Midazolam**

<table>
<thead>
<tr>
<th>Duration in minutes</th>
<th>Intranasal midazolam</th>
<th>Intravenous midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to give drug</td>
<td>0.379</td>
<td>1.598</td>
</tr>
<tr>
<td>Time to cessation of seizure after giving drug</td>
<td>3.001</td>
<td>1.009</td>
</tr>
<tr>
<td>Total time to cessation of seizure after commencement of treatment</td>
<td>3.380</td>
<td>2.608</td>
</tr>
</tbody>
</table>

Unpaired ‘t’ test P=0.003
Our results were in accordance with the study conducted by responded to treatment, they were treated as per protocol. Patients were responded to treatment and 4 were not absorbed of drug. Maximum treatment failure is due to in those children who were suffering from URTI as nasal secretion interfere with absorption to the nasal mucous membrane, the presence of nasal secretions could dilute the midazolam solution and interfere with its contact with the absorbing surface. Most of the children in our study had upper respiratory tract infections, but this only affect the absorption of midazolam and subsequent seizure control. As we have shown in table 3 that 44 patients (group A) were treated with Intranasal Midazolam in which 20 patients were responded to treatment and 24 were not responded to treatment. Maximum treatment failure is due to in those children who were suffering from URTI as nasal secretion interfere with absorption of drug. In table 4 we showed that 40 patients (group B) were treated with Intravenous Midazolam in which 36 patients were responded to treatment and 4 were not responded to treatment, they were treated as per protocol. Our results were in accordance with the study conducted by Fisgin et al who compared IN midazolam with PR diazepam for the treatment of paediatric seizures and founded Intrasenal midazolam was more likely to treat seizure activity within the first 10 minutes (87%, 20/23 vs. 60%, 13/22; P < 0.05). In addition, more patients required a second anticonvulsant to stop seizures in the diazepam group (P < 0.05), Jeannet et al used IN midazolam to control seizure activity in 26 patients (11 treated at home and 17 treated in the hospital). 

Fig 1. Response observed by IN Midazolam and IV Midazolam as primary treatment.

Discussion
The safety and efficacy of midazolam has been shown by several clinical studies in epileptic adults and children, and continuous infusion of midazolam has successfully controlled status epilepticus in adults and children. Midazolam given intravenously or intramuscularly is not associated with respiratory changes, as reported by Rainbow et al who demonstrated that IM or IV midazolam controls seizures as effectively as IV or PR diazepam in the prehospital setting. Here, patients treated with midazolam had less respiratory depression and decreased time to treatment.

The elimination half-life of intranasal midazolam at a dose of 0.2 mg/kg is similar to that when the drug is given intravenously and no significant complications have been reported when it is given by the intranasal route. Therefore, it seemed pertinent to investigate the use of intranasal midazolam in the management of acute seizures, especially in children, where the introduction of an intravenous line is frequently unsuccessful.

Our study was designed to investigate an alternative means of treating prolonged febrile seizures in an emergency setting, we chose to compare intranasal midazolam with intravenous midazolam.

To our knowledge, no controlled studies have been found that the safety of intranasal midazolam with intravenous midazolam for the management of febrile seizures. Therefore this study was carried out and we found that seizures were controlled faster with intravenous midazolam than with intranasal midazolam but as far as safety is concerned both the routes i.e. Intranasal Midazolam and Intravenous Midazolam found to be on same ground.

Although upper respiratory tract infection decreases the absorption of drug to the nasal mucous membrane, the presence of nasal secretions could dilute the midazolam solution and interfere with its contact with the absorbing surface. Most of the children in our study had upper respiratory tract infections, but this only affect the absorption of midazolam and subsequent seizure control. As we have shown in table 3 that 44 patients (group A) were treated with Intranasal Midazolam in which 20 patients were responded to treatment and 24 were not responded to treatment. Maximum treatment failure is due to in those children who were suffering from URTI as nasal secretion interfere with absorption of drug.

In table 4 we showed that 40 patients (group B) were treated with Intravenous Midazolam in which 36 patients were responded to treatment and 4 were not responded to treatment, they were treated as per protocol. Our results were in accordance with the study conducted by Fisgin et al who compared IN midazolam with PR diazepam for the treatment of paediatric seizures and founded Intrasenal midazolam was more likely to treat seizure activity within the first 10 minutes (87%, 20/23 vs. 60%, 13/22; P < 0.05). In addition, more patients required a second anticonvulsant to stop seizures in the diazepam group (P < 0.05), Jeannet et al used IN midazolam to control seizure activity in 26 patients (11 treated at home and 17 treated in the hospital). 

Fisgin et al administered IN midazolam to 22 children for a total of 54 seizures that were stopped on 48 occasions (89%) without any respiratory compromise. Questionnaires were given to all those who used IN midazolam (30 parents, school assistants, and teachers). Ninety percent had no difficulty giving the medication and of the 15 people who had also administered PR diazepam in the past, 14 preferred IN midazolam.

D.G.shirodkar et al had worked on efficacy of intranasal midazolam and intravenous midazolam and found that there is no significant difference between these two routes. 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). Our findings 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 Mittal P 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.

Conclusion
Midazolam given intranasally is a safe and effective treatment for prolonged febrile seizures in children. Control of seizures in children is faster with intravenous midazolam than with intranasal midazolam, but the time to cessation of seizures after commencement of treatment at hospital is faster with intravenous midazolam. Intranasal midazolam may be used in general practice and, with appropriate instructions, by the parents of children with recurrent febrile seizures at home.

Adverse effects of nasal medications are infrequent. The most common adverse effect noted is nasal burning and irritation after administration of midazolam. Although this discomfort is transient, parents and older patients should be forewarned of this adverse effect before drug delivery. Intranasal medication delivery is also quite cost-effective, especially when time and resource use as well as patient
satisfaction are concerned. Costs of intranasal medication is far less as compared to intravenous delivery.

What this study adds:

1. What is known about this subject?
Midazolam given intranasally is a safe and effective treatment for prolonged febrile seizures in children.

2. What new information is offered in this study?
Control of seizures in children is faster with intravenous midazolam than with intranasal midazolam, but the time to cessation of seizures after commencement of treatment at hospital is faster with intravenous midazolam. Intranasal midazolam may be used in general practice and, with appropriate instructions, by the parents of children with recurrent febrile seizures at home.

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