INTRANASAL MIDAZOLAM VERSUS INTRAVENOUS DIAZEPAM IN STATUS EPILEPTICUS IN CHILDREN
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ABSTRACT: A seizure or convulsion is a paroxysmal, time limited change in the motor activity and/or behaviour that results from abnormal electrical activity in the brain. Seizure is common in the paediatric age group and occurs in 10% of children. In our study 170 patients aged between 3 months to 12 years with acute seizures were included. 85 of the randomized patients were given intranasal midazolam (Group M) and rest of the 85 patients (Group D) were given intravenous diazepam. The patients were comparable in the baseline demographic characteristics the clinical cessation of seizures was seen in Group M at 175.57±45.28 seconds and in Group D it was seen at 185.64±55.14 which had no statistical significance. From our study we could conclude that intranasal midazolam is as effective as intravenous diazepam in control of status epilepticus in children.

KEYWORDS: Intranasal, Intravenous, Midazolam, Diazepam, Seizure, Pre-hospital, Status epilepticus.

INTRODUCTION: A seizure or convulsion is a paroxysmal, time limited change in the motor activity and/or behaviour that results from abnormal electrical activity in the brain. Seizure is common in the paediatric age group and occurs in 10% of children (1). Prolonged or recurrent seizure activity persisting for 30 minutes or more can cause significant morbidity and mortality. The administration of anticonvulsant in pre-hospital settings may shorten the duration of seizure. (2-4) Benzodiazepines are currently the first line of therapy in for seizure therapy. Midazolam can be administered by different routes intravenous, intramuscular, buccal route and intranasal. It is a water soluble drug but at physiological pH it becomes fat soluble and can cross the nasal mucosa into the cerebrospinal fluid and may act rapidly. Intranasal midazolam has been administered by nasal spray by atomisation device with rapid absorption and achieving plasma and CSF concentration. Nasal spray can be administered rapidly with minimal training, less amount of drug administered. The present study aims to compare the efficacy of intranasal midazolam with intravenous diazepam.

Diazepam is used for control of all seizure in adults and children it can be administered by iv, or intramuscular, or per rectal, or through endotracheal tube. When given intranasally it is not effective in the control of seizures. (5,6,7) Intravenous diazepam is effective in the treatment of acute seizures but the need for placement of intravenous lines in emergency situation and its potential to cause respiratory depression is its drawback.

METHODOLOGY: After obtaining the institutional ethical committee clearance a total of 170 cases meeting the eligibility criteria were included in the study. A comparative study was
proposed on intranasal midazolam versus intravenous diazepam in status epilepticus in children aged between 3 months to 12 years. All types of active seizures were considered in the study. Informed consent was taken from the parents/guardians of the patients. i.v. canulation was done for all the patients, emergency drugs and resuscitation equipments were kept ready at all times. Air way, breathing and circulation were being supported. Patients were being monitored continuously for recurrence of seizure activity if any. Patients were randomised into two groups of 85 each by computer generated randomization charts. 85 children in Group M who received intranasal midazolam and 85 children in Group D who received intravenous diazepam for control of active seizures.

**Inclusion Criteria:**
1. Parents/guardian who gave consent for the study
2. Children with active seizures brought to emergency ward of our hospital, who were aged between 3 months to 12 years with seizure of more than 5 minutes.

**Exclusion Criteria:**
1. Children with upper respiratory tract infection.
2. Patients with known allergy to study drugs.

Group M received intranasal midazolam 0.3 mg/kg and Group D received 0.2 mg/kg of diazepam intravenously. Stop clock was started at the time of drug administration. The time taken for i.v canulation was not counted. The intranasal midazolam was administered by atomised device which delivered 500 microgram of drug per spray. (5 mg/ml midazolam spray was used). Once the patient had been stabilized the details were noted in a predesigned proforma.

Successful end point was taken as end of seizures or return of purposeful movements, within period of ten minutes. Seizures that stopped within 10 minutes of drug administration were considered as being successful control of seizure. Those which did not subside even after 10 minutes of drug administration were considered as treatment failure. Seizures that were controlled with midazolam or diazepam but recurred within 60 minutes were defined as recurrent seizures. Seizures that did not subside even after 10 minutes of drug administration or seizures with recurrence were managed as per hospital protocol.

Statistical analysis was done with percentages, arithmetic mean, standard deviation, independent samples t-test for comparing the two groups were employed using EPIINFO software for windows. P <0.05 was considered significant.

**RESULTS AND ANALYSIS:**

|          | Group m | Group d |
|----------|---------|---------|
| Male     | 40      | 44      |
| Female   | 45      | 41      |

Table 1: Sex distribution
There were 40 male children and 45 female children in Group M as compared to 44 male children and 41 female children in Group D. Both groups were found to be comparable with respect to sex distribution.

Table 2: Age distribution

| Age               | Group M | Group D |
|-------------------|---------|---------|
| N  | percentage | N  | percentage |
| 3 months-1 year  | 43      | 36.55   | 44  | 37.4   |
| 1-2 years        | 22      | 18.70   | 15  | 12.75  |
| 2-5 years        | 13      | 11.05   | 11  | 9.35   |
| 5-12 years       | 7       | 5.95    | 5   | 4.25   |

P=0.628.
Majority of cases were in the age group 3 months to 1 year i.e. 36.35% in Group M and 37.4% in Group D followed by 1 year to 2 year age group which had 18.7% and 12.75% in respective groups. The variation the age wise distribution was not statistically significant (p>0.05).

| Group | Mean time duration in seconds |
|-------|-------------------------------|
| Group M | 175.57±45.28 |
| Group D | 185.64±55.14 |

Table 3: Mean time duration for cessation of seizures (Seconds)

p=0.195.

The mean time taken from administration of the drug to stoppage of seizure was comparable in both the groups, the difference was not statistically significant.

| Group | N  | Percentage |
|-------|----|------------|
| Group M | 12 | 10.2       |
| Group D | 10 | 8.5        |

Table 4: Treatment failure

P=0.824.
The treatment failure was similar in both the groups. The p value being greater than 0.05 and had no statistical significance.

| Group | N  | percentage |
|-------|----|------------|
| Group M | 10 | 8.5        |
| Group D | 12 | 10.2       |

Recurrence of seizures

P=0.638.

Recurrences of seizures were similar in both groups and the difference was not statistically significant.

**DISCUSSION:** The present study included 170 patients. The distributions of age groups were comparable in both the groups. There was no difference in the sex distribution between the groups. Both the groups had similar occurrence of failure of treatment i.e., 12 in Group M and 10 in Group D. Recurrence of seizures was similar in both the groups i.e., 10 cases in Group M and 12 cases in Group D. There was no significant statistical difference in both the groups with reference to failures or recurrence of seizures (p= 0.824 and 0.638 respectively). The mean time duration for cessation of seizures in the intranasal midazolam group was 175.57±45.28 seconds and in the intravenous diazepam group was 185.64±55.14 seconds. The difference in the meantime duration was not statistically significant (p=0.195). The mean time to control of seizures was 3.58 (SD 1.68) minutes in the midazolam group and 2.94 (SD 2.62) in the diazepam group, not counting the time required to insert the intravenous line. The time needed to control
seizure using intranasal midazolam (3.16±1.24) was statistically shorter than intravenous diazepam (6.42±2.59) if the time needed to establish IV line in patients treated by intravenous diazepam is taken into account.9

The present study is done in a hospital setting but midazolam intranasal administration is easy and can be done faster even before I.V canula could be inserted. In our study we have not considered the time for insertion of I.V canula as both groups had a I.V canula insertion as per study protocol. Previous studies done with use of intranasal midazolam in pre-hospital settings.10

Other studies considered per rectal diazepam with intranasal midazolam.11,12

CONCLUSION: Thus intranasal midazolam is as effective as intravenous diazepam in control of status epilepticus in children. Advantage of intranasal midazolam being the flexibility to use in pre-hospital settings and in emergency settings without the need for i.v canulation. In this regard a larger study needs to be done.

LIMITATION: The EEG monitoring was not done and hence non convulsive status epilepticus could not be assessed.

BIBLIOGRAPHY:
1. Micheal. v. Johnston. Kliegman: nelson textbook of paediatrics,18th ed. Seizures in childhood. 593
2. Pellock JM. Status epilepticus in children: update and review. J Child Neurol. 1994; 9 (suppl) s 527-5535.
3. Verity CM. Do seizures damage the brain? The epidemiological evidence. Arch diseases of childhood 1998; 78: 78-84.
4. Alldredge B K, Wall D, Ferriero DM. effect of prehospital treatment on outcome of status epilepticus in children. pediatric neurul 1995; 12: 213-216.
5. Treiman DM. Pharmacokinetics and clinical use of benzodiazepenes in management of status epilepticus. Epilepsia. 1989. 30(suppl) s 4-10.
6. Treiman DM, Meyers PD, Watson NY et al. A comparison of four treatments for generalised convulsive status epilepticus. Veterens affairs status epilepticus co-operative society group. N Engl J Med 1998. 339(12); 792-798.
7. Eli Lahat, etal; Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study BMJ 2000; 321.
8. Mahmoudian T, Zadeh MM. Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. Epilepsy Behav. 2004; 5:253–5.
9. M javadzadeh et al, intranasal midazolam compared with intravenous diazepam in patients suffering from acute seizure: a randomized clinical trial.iran j pediatr. 2012 mar; 22(1): 1–8)
10. Warden CR, Frederick C. Midazolam and diazepam for pediatric seizures in the prehospital setting. Prehosp Emerg Care. 2006; 10: 463–7.
11. Bhattacharyyya M, Kalra V, Gulati S. Intranasal midazolam vs. rectal diazepam in acute childhood seizures. Pediatr Neurol. 2006; 34: 355–9.
12. Fisgin T, Gurer Y, Tezic T, et al. Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study. J Child Neurol. 2002; 17:123-6.
ORIGINAL ARTICLE

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