Section: General Surgery

Research

STUDY OF INTRANASAL MIDAZOLAM TO ABORT CHILDHOOD SEIZURE

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Abstract

Background: Seizures are the most common medical problem for emergency medical services (EMS) transport in pediatric patients, accounting for roughly 15% of all pediatric EMC calls in the United States. In the prehospital setting, midazolam, a benzodiazepine may provide an alternative to per rectal (PR) diazepam. Midazolam can be administered via different routes: IV, IM, endotracheal tube, per rectal, buccal and intranasal. Because intranasal midazolam is directly absorbed into the cerebrospinal fluid, it is not subject to hepatic first pass metabolism and less likely to accumulate. **Materials and Methods:** This study is a single blind and experimental study. The study population was selected from the outdoor, emergency and indoor patients admitted at the Pediatric ward of PRM MCH Baripada. Patients ranging from age 3 year to 14 years and all types of seizures like simple partial seizure, generalized tonic clonic seizure and febrile seizures are included. Children with absence seizure, myoclonic seizure, hypoglycemic seizure & hypocalcemic seizure were excluded from the study. Patient's blood sugar and serum calcium were detected soon after the seizure episode. If there was evidence of hypoglycemia or hypocalcemia, the patient was excluded from the study. **Result:** In our study, out of 134 patients, 78 were boys & 56 were girls. Hence, boys represent 58% of the total study population whereas girls represent 42% of the study population. In our study out of 134 patients, 69 patients (52%) presented with simple partial seizures, 31 patients (23%) presented with generalized tonic clonic convulsions, 34 patients (25 %) patients presented with febrile seizures. In intranasal midazolam group, mean time taken for drug administration was 3.8 min where as in IV diazepam group, mean time taken for drug administration was 5.8 min. In midazolam group, cessation of seizure was observed in 18 (90%) patients, whereas in diazepam group, cessation of seizure was seen in 12(60%) patients. **Conclusion:** In comparision to midazolam, more number of patients had cessation of seizure. It is high time that we must use intranasal midazoalm for acute childhood seizures. In india, time will come when people keep this miracle medicine just like paracetamol & cough syrup at home for their convulsing child to treat the most devastating treatable disease.

INTRODUCTION

Seizures are the most common medical problem for emergency medical services (EMS) transport in pediatric patients, accounting for roughly 15% of all pediatric EMC calls in the United States.[1] Prolonged or recurrent seizure activity persisting for 30 minutes or more can cause significant morbidity and mortality that is directly correlated with seizure duration. The sooner that a seizure is treated, the more likely the seizure will be controlled. It is recommended that seizures lasting longer than 5 minutes should be treated with an anticonvulsant. The administration of anticonvulsant therapy in the prehospital setting may shorten the duration of seizure.[2,3]

Early domiciliary treatment of seizures in the community, school or home with drugs that can be

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administered by parents, teachers or non-medical staffs may be beneficial and can decrease morbidity and mortality.[3] In planning domiciliary therapy, the safety, ease of administration, choice of drug, route of thrapy and practicability of familiarization by the user are important issue. Various drugs administered through different routes have been tried in the management of acute seizures.[4]

Benzodiazepines are currently the first line therapy for seizures. Diazepam is typically the sole anticonvulsant medication available on most ambulances for the acute management of all types of seizures in the prehospital setting.[5] Diazepam may be administered intravenously (IV), rectally (PR) or through endotracheal tube; it is ineffective for seizure control when given intramuscularly (IM) and is not suitable for intranasal (IN) administration.[6]

Rectal diazepam has been available for seizure control in the prehospital setting for more than 20 yrs. Its popularity is due partly to the potentially difficult task of IV placement, especially in a child with seizures. However, disadvantages of PR diazepam include the social awkwardness for patients and providers, potential for ejection, variable and unpredictable drug absorption, hepatic first pass metabolism and possible higher doses for clinical response.[7] Diazepam accumulation can cause respiratory depression, which may require endotracheal intubation, especially if used in conjunction with other anticonvulsants. Moreover, some special arrangement is required to administer it, which is difficult to arrange in homes, schools, and day care centers.[8]

In the prehospital setting, midazolam, a benzodiazepine may provide an alternative to per rectal (PR) diazepam. Midazolam can be administered via different routes: IV, IM, endotracheal tube, per rectal, buccal and intranasal. Midazolam is water soluble but becomes fat soluble at physiological pH allowing it to cross the nasal mucosa into the cerebrospinal fluid with a rapid onset of action and rapid metabolism.[9] Because intranasal midazolam is directly absorbed into the cerebrospinal fluid, it is not subject to hepatic first pass metabolism and less likely to accumulate. Because PR diazepam is absorbed through the gastrointestinal tract, it is subject to first pass metabolism and is more likely to accumulate with successive doses than midazolam. In addition to the pharmacological advantages, the convenient of IN administration and the social acceptability may make intranasal midazolam the preferred treatment of seizures in prehospital setting.[10]

To abort a seizure, there are many options in the intravenous & intramuscular route. But to save a life, to get rid of neurologic sequelae, these times taking methods are not patient-friendly. So, intranasal rout is the only option. again, seizure is the prime manifestation of any neurologic disease. So, treating seizure in a easier way, with little side effects should be3 given prime importance.

In the light of the above background, the present study was undertaken to study the efficacy and side effects of IN midazolam in the treatment of acute childhood seizures.

MATERIALS AND METHODS

This study is a single blind and experimental study. The study population was selected from the outdoor, emergency and indoor patients admitted at the Pediatric ward of PRM MCH Baripada.

Inclusion Criteria

Patients ranging from age 3 year to 14 years and all types of seizures like simple partial seizure, generalized tonic clonic seizure and febrile seizures are included.

Exclusion Criteria

Children with absence seizure, myoclonic seizure, hypoglycemic seizure & hypocalcemic seizure were excluded from the study.

Patient's blood sugar and serum calcium were detected soon after the seizure episode. If there was evidence of hypoglycemia or hypocalcemia, the patient was excluded from the study.

Data Collection Method

Midazolam was instilled into the anterior nares with the help of a nasal dropper in a dose 0.2 mg/kg (formulation containing 5 mg/ml) dripped out onto a tissue paper. This was done to prevent accidentally giving too much. Half the dose was given in one nostril followed by half the dose to the other nostril.

The end of the seizure episode (clinically) was defined as the cessation of visible epileptic phenomenon on returnof purposeful response to external stimuli. If the seizure did not end within 10 minutes of drug administration, the treatment was deemed to be ineffective.

Heart rate, respiratory rate, blood pressure and oxygen saturation by pulse oximetry were measured before drug administration and monitored at 5 min, 10 min and 30 min after drug administration. Recurrence of seizure within 60 min of drug administration was also evaluated. The children were monitored for side effects such as vomiting, excessive somnolence, respiratory depression and apnea after drug administration. A stop watch was used to measure all time accurately.

Out of the 134 patients, 20 patients were choosen of the age 6 – 10 years. Intravenous diazepam was given in another 20 patients of the same age. Then the observations were observed in the following tabular forms.

Data Analysis

All the data collected in the above study was analysed by using EPINFO software.

RESULTS

In our study, out of 134 patients, 78 were boys & 56 were girls. Hence, boys represent 58% of the total

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study population whereas girls represent 42% of the study population.

Table 1: Shows sex distribution in our study

Gender	Number (n=134)	Percentage (%)
Male	78	58
Female	56	42

Table 2: Shows age distribution in our study

Age (in year)	Number Of Patients (n = 134)	Percentage Of Patients (%)
3 - 5	43	32
6 - 8	29	22
9 -11	25	18
12 - 14	37	28

In our study, age range was 3 montth to 14 year. Out of 134 patients, 43 patienys (32%) were of 3-5 years age. In the age grop 6-8 year, there were 29 patients (22%). 25 patients (18%) of the total population were of age 9-11 years. IIn 12-14 years we found 37 patients (28%).

Table 3: Shows types of seizure among the study population

Types of seizure	Number of patients (n = 134)	Percentage of patients (%)
Simple partial	69	52
General tonic clonic	31	23
Febrile seizure	34	25

In our study out of 134 patients, 69 patients (52%) presented with simple partial seizures, 31 patients (23%) presented with generalized tonic clonic convulsions, 34 patients (25 %) patients presented with febrile seizures.

Table 4: Shows CT SCAN findings

Ct scan finding	No of patients (n=134)	percentage
Normal	55	41
Calcification	10	07
Hemorrhage	08	06
Tuberculoma	25	18
Hydrocephalus	18	14
Malformations	18	14

Out of 134 patients, 55 (41%) had normal CT SCAN, 10 (7%) patients showed calcification, 8 (6%) had hemorrhage, 25 (18%) were having tuberculoma. In the study, 18 (14%) patients had hydrocephalus in CT SCAN, whereas 18 (14%) had malformations.

Table 5: Shows EEG finding in patients before and after treatment

	Before treatment	After treatment	Percentage improvement(%)
Abnormal EEG findings	78	19	75 %

In our study, abnormal EEG was found in 78 patients out of 134 (58%). After administration of intranasal midzolam, 59 patients showed improvement in EEG findings. That means, in 75 % patients EEG findings become normal after intranasal midazolam administration.

Table 6: Shows side effects after intranasal midazolam administration

Side effects	No. Of patients (n= 134)	Percentage (%)
Vomiting	04	3
Excessive drowsiness	10	8
Respiratory distress	02	1
Apnea	00	0
Nasal irritation	04	3

In our study, out of 134 patients 4 (3%) patients complained vomiting while excessive drowsiness was seen in 10 (8%) patients. Respiratory depression was seen in 2 (1%) patients. There were no complaints of apnea in any patients. Nasal irritation was found in 4 (3%) patients.

Table 7: Shows change in vital parameters after intranasal midazolam administration after 5 min, 10 min & 30 minutes

Parameters	Change after 5 min	Change after 10 min	Change after 30 min
Mean heart rate	No change	2	2
Mean respiratory rate	No change	1	1
Mean Blood Pressure (mm Hg)	No change	2	2
Mean oxygen saturation (%)	No change	1	1

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In our study, vital parameters were observed 5 minutes, 10 minutes, & 30 minutes after administration of intranasal midazolam. There was no change in vital parameters after 5 minutes. After 10 & 30 minutes, there was a little change in vital parameters.

Table 8: Shows response to treatment after intranasal midazolam administration

Cessation of seizure	No. Of patients (n=134)	Percentage (%)
Yes	120	89.5
No	14	10.5

In our study, out of 134 patients 120episodes (89.5%) were controlled within 10 minutes. Seizure remained uncontrolled in 14 (10.5%) episodes.

Table 9: mean time duration of control of seizure

Type of duration	In midazolam n=20	Iv diazepam n=20
Time to giving drug after arrival at hospital (min)	3.8	5.8
Time of cessation of seizure after giving drug (min)	3.5	3.0
Time of cessation of seizure after arrival at hospital (min)	7.3	8.8

In intranasal midazolam group, mean time taken for drug administration was 3.8 min where as in IV diazepam group, mean time taken for drug administration was 5.8 min.

Table 10: Response of Seizure to Treatment

Cessation of seizure	In midazolam	Percentage (%)	Iv diazepam	Percentage (%)
Yes	18	90	12	60
No	02	10	08	40

In midazolam group, cessation of seizure was observed in 18 (90%) patients, whereas in diazepam group, cessation of seizure was seen in 12(60%) patients.

DISCUSSION

In our study, out of 134 patients, 78 were boys & 56 were girls. Hence, boys represent 58% of the total study population whereas girls represent 42% of the study population. Kutlu et al (2000), in the study of "intranasal midazolam for prolonged convulsive seizures" Brain dev (6): 359-61 included nine patients out of which six were boys and three were girls.[11] Boys represented 67% of the study population, whereas girls represented 33% of the study population. In the study by Lahat et al. boys were 13 (62%) out of 21 & girls were 8 (38%).[12]

In our study, age range was 3 months to 14 year. Out of 134 patients, 43 patients (32%) were of 3-5 years age. In the age group 6-8 year, there were 29 patients (22%). 25 patients (18%) of the total population were of age 9-11 years. IIn 12-14 years we found 37 patients (28%). In the study of Holsti at al, the madian age was 4.5 years & age range was 8 months to 16 years.[13]

In our study out of 134 patients, 69 patients (52%) presented with simple partial seizures, 31 patients (23%) presented with generalized tonic clonic convulsions, 34 patients (25 %) patients presented with febrile seizures. In the study by Lahat et al. simple partial seizure was present in 48.9 % cases, generalized tonic clonic convulsions were present in 37% cases, whereas myoclonic seizures was present in 10.1 % cases and other seizures present in 3.8 % of cases.[12]

In our study, abnormal EEG was found in 78 patients out of 134 (58%). After administration of intranasal midzolam, 59 patients showed improvement in EEG findings. That means, in 75 % patients EEG findings become normal after intranasal midazolam administration. In a study by O'Regan et al (1996), there was 79 % improvement in EEG findings after administration of intranasal midazolam in 19 children.[14] That means 15 patients showed improvement in EEG even 2-5 minutes after administration of intranasal midazolam.

In another study by Jeannet et al (1999), out of 15 children, EEG findings disappeared in 10 (67%) and decreased in 3.[15] In our study, out of 134 patients 4 (3%) patients complained vomiting while excessive drowsiness was seen in 10 (8%) patients. Respiratory depression was seen in 2 (1%) patients. There were no complaints of apnea in any patients. Nasal irritation was found in 4 (3%) patients. In a study by Mc Glone et al. there was no patients suffering from any respiratory depression or any other side effects.[16]

In the study by Kutlu et al (2000), out of 9 patients, there was no significant side effects noted except for one patient who had seizures secondary to serious Cns infection and respiratory depression after administration of intranasal midazolam.[6] In another study by Mahmoudian, T et al. (2004), no significant adverse effects were observed in patients.[18] In the study of Lahat et al (2000), the observation was that none of the children had clinical signs of respiratory distress , bradycardia or other side effects.[12]

In our study, vital parameters were observed 5 minutes, 10 minutes, & 30 minutes after administration of intranasal midazolam. There was no change in vital parameters after 5 minutes. After 10 & 30 minutes, there was a little change in vital parameters. Mean respiratory rate increased after

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intransal midazola administration. This finding indicates that intranasal midazolam probably has no significant respiratory depressant effect in children with acute seizures. Karla et al. detected tachypnea in their study in intranasal midazolam group in a study of comparison of intranasal midazolam with rectal diazepam in acute childhood seizures.[19]

A possible explanation may be nasal mucosal irritation by local application of drugs. There was no change in oxygen saturation value at 5, 10 and 30 minutes after drug administration. O'Regan et al. found a severe decrease in o2 saturation that corrected spontaneously in 1 of 19 children with intractable seizures who received intranasal midazolam.[14] Madhumita et al al. found no such difference in o2 saturation after intranasal midazolam administration.[15] No other studies found any significant fall in oxygen saturation after administration of intranasal midazolam.

In our study, out of 134 patients 120episodes (89.5%) were controlled within 10 minutes. Seizure remained uncontrolled in 14 (10.5%) episodes. Lahat et al. reported that intanasal midazolam was efective in ending seizures within 10 minutes in 88.4% of study children.[12] Karla et al. also demonstrated that intranasal midazoalm was effective within 10 minutes in ending seizures in 96.7% of children.[16]

In intranasal midazolam group, mean time taken for drug administration was 3.8 min where as in IV diazepam group, mean time taken for drug administration was 5.8 min. In intranasal midazolam group mean time for seizure control was 3.5 min where as in IV diazepam group mean time for seizure control was 3.0 min. In intranasal midazolam group the mean time from arrival to seizure cessation was 7.3 minutes where as in IV diazepam group the mean time from arrival to seizure cessation was 8.8 minutes. In the study by Lahat et al, in intranasal midazolam group, mean time taken for drug administration was 3.5 min. where as mean time for seizure control was 3.1 min.[12] Hence the mean time from arrival to seizure cessation was 6.1 minutes. In IV diazepam group, mean time taken for drug administration was 5.5 min. whereas mean time for seizure control was 2.5 min. Hence the mean time from arrival to seizure cessation was 8.0 minutes.

In midazolam group, cessation of seizure was observed in 18 (90 %) patients, whereas in diazepam group, cessation of seizure was seen in 12(60%) patients. In the study by Lahat et al. 18 (85%) patients had seizure cessation in midazolam group, whereas 19 (83%) patients had no seizure after treatment in diazepam group.[12] Hence it shows that intranasal midazolam is more effective than IV diazepam in controlling seizure.

CONCLUSION

Intranasal midazolam can be administered in a convulsing patient with more ease. As intravenous line is a time taking procedure, so in comparision to IV diazepam the drug administration is quicker in intranasl midazolam group. There are no significant side effects after administration of intranasal midazolam. The vital parameters show no significant changes after administration of intranasal midazolam. There is significant improvement in EEG findings after administration of intranasal midazolam. In comparision to midazolam, more number of patients had cessation of seizure. It is high time that we must use intranasal midazoalm for acute childhood seizures. In india, time will come when people keep this miracle medicine just like paracetamol & cough syrup at home for their convulsing child to treat the most devastating treatable disease.

REFERENCES

1. Shawagfeh M, Sbaihat AS, Mayyas EA, Alomari AD, Fawaris G. Low-dose Bupivacaine with fentanyl spinal anesthesia to prevent spinal-induced hypotension in adults. Rawal Med J. 2011;36:116–9.
2. Biswas BN, Rudra A, Bose BK, Nath S, Chakrabarty S, Bhattacharjee S. Intrathecal fentanyl with hyperbaric bupivacaine improves analgesia during caesarean delivery and in early post-operative period. Indian J Anaesth. 2002;46:21-4.
3. Abouleish E, Rawal N, Shaw J, Lorenz T, Rashad MN. Intrathecal morphine 0.2 mg versus epidural bupivacaine 0.125% or their combination: effects on parturients. Anesthesiology. 1991;74(4):711-6. doi: 10.1097/00000542-199104000-00015.
4. Hunt CO, Naulty JS, Bader AM, Hauch MA, Vartikar JV, Datta S, et al. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for cesarean delivery. Anesthesiology. 1989;71(4):535-40. doi: 10.1097/00000542-198910000-00009.
5. Dahlgren G, Hultstrand C, Jakobsson J, Norman M, Eriksson EW, Martin H. Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for cesarean section. Anesth Analg. 1997;85(6):1288-93. doi: 10.1097/00000539-199712000-00020.
6. Kumar B, Williams A, Liddle D, Verghese M. Comparison of intrathecal bupivacaine-fentanyl and bupivacaine-butorphanol mixtures for lower limb orthopedic procedures. Anesth Essays Res. 2011;5(2):190-5. doi: 10.4103/0259-1162.94775.
7. Bansal N, Ladi S. Premixed versus sequential administration of intrathecal fentanyl and bupivacaine in elective caesarean section– A Comparative Study. Indian J Appl Res. 2016; 6(2):633–6.
8. Mehta S, Dalwadi H, Shad T. Comparative study of low dose bupivacaine-fentanyl Vs. conventional dose of bupivacaine in spinal anaesthesia for orthopedic procedures in elderly patients. Gujarat Med J. 2015;1:25–8.
9. Goel S, Bhardwaj N, Grover VK. Intrathecal fentanyl added to intrathecal bupivacaine for day case surgery: a randomized study. Eur J Anaesthesiol. 2003;20(4):294-7. doi: 10.1017/s0265021503000462.
10. Joshi S, Tailor R, Pandya M, Vachhrajani. Two Syringe Technique for Spinal Anesthesia in Cesarean Section: A Study of a Simple Way to Achieve more Satisfactory Block, Less Frequency of Hypotension and Prolong Analgesia. Int J Sci Res. 2018;7(1):1964–8.
11. Keera AAI, Elnabtity AMA. Two syringe spinal anesthesia technique for cesarean section: A controlled randomized

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study of a simple way to achieve more satisfactory block and less hypotension. Anesth Essays Res. 2016;10:312–8.
12. Sachan P, Kumar N, Sharma JP. Efficacy of premixed versus sequential administration of clonidine as an adjuvant to hyperbaric bupivacaine intrathecally in cesarean section. Anesth Essays Res. 2014 ;8(1):20–5.
13. Desai S, Lim Y, Tan CH, Sia AT. A randomised controlled trial of hyperbaric bupivacaine with opioids, injected as either a mixture or sequentially, for spinal anaesthesia for caesarean section. Anaesth Intensive Care. 2010;38(2):280-4. doi: 10.1177/0310057X1003800209.
14. Kestin IG. Spinal anaesthesia in obstetrics. Br J Anaesth. 1991;66(5):596-607. doi: 10.1093/bja/66.5.596.
15. Hocking G, Wildsmith JA. Intrathecal drug spread. Br J Anaesth. 2004;93(4):568-78. doi: 10.1093/bja/aeh204.
16. Kim EJ, Lee JH, Ban JS, Min BW. Patient Variables Influencing the Sensory Blockade Level of Spinal Anesthesia Using Hyperbaric Bupivacaine in Term Parturients. Korean J Anesthesiol. 2003;45(5):627-631.
17. Kyokong O, Charuluxananan S, Sriprajittichai P, Poomseetong T, Naksin P. The incidence and risk factors of hypotension and bradycardia associated with spinal anesthesia. J Med Assoc Thai. 2006;89 Suppl 3:S58-64.
18. Somboonviboon W, Kyokong O, Charuluxananan S, Narasethakamol A. Incidence and risk factors of hypotension and bradycardia after spinal anesthesia for cesarean section. J Med Assoc Thai. 2008;91(2):181-7.

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