ORIGINAL ARTICLE

COMPARATIVE STUDY ON THE EFFICACY OF INTRANASAL MIDAZOLAM VERSUS INTRAVENOUS MIDAZOLAM AND INTRAVENOUS DIAZEPAM IN CONVULSING NEONATES AND CHILDREN

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Abstract

Aim: To compare the clinical efficacy of two routes of midazolam intranasal vs. intravenous, in relation to intravenous diazepam for control of seizures.

Methods: A prospective randomized study conducted on 150 convulsing patients of 0-19 years of age hospitalized in pediatric emergency ward and neonatal intensive care unit (NICU). Group-I was given intranasal midazolam at 0.3 mg /kg, Group-II was given intravenous midazolam at 0.3mg/kg and Group-III was given intravenous diazepam at 0.3 mg /kg. Outcome was measured in terms of time taken from physician contact to drug administration and the time taken from drug administration to cessation of seizures.

Results: Mean time from physician contact to drug administration was significantly shorter with intranasal midazolam as compared to intravenous midazolam and intravenous diazepam (0.40±0.10min vs. 1.06±0.40 min and 1.06±40 min) (p-0.03). Mean time from drug administration to cessation of seizures was lesser in midazolam [1.6 ± 0.3mins(IN) and 1.6±0.3min(IV)] as compared to diazepam (2.26±0.6 min) (p-0.06). However this difference was statistically insignificant. The vital parameters or oxygen saturation did not reveal any statistically significant difference between the three groups.

Conclusion: Seizure control was most prompt with intranasal midazolam.

Keywords: Midazolam, Diazepam, Intranasal, Intravenous, Seizures.

Introduction

Seizure is defined as paroxysmal change in motor activity and or behavior that results from abnormal electrical activity in the brain. (1) It constitutes about 70% of pediatric neurological disorders. It is a life threatening event and longer duration is associated with higher mortality and morbidity. Till date short acting anticonvulsants like benzodiazepines have mainly been used to control seizures. Benzodiazepines cross the blood brain barrier promptly achieve peak cerebrospinal (CSF) concentration within minutes of administration. Conventionally short acting benzodiazepines (Diazepam, Midazolam) are given by parental routes (IV or IM) for acute management of seizures. However intravenous (IV) line is often difficult to establish in a convulsing child and requires expertise. Intramuscular (IM) route cannot be relied upon as it has erratic absorption and delayed central nervous system (CNS) effects.(2) Thus various alternative routes of administration are under evaluation. Currently emphasis is being laid not only to control an acute episode in hospital setting but also for management of seizures at home. Various alternative routes of administration are intranasal, rectal, sublingual and buccal. Buccal and sublingual routes are difficult because of frothing and clenching associated with seizures. (3) Rectal route is socially less acceptable (especially in an adolescent. (4) Therefore intranasal (IN) route assumes more relevance as far as its convenience in drug administration is considered.

Midazolam is a water-soluble triazole-benzodiazepine. It has imidizole ring different from other benzodiazepines. At a pH less than 4 it is water soluble but at physiological pH it is highly lipophilic which accounts for its rapid absorption by rich vascular nasal mucosa reaching peak plasma and CSF concentrations within minutes of administration. It has shorter duration of action and rapid clearance twenty times faster than diazepam. (5) Thereby making it ideal for intranasal administration. We conducted this study to evaluate the efficacy of intranasal midazolam vs. intravenous midazolam and intravenous diazepam in convulsing neonates and children.

Methods & Materials

A prospective randomized study was conducted on 150 children over a period of one year in the Department of Pediatrics SMGS hospital Government Medical College, Jammu. One hundred and fifty patients between the age of 0-19 years hospitalized in pediatric emergency and neonatal intensive care unit (NICU) in a convulsing state were included in the study. The trial was permitted by the Ethical Committee of the institution. A written informed prior consent was taken from parents/guardians. Neonates were administered the drug only after excluding the metabolic causes. Neonates were given midazolam only as diazepam is known to interfere with bilirubin metabolism. Patients were randomized into three groups by serially numbered 150 opaque envelops. Treatment was then allocated by permuted block randomization to keep number equal in all the groups. The groups and drug administration are depicted below:

GROUP-I:- Administered commercially available preparation of midazolam @ 0.3 mg / kg as drops in each nostril through a syringe without needle .

GROUP II:- Administered commercially available preparation of midazolam @ 0.3 mg/kg through IV route by placing an IV cannula of appropriate size.

GROUP III:- Administered IV diazepam @ 0.3mg/kg.

After administering the drugs, vital parameters and oxygen saturation (saO2) was monitored for 30 minutes. Outcome was measured in terms of time consumed from physician contact to drug administration and from drug administration to cessation of seizures. The results were statistically analyzed using analysis of variance followed by post hoc comparisons by Bonferroni test. All analysis were performed using intention to treatment principle.

Results

All the three groups were comparable in terms of age, sex, prior history of seizure and intake of anticonvulsants (Table 1). Mean time from physician contact to drug administration was significantly shorter in Group-I (0.40±0.1 min) as compared to Group-II (1.06±0.40mins) and Group-III (1.06±0.40mins) (p=0.03). Time from drug administration to cessation of seizures was lesser in Group-I (1.6+ 0.3 mins) and Group-II (1.6±0.3mins) as compared to Group-III (2.26±0.3mins) (p-0.06). Effect of drugs on heart rate, respiratory rate, blood pressure and oxygen saturation is depicted in Table-2. Twelve (24%) had uncontrolled seizures and required another anticonvulsant to control seizures of which 3 (6%) are in group I, 4 (8%) in group II and 5 (10%) in group III.

Discussion

Intranasal administration of midazolam has been area of tremendous interest in recent years. The ability of rich vascular nasal mucosa to absorb drug readily reaching peak plasma and CSF concentrations within minutes of administration make it the prime route for fast and easy drug delivery. (6, 7) Our study included subjects from 0-18 years of age which is also similar to reported in other studies. (8) Majority of authors have studied children between 1-15 years of age excluding the neonatal period citing physiological differences and dissimilarity in seizure type. (9,10) Seizure control with midazolam has ranged from 75%-100% (11,12) which is similar to our study. In our study we observed that intranasal midazolam is a safe and effective anticonvulsant for acute management of seizures as time required from physician contact to drug administration was considerably shorter. Such situations where seconds matter, saving time can have significant impact on clinical outcome of a critically ill convulsing child and helps emergency physician to look into other aspects of critical care management. Reducing the duration of seizure also decreases the associated mortality and morbidity. Mean time from drug administration to cessation of seizures was similar in both the groups. The results obtained are in concordance with other studies. (13) No adverse cardio respiratory effect was noted. These observations were comparable to other studies. (14-16) Thus, we conclude that intranasal midazolam is a rapid, efficacious, socially more acceptable route of drug administration. It can be used not only in hospital setting but also for home management of seizures with proper education of the parents and caregivers.

Table 1: Baseline profile of patients in each group

Parameters	Group I	GP II	Group III	P value
Age				
< 1 month	4 (8%)	3 (6%)	0	
1month-1year	12 (24%)	14 (28%)	10 (20%)	0.31
1-6 years	24 (48%)	22 (44%)	24 (48%)	
6-12 years	8 (16%)	8 (16%)	12 (24%)	
12-18 years	2 (4%)	3 (6%)	4 (8%)	
Gender				
Male	30 (60%)	25 (50%)	26 (52%)	0.43
Female	20 (40%)	25 (50%)	24 (48%)	
Prior seizure	13 (26%)	14 (28%)	18 (36%)	0.51
Prior anticonvulsant usage	12 (24%)	14 (28%)	16 (32%)	0.80
Type of seizure				
GTC	31 (62%)	34 (68%)	35 (70%)	
Partial	11 (22%)	12 (24%)	10 (20%)	
Atonic	2 (4%)	1 (2%)	2 (4%)	
Multifocal	6 (12%)	3 (6%)	3 (6%)	

Table 2: Comparison of vital parameters in various groups.

Vital Parameters	Group-I MEAN±SD	Group-II MEAN±SD	Group-III MEAN±SD	p value
Hear rate/min	114 ± 27.54	110 ± 25.65	103 ± 21.32	0.06
Respiratory rate/min	39.68 ± 15.46	34.66 ± 16.07	31.1 ± 14.56	0.31
Blood pressure (mm Hg)	110/86	102/84	104/88	0.06
Oxygen saturation (%)	94.68 ± 5.69	94.58 ± 5.08	93.54 ±4.20	0.06

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