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Comparative Study on the Efficacy of Intranasal Midazolam vs Intravenous Midazolam in Convulsing Neonates and Children.

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ABSTRACT

To compare the efficacy of intranasal midazolam in relation to intravenous midazolam for control of seizures. To observe variability if any amongst the two groups in terms of heart rate, respiratory rate, blood pressure and oxygen saturation. A Prospective Randomized study conducted on 100 patients of 0-19 years of age hospitalized in emergency ward and NICU in a convulsing state. They were divided into two groups. GP-I was given intranasal midazolam @ 0.3 mg/ kg and GP-II was given intravenous midazolam @ 0.3 mg/ kg. Outcome was measured in terms of: Time taken from physician contact to drug administration. Time taken from drug administration to cessation of seizures. Mean time from physician contact to drug administration was significantly shorter with intranasal midazolam as compared to intravenous midazolam viz [0.40$\pm$ 0.10min vs 1.06+0.40$\pm$min) [p< 0.05].Mean time from drug administration to cessation of seizures was comparable in both the groups 1.0 $\pm$ 0.31 min and 1.0$\pm$0.32 min (p> 0.05). However this difference was statistically insignificant. The readings for oxygen saturation and vital parameters did not show a statistically significant difference amongst the groups. Seizure control was more prompt with intranasal midazolam as compared to intravenous midazolam. As time needed for drug administration was lesser. Intranasal midazolam is a rapid, efficacious, easy to administer and socially more acceptable route of drug administration. It can be used not only in hospital setting but also for home management of seizures after proper instructions to parents.

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 paediatric 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 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 [2]. However intravenous (IV) line is difficult to establish in a convulsing child and requires expertise. Intramuscular (IM) route cannot be relied upon as it has erratic absorption and delayed CNS effects [3]. 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 [4]. Rectal route is socially less acceptable especially in adolescent [5]. Therefore intranasal (IN) route assumes more relevance as for its convenience in drug administration is considered. Midazolam is a watersoluble 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, shorter duration of action and rapid clearance [6]. There by making it ideal for intranasal administration.

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We have conducted this study to evaluate the efficacy of intranasal midazolam vs intravenous midazolam in convulsing neonates and children at Shri Maharaja Gulab Singh Hospital Government Medical College Jammu.

MATERIALS AND METHODS

A prospective randomized study conducted was on 100 subjects over a period of one year in the department of Pediatrics SMGS hospital Government Medical College Jammu. All patients between the age of 0-19 years hospitalized in emergency and NICU in a convulsing state were the subjects of this study. Strict ethical considerations were followed after seeking permission of the ethical committee of the institution. Accordingly a written informed consent was taken from Parents/Guardians. Neonates were administered the drug only after excluding the metabolic causes. Hundred subjects were randomized into two groups by serially numbered 100 opaque envelops. Treatment was then allocated by permuted block randomization to keep number equal in all the groups. The groups and drug administration is as under:

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

GP-II: They were administered commercially available preparation of midazolam @ 0.3 mg/kg through IV route by placing an IV cannula of appropriate size.

After administering the drugs vitals and SaO2 was monitored for 30 minutes.

Outcome was measured in terms of time taken from physician contact to drug administration and from drug administration to cessation of seizures. The results were presented as mean and standard-deviation and statistically analyzed. Using analysis of variance followed by posthoc comparisons by Bonferroni test. p-value (<0.05) was regarded as statistically significant. All analysis was performed using intention to treatment principal.

OBSERVATIONS AND RESULTS

A total of 100 subjects were studied over a period of one year. The two groups were comparable in terms of age, sex (Table 1) prior history of seizure and intake of anticonvulsants. (Table 4). Mean time from physician contact to drug administration was significantly shorter in GP-I (IN MDZ) as compared to GP-II (IV DZP) and the difference was statistically significant p (<0.05) (Table 2). Time from drug administration to cessation of seizures was lesser in GP-I (IN-MDZ) as compared to GP-II (IV DZP) however the difference was insignificant (Table 3). Effect of drugs on heart rate ,respiratory rate and blood pressure (Table 4) as observed in intergroup comparisons drawn by bonferroni test was statistically significant between GP-I & II but the results cannot be taken as conclusion because of heterogeneity of age group (as midazolam group comprised of neonates also) (Table 4). And larger scale clinical trials are needed to unravel the clinical significance of such subtle differences. No significant effect was observed on SaO2, recurrence rate and number of uncontrolled seizures.

Table 1: Median distribution of age in the groups treated with midazolam by different routes (for each group sample size has been fifty n=50)

Age	Group-I	Group-II
< 1 month	4	3
1 month-1 year	12	14
1-6 years	24	22
6-12 years	8	8
12-18 years	2	3
Total	50	50

For distribution of sexes $\chi^2 = 1.127$, $p>0.05$, testing the homogeneity of sex ratios by Brandt & Snedecor's formula.

Table 2: Depicting the underlying etiology of seizures in both the groups

Etiology	Group-I	Group-II
Febrile seizures	13	14
meningitis	10	9
Epilepsy	8	10
Septicemia	2	1
Birth anoxia	2	2
Cerebral palsy & MR	7	8
Other causes	8	6

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Table 3: Distribution according to seizure type

Seizure Type	Group I	Group II
GTC	31	34
Partial	11	12
Atonic	2	1
Multifocal	6	3

Table 4: Showing past history of seizure and intake of antiepileptic medication

Prior H/O seizures	Group-I	Group-II
Yes	13	14
No	37	36
Prior AED intake	Group-I	Group-II
Yes	12	14
No	38	36

Table 5: Outcome of seizures in two groups

Outcome	Group-I	Group-Ii
Controlled	45	44
Uncontrolled	3	4
Recurrence	2	2

Table 6: Depicting time from physician contact to drug administration

Time from Physician contact to drug administration	Group-I	Group-II
Mean time and SD (n=50)	0.40 + 0.10 min	1.06+0.40min

P<0.05 which is highly significant.

Table 7: Time from drug administration to cessation of seizures

Time from drug administration to cessation of seizures	Group-I	Group-II
Mean time and SD (n=50)	1.0+ 0.32 min	2.26+0.32min

p>0.05 which is insignificant.

Table8:-Comparison of vital parameters and SaO2 in the patients treated with midazolam through different routes.

Mean and SD of Parameters	Group-I		Group-II	
	Mean	SD	Mean	SD
HR (per minute)	114	(27.54)	110	(25.65)
RR (per minute)	39.68	(15.46)	34.66	(16.07)
BP (mm Hg)	110/86	(27.4)/(12.38)	108/84	(25.69)/(11.82)
SaO2 (%)	96.16	(4.66)	96.38	(4.41)

P(<0.05) which is insignificant

DISCUSSION

Seizure is a life threatening event and frightening experience for both parents and caregivers. Longer duration of seizure is associated with higher mortality and morbidity. Hence to abort an acute attack is the immediate need of a convulsing child. Parental routes like intravenous and intramuscular require hospital setting and expertise whereas rectal route has its own social and personal adverse effects (more so in adolescents). Therefore 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. This study was conducted on 100 patients (0-19 years of age) brought to hospital in a convulsing state or who had a convulsion during the hospital stay. They were randomized into two groups each comprising of fifty patients. Group–I was administered intranasal midazolam and group-II was given intravenous midazolam. Outcome was measured in terms of time taken from physician contact to drug administration and time from drug administration to cessation of seizures. Majority of subjects were of 1-6 years of age and fairly uniformly distributed amongst the two groups. There are reports of similar study groups by [7, 8]. However our study even included the neonatal period which was only studied by [12]. Majority of seizures were generalized tonic-clonic convulsion -62% in group-I and 68% in group-II which is in concordance with 70% reported frequency of GTC in childhood seizures [1]. One third of patients in the study group were already on anticonvulsant treatment and fairly uniformly distributed amongst the sub groups and the profile of patients was

similar with other studies [18]. 94% of the seizure episodes were controlled in both the groups' recurrence rate and uncontrolled seizures were similar in both the groups and 2% of the patients presented with status epileptics. The results are comparable with studies available in literature were seizure control with midazolam ranged from 75%-100% [6, 10, 17, 18, 19]. 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 0.40 min in group-I (IN MDZ) as compared to 1.06 min group-II (IV MDZ). And 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 [11, 12, 13, 14, 15]. No adverse cardio respiratory effect was noted. These observations were comparable to other studies by [10, 16, 17, 18].

CONCLUSION

Intranasal midazolam is a rapid, efficacious, dignified and socially more acceptable route of drug administration. It can be used not only in hospital setting but also for home management of seizures.

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