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Intranasal Vs Intravenous use of Midazola Comparison Between m in Patients Presenting to Emergency with Department Seizures

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ABSTRACT

Objective: To compare the efficacy of intranasal (IN) vs intravenous (IV) midazolam in patients presenting to the emergency department (ED) with seizures.

Study Design: Quasi-experimental study.

Place and Duration of Study: Emergency Department Combined Military Hospital Rawalpindi, Pakistan, from Aug 2023 and Feb 2024.

Methodology: All patients presenting with seizures were included except those who had already received treatment or had IV access. Convenience sampling was performed to include 74 patients divided into IN (Group-A) and IV (Group-B) groups. Efficacy was determined using four parameters: time-to-administration of medication (TA), Time-to-termination of seizure (TT), total time from arrival-to-termination of seizure (TTL), frequency of recurrence of seizure. Data was collected using a self-administered standardized questionnaire.

Results: Of 74 patients, 62(83.8%) were male and 12(16.2%) were female. The mean time in the groups A and B was: TTL 5.72+1.07 min and 5.05+1.07 min, respectively (p<0.001); TA in the groups was 2.97+1.236 min in Group-A and 4.16+1.14min in Group-B, (p=0.182); and TT 2.64+1.22 min and 1.85+1.22min, (p=0.984), respectively. There was no recurrence of seizures in either group.

Conclusion: For the management of seizures in the ED, it is quicker to administer midazolam intranasally as compared to the IV route. Overall, the TTL is between 5 – 6 minutes in both groups. Furthermore, the in route is safer and avoids risk of needle-stick injury, making this route equally effective, but safer and thus clinically more efficient.

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

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INTRODUCTION

Seizures are more common in children than adults, and 10% of children have at least one seizure during their lifetime.[1] Seizures are one of the most common presentations to the Emergency Department (ED), accounting for 1% of ED attendance.[2] They can cause irreversible brain damage, leading to mortality and morbidity, if not treated timely.[3]

Most seizures are transient and typically persist for a short duration, ranging from a few seconds to minutes usually less than three minutes.[4] Refractory status epilepticus (RSE) refers to persistent seizure activity despite intravenous (IV) administration of adequate amounts of two antiepileptic agents, and usually exceed 60 minutes.[5] Untreated status epilepticus (SE) may progress to RSE (29-43%), which may further progress to super-RSE (13-42%), advocating the need to initiate early therapy.[6]

Benzodiazepines (BZDs) are the first-line treatment for the management of active seizures, both pre-hospital and in-hospital settings.[7] Although available BZDs do not have much pharmacological benefit over one another, slight variations in their rate of absorption, duration of action, and mode of administration sometimes influence the choice of BZDs in different clinical scenarios.[8] In patients presenting to the ED with active seizure, the IV route is preferred as onset of action is very rapid. However, in seizing patients, it is difficult to secure IV access. For this reason, alternate routes of BZD administration such as intranasal (IN), buccal and per rectum (PR) are frequently used in patients presenting to the ED with seizures.[9]

Midazolam, one of the most commonly used BZDs for the termination of seizures, is water-soluble and may be given orally, buccally, IM, IV, IN, or PR.[10]

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We conducted study to compare the efficacy of IV versus IN midazolam in patients who present to the ED with seizures.

METHODOLOGY

This quasi-experimental trial was conducted in the Emergency Department of Combined Military Hospital Rawalpindi, Pakistan, between August 2023 and February 2024. Approval was secured from the hospital's Ethical Review Committee (certificate number 578) prior to data collection.

Inclusion Criteria: All patients of either gender, up to the age of 60 years, presenting to the ED with active seizures were included.

Exclusion Criteria: Patients who had already received pre-hospital treatment with antiepileptics and/or BZDs, had a functional IV access, allergic to midazolam and patients with acute major trauma with active seizure were excluded.

Sample size was calculated using OpenEpi calculator taking mean and standard deviation of IN (3.7684±1.4722) and IV (2.9428±0.9811) groups respectively.[11] The estimated sample size came out to be 74 patients, with 37 patients being place each in group: Group-A (IN midazolam) and Group-B (IV midazolam), randomly using the lottery method (Figure-1). Non probability convenience sampling was used, and informed written consent was obtained from parents of patients under the age of 18 years, guardians, or accompanying attendants, as appropriate.

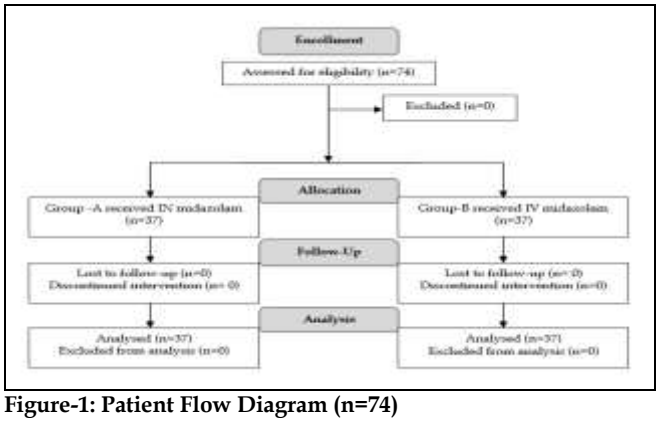


Figure-1: Patient Flow Diagram (n=74)

Dose was calculated according to the 2022 NASEMSO guidelines, with a recommended dosage of 0.2 mg/kg (max. 10 mg in total) for the IM or IN routes and 0.1 mg/kg for the IV route.[12] For the IN group (Group-A), half of the calculated dose of midazolam was delivered into each nostril which increases the surface area allowing for enhanced drug absorption.[13]

Due to the non-availability and high cost of a commercial nasal atomizer, an improvised mucosal devise was employed to administer midazolam via the IN route. All emergency physicians (mostly emergency medicine residents) working in the department received sufficient training on the IN technique to ensure standardization prior to starting the trial. In Group-B, rapid IV access was secured using a standard cannula (18G-24G), followed by IV administration of the calculated dose of midazolam. This was immediately followed by a 10 - 20 mL flush of normal saline (0.9% sodium chloride).

As convenient, the treating physicians completed a self-administered questionnaire for each patient in real-time. The questionnaire employed was self-structured and subsequently validated under the guidance of supervisor. It yielded a Cronbach's Alpha coefficient of 0.742. It includes required information such as, demographic characteristics, time of arrival to the ED, time of administration of drug, route used for drug administration, time of seizure termination, outcome of seizure (successful termination, delayed termination, resistant seizure, seizure recurrence), total time from arrival in ED to administration of drug (TA), time from drug administration to seizures termination (TT), total time from arrival to termination of seizures (TTL). Also documented were any complications that occurred, dose of drug used, and change in the route of administration of drug. Time was recorded in minutes and dose of medication was expressed in milligrams (mg).

Statistical Package for Social Sciences (SPSS) version 26.0 was used to analyze data. The Mean± SD was computed for quantitative data, while frequency and percentage were determined for qualitative data. Efficacy was determined using four parameters: time-to-administration of medication (TA), time to termination of seizure (TT), total time from arrival to termination of seizures (TTL) and frequency of recurrence of seizure within 60 minutes. Independent samples t test was applied between variables and a *p*-value of ≤ 0.05 was considered statistically significant.

RESULTS

In total 74 patients were enrolled in the study, consisting of 62(83.8%) male and 12(16.2%) female patients with a mean age of 10.44±16.65 years (Table-I).

Table-I: Characteristics of Study Patients (n= 74)

Age groups (years)	Total patients n=74		Male n=62		Female n=12	
	Group A n(%)	Group-B n(%)	Group A n(%)	Group-B n(%)	Group A n(%)	Group-B n(%)
1-16	28(37.8)	33(44.6)	22(35.5)	29(46.77)	6 (50)	4(33.33)
17-40	3 (4.05)	1 (1.35)	2 (3.22)	1 (1.61)	1(8.33)	-
41-60	6 (8.11)	3 (4.05)	5 (8.06)	3 (4.83)	1(8.33)	-

The mean dose of midazolam used in the Group-A was 2.26+0.99 mg, while 2.58+1.50 mg was used in the Group-B, (p=0.076). The mean time from arrival to seizure- termination (TTL) in both Group-A and Group-B were 5.72+1.07 minutes and 5.05+1.07 minutes, respectively (p<0.001). The mean time from arrival to administration of medication (TA) in the Group-A and Group-B were 2.97+1.236 minutes and 4.16+1.14 minutes, respectively (p=0.182). The mean time from administration of medication to seizure termination (TT) in Group-A and Group-B were 2.64+1.22 minutes and 1.85+1.22 minutes, respectively (p=0.984).

No change in route of administration of drug was done in either group at any stage of management, and no recurrence of seizure or complication was observed.

Mean time from arrival at ED to drug administration, time of cessation of seizures after drug administration, mean time from arrival at ED to seizures termination and p<0.001 were noted Table-II).

Table-II: Comparison of Time Interval between Groups (n=74)

	Group A (n=37) Mean ± SD	Group-B (n=37) Mean ± SD	*p*-value
TA (min)	2.97+1.236	4.16+1.14	0.182
TT (min)	2.64+1.22	1.85+1.22	0.984
TTL (min)	5.72+1.07	5.05+1.07	<0.001

**TA: Time from arrival at ED to drug administration, TT: Time of cessation of seizures after drug administration, TTL: mean time from arrival at ED to seizures termination*

DISCUSSION

Seizures are a common presentation to the ED, carrying a low mortality rate with timely intervention to control to the airway and terminate the seizure. Time is of the essence in these patients and thus the speed and efficacy with which the medication is administered is crucial. This need for timely management, while ensuring patient and healthcare staff safety leads to exploring various routes of drug administration. Our study show that midazolam effectively terminates seizures within five minutes in the ED, via both the IV and IN routes. Similar results are reported by other studies.[14-17] Furthermore, initiation of treatment is faster as TA in the Group-A (2.97 ± 1.23min) was half of that of the Group-B (4.16±1.14 min). This is because obtaining IV access in Group-B is time consuming and can be challenging in a seizing patient. While not statistically significant, these findings hold high clinical relevance, as perceived delay in initiating treatment (IV Group) can be frustrating for the healthcare provider and distressing for the patient's family. On the other hand, IN midazolam is easier and quicker to administer, carrying a low risk of needlestick injury thereby enhancing patient satisfaction and confidence in healthcare delivery. Interestingly, once the midazolam has been administered through the IV route, its onset of action is very rapid (TT: 1.85±1.22 min). This compensates for the slight delay earlier (TA). Although this shows that the IV route has a slight edge over the IN route, it is clinically acceptable as the mean total time to termination (TTL) for both groups of 5-6 minutes is comparable. These results are also comparable to those from a study by Fateh *et al.*, where they found that the IN route of midazolam administration is as effective as the IV route of diazepam administration in terminating seizures.[18] However, the present study has superiority as it focused on IN vs IV route of the same drug, midazolam, for termination of seizures.

A study by Batool et al. also shows that IN midazolam is effective for seizure control in children.[19] Our study, involving a mix of adult and paediatric population, echoes similar results.

During our study, we also obtained interview-based feedback from various ED doctors and nurses involved in the care of these patients. While there were no reported incidents of injury, most healthcare providers expressed a fear of accidental needlestick injury when trying to secure IV access in actively seizing patients, especially adults. Also, for these patients, especially adults, more human resources are required to physically restrain the patient. Attempts to restrain can be equally distressing in children and their parents, and may cause physical injury. In contrast, more satisfaction was reported in the Group-A, as it did not require additional staff or physical restraining, with a low risk needlestick injury. This was previously demonstrated in an Iranian study, where midazolam was easier to deliver through the IN route.[20]

The route and dose of midazolam impacts treatment outcome. Some literature suggests that for status epilepticus, IN delivery might be less successful than IV administration in stopping seizures, while IM administration falls between the two in effectiveness.[21] However, our study demonstrates that IN route was as effective as IV route in terms of termination of seizures. This is supported by the use of a pre-prepared FDA-approved IN midazolam formulation that is available for treating frequent seizures. It is easy to use and is effective outside of hospital settings and allows non-medical individuals to administer, enhancing accessibility. Studies show it stops seizures faster than rectal diazepam, the previous standard treatment, and is especially useful when IV administration is not an option, particularly in children.[22]

LIMITATIONS OF STUDY

The primary limitations of this study include its non-randomized, quasi-experimental design and the use of non-probability convenience sampling with a relatively small sample size (n=74), which introduces selection bias and limits the generalizability of the findings. Additionally, the extreme gender imbalance (83.8% male) skews the demographic distribution. Finally, relying on a self-administered questionnaire to capture precise time intervals during acute emergency seizure events creates a high potential for recall and measurement bias.

CONCLUSION

The IN route is equally effective, easier to use, carries a low risk of injury to patient and healthcare provider, and requires fewer resources compared to the IV route; making it more efficient in the ED. Further large-scale multicenter trials are required to validate the findings of our study, as well as conduct a cost-benefit analysis.

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Authors Contribution:

Following authors have made substantial contributions to the manuscript as under:

MUA & TP: Conception, study design, drafting the manuscript, approval of the final version to be published.

KB & HR: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AAM & MMN: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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