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COMPARISON OF INTRAVENOUS, INTRANASAL OR BUCCAL MIDAZOLAM AS RESCUE MEDICATION FOR TERMINATION OF SEIZURES IN ACUTE CONVULSIVE STATE

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ABSTRACT

This study evaluated the anticonvulsant efficacy of midazolam to terminate seizures when administered by different routes (intravenous, intranasal or buccal route). This is a randomized controlled study done on 65 patients, who had seizure for more than 3 minutes or more than 3 seizures in 30 minutes. Patients were divided into 3 groups-Intra nasal midazolam (INM) group had 23 patients, 20 patients in intravenous midazolam (IVM) and 22 patients in buccal midazolam (BCM) group. Results showed that there was significant difference in decision to drug time [IVM (4.4+0.31), INM (1.2+1.1) and BCM (1.3+0.19) with p value of 0] , response time [IVM (1.6+2.1), INM(3.3+1.9), BCM(6.5+1.1) with p value 0]and Net time[IVM (5.7+1.8), INM(4.4+0.7),BCM (7.7+1.1) with p value 0]. But there was no significant difference in patients who did not respond to drugs, repetition of seizures and adverse effects. Present study shows that intranasal midazolam is one of the good options as rescue medication acute convulsion setting. This can be used in out of hospital setting also.

Keywords: Acute seizures, Midazolam, Route of administration, intravenous,intranasal, buccal .

INTRODUCTION

Epilepsy is second most common and frequently encountered neurological condition that imposes heavy burden on individuals and health care system. There are 12 million people with epilepsy in India, which contributes to 1/6 of global burden.[1] Prompt treatment of prolonged seizure is of paramount importance for patient safety.[2] Administration of rescue medication is usually required.[3] Anti-seizure drugs which are used as rescue medication have rapid penetration into CNS, this is critical feature of ASD for its efficacy. In addition to efficacy pharmacokinetics, route of administration, route and ease of administration also plays role.[3]

Benzodiazepines are the first line agents for treatment of acute seizures. Midazolam is one the rescue drug used to treat sever epilepsy, midazolam can be administered through various routes.[4]

The present study was performed to the compare the anticonvulsant effectiveness and safety of midazolam in seizures when it was administered by the intravenous, intranasal or buccal route.

PATIENT AND METHODS:

STUDY DESIGIN:

A randomized control trail performed on 65 patients with seizures.
Study period: November 2018 to November 2019.
Consent was obtained from the patient's attenders.

INCLUSION CRITERIA: Age above 15 years**,** criteria for rescue medication: Seizure more than 2 minutes, 3 seizures occurring in 30 min.

EXCLUSION CRITERIA: Children less than 15 years**,**

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Pregnant patients.

Patients who presented to emergency room with seizures and admitted patients who had seizures -who were with inclusion criteria were taken for the study. Irrespective of their previous anti-seizure drug intake status and type of seizures and cause of seizures, patients were considered in the study.

Patients were randomly divided into 3 groups,

IVM group: Patients who received 0.15 mg /kg (max 10 mg) intravenous midazolam. Drug administered through patent IV cannula secured in forearm. Drug used contained midazolam 1mg/ml and benzyl alcohol 1% v/v.

INM group: Patients who received 0.2 mg /kg (max 10 mg) intranasal midazolam. Drug administered nostril half dose in each nostril in form nasal spray.

Spray used in this study was midazolam delivers 0.5mg per each spray. (5mg/ml, aqueous intranasal spray, composition: Midazolam 0.5%w/v, benzalkonium chloride :0.01% w/v)

BCM group: Patients who received 0.3 mg/kg (max 10 mg) buccal midazolam. Drug administered through syringe in between gums and cheek. Drug which was used for IV form was only used.

Patients were given midazolam through any of the above route and time was noted. Decision to drug time: time between decision making to time of drug administration, response time: time taken for seizure cessation after drug administration, net time: total time i:e decision to drug time plus response time.

In Patients who did not respond to the first dose of rescue medication in 8 minutes, alternate intravenous anti-seizure drugs were administered, according to the clinical diagnosis. All the patients in the study were monitored for 24 hours in intensive care unit after rescue medication, they were observed for adverse effects: hypotension: MAP<65mmhg, respiratory depression: decreases in SpO2, apnoea and if respirator depression occurred patients were ventilated and repeated seizure episodes .

RESULTS:

Sixty-five patients were considered in the study. IVM group comprised 20 patients, INM group comprised 23 patients and BCM group comprised of 22 patients. Baseline characteristics of the patients are listed in table 01. Average age group in the study is 40. There is no significant difference in gender in 3 groups.

Drug administration and response time (table :02): It was observed that decision to drug time is significantly different among 3 groups: IVM (4.4+0.31), INM (1.2+1.1) and BCM (1.3+0.19) ,p value of 0 which is significant. There is significant difference in response time, IVM (1.6+2.1), INM(3.3+1.9), BCM(6.5+1.1) with p value 0. Net time was also significantly different- IVM (5.7+1.8), INM(4.4+0.7),BCM (7.7+1.1) with p value 0. Among 3 groups, p values of patients who did not respond to the drug and who had repeated seizures in 24 hrs was not significant (p value of 0.8 and 0.9 respectively).

Adverse effects: there was no significant difference in the adverse effects among 3 groups.

Statistical analysis: One-way ANOVA and chi squared test were used to test for differences among three groups.

Table 1. Patient characteristics

	IVM (n= 20)	INM(n=23)	BCM(n=22)
Age	40	42	39
Gender: male	12	11	12
Female	08	12	10
New onset seizures	3	4	4
Known case of seizures on regular antiseizure drugs	7	8	7
Known case of seizures on irregular antiseizure drugs	10	11	11

Table 2. Drug administration and the response

	IVM (n=20)	INM (n=23)	BCM (n=22)	P value
Decision to drug time	4.5 min	1.2 min	1.5min	0
Response time: Time of seizure cessation after drug administration	1.2 min	3.2min	6.2 min	0
Net time: decision to response time	5.7 min	4.4 min	7.7 min	0
Patients who did not respond in 8 min	3	3	4	0.8
Patients who required repetition of dose within 24 hours	2	2	2	0.9

Table 3. Adverse effects/ complications

	IVM (n=20)	INM (n=23)	BCM (n=22)	P value
Hypotension.	3	1	0	0.11
Respiratory depression	3	1	1	0.33
Ventilated patients	3	2	1	0.5

Other complications	Extravasation of drug (2 members)	Nasal irritation (6 members)	Bad taste (8 members)	
Problems encountered while administering the drug	Difficulty in securing cannula if patient is seizing	Septal injury/ bleed	gum/mucosal injury	
Cost effectiveness	Along with cannula approximately 200 rupees	450 Rs	70 Rs.	
Advantages	Rapid action	Easy to administer	Easy to administer	

DISCUSSION:

There are many studies comparing intranasal with rectal benzodiazepines, intravenous versus intra nasal benzodiazepines and various studies which compared efficacy of various drugs in benzodiazepine group for seizures.[5] Most of the studies have compared different drugs through different route. Present study compares the efficacy of same drug when administered in different routes.

In this study, efficacy, ease of administration and adverse effects of midazolam were compared when administered through intravenous (0.15mg/kg), intranasal (0.2mg/kg) and buccal (0.3 mg/kg) route. Dose of the drug was calculated according to the route of administration, because the bioavailability of the drug depends on the route of administrations.

Midazolam is proved to be an effective anticonvulsant drug. It's one of the commonly used alternative rescue medication use in acute seizures setting.[2]

Midazolam is water soluble, has small molecular weight, easily crosses blood brain barrier. It can be administered through various routs oral, sublingual, subcutaneous, intranasal, buccal, intramuscular, intravenous or per rectal.[3] Bioavailability of the drug has been shown to vary widely with rout of administration, with mean values of about 40% for oral, 52% for rectal, 75% for buccal, 83% for nasal, and 85% for intramuscular route[6].

In the event of seizures, the oral route of administration is rarely an option as swallowing is transiently impaired during a seizure or in the postictal state, and patients are prone to nausea and vomiting posing a high aspiration risk.[3] The most frequently used alternative is intravenous (IV) administration, which requires that a secured IV access be available at all times, which may affect patient comfort and does not guarantee that the access is patent when drug administration is needed.[3]

Midazolam has rapid entry in the CNS when transmucosal routes, richly vascular routes (intranasal, buccal and per rectal) were used. Intranasal route of midazolam administration (INM) demonstrated a time to maximum concentration (tmax) of 12 min, though time to minimum effective concentration is much faster at 2.5 min.[7]. INM is alternative to IV drug administration for seizure termination has been proven effective in the paediatric setting, including in convulsive status epilepticus. Buccal route the seizures terminated in about 6 to 7 minutes, it was easy to administer and safe, when compared to IVM but drug wash out is more in case of with salivation and prone for aspiration.[4]

The study by Silbergleit et al.[9] the interval between drug administration and seizure cessation was shorter in the IV BDZ group (median = 1.6 minutes vs. 3.3 minutes). Drug administration from the moment of decision was faster in the non-IV BDZ group (median = 1.2 minutes vs. 4.8 minutes). The end result is a nonsignificant difference in favour of non-IV BDZ. Mittal et al.[10] in their study also concluded with an overall faster seizure cessation from the point of hospital presentation in the non-IV BDZ group (mean ± standard deviation = 5.25 ± 0.86 vs. 6.51 ± 1.06).[5]

Advantages of administering drug through intranasal route over buccal route or intravenous route is 1) Performance of INM in aborting and preventing seizures is good. [11], [8], [12]; 2) complications or adverse effects were less in INM 3) improved patient safety even in absence of peripheral IV access, or difficulty using a peripheral IV due to ictal motor activity 4) can be administered in out of hospital setting.[3] 5)cost effective.

Limitations: Our study had some limitations, the underlying cause of the seizures, use of other anti-seizure drugs could play a role in the response to midazolam. Sample size is small.

CONCLUSION:

Present study suggests that intranasal midazolam is efficient and safe for treatment of acute seizures. Though the time of seizure cessation is significantly less in Intravenous midazolam group the net time is less in Intranasal midazolam group. Adverse effects were relatively less in INM and BCM groups. INM and BCM can be used in out of hospital setting also.

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