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STUDY OF THE COMPARISON OF SAFETY AND EFFICACY OF INTRAMUSCULAR MIDAZOLAM VERSUS RECTAL DIAZEPAM ACT AS ANTICONVULSANT IN CHILDREN

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Abstract:

Objective: *The aim of the study was to determine the efficacy and safety of midazolam given intramuscular to seize seizures in children as compared to rectal diazepam.*

Study Design: *Hospital based descriptive study.*

Place and Duration: *In the Pediatric department Holy Family Hospital Rawalpindi for one year duration from November 2017 to November 2018.*

Methods: *Children from 1 month to 18 years old had an acute seizure were included in the analysis. Patients were divided into two groups with intramuscular midazolam or rectal diazepam to terminate seizures. The interval duration of the drug administration was compared to stop the seizure. For determination of statistical analysis long range analysis was used. Side effects of both drugs were evaluated.*

Results: *Of the 66 patients, 33 were included in the analysis. For controlling seizures with intramuscular midazolam 45 seconds was the median time interval; There was a significant statistically variation between 2 time groups (p <0.02). In five patients, seizure duration was more than 5 minutes. The side effects in both groups are not statistically significant.*

Conclusion: *In children, Intramuscular midazolam is effective in stopping seizures. It may be alternative management for acute seizures in subjects with rectal or intravenous problems.*

Key words: *Muscular Midazolam, Seizure, Efficacy, Safety.*

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INTRODUCTION:

A seizure defined as abnormal paroxysmal neuronal discharge related with sensory, motor, behavioral or autonomic disorders [1]. It is thought to be due to the imbalance between inhibitory and stimulatory activity in the brain. According to data from pediatric assessment, seizures are two main stages in 10 primary pediatric neurological diseases [2]. In the United States about 150,000 adolescents and children going to health care for a kind of seizure issue every year [3]. In the United States and Europe2% to 4% of all children had at least 1 attack related to a fever before the age of 5 [4]. In developing countries, the incidence of infections is slightly higher. Benzodiazepine is generally regarded as the drug of choice in the seizures management, also with status epilepticus [6]. The management of rectal diazepam has been studied and tested in controlled trials [7]. Other safe and effective caregivers are offered to treat emergencies from families seized in a hospital environment. Diazepam rectal administration absorption differs and also embarrassing and has some draw bags like a relatively short life and half life, slow absorption of the drug, a loss of absorption by defecation and not being accepted by the patient[8]. Intravenous (IV) access is difficult to use and therefore requires more time. Midazolam is imidazobenzodiazepine with sedative, amnestic, anxiolytic, muscle stimulant and anticonvulsant properties. Diazepam has a more powerful and quicker onset of action [9]. Midazolam may be administered intravenously, intramuscularly, buccally or intranasally. The midazolam only among the benzodiazepines has physical-chemical properties that helps fast absorption after injection given I.M. When selecting a medication for the control crisis, the physician should consider the following criteria: a quick start for the small volume, fast, easy and safe use should be given to the application methods [10]. These analysis suppose that midazolam given intramuscular meets these criteria and may be useful in the treatment of seizures, but controlled studies are requires to test the efficacy of this treatment, especially in children.

MATERIALS AND METHODS:

This hospital based descriptive study was held in the Pediatric department of Holy Family Hospital Rawalpindi for one year duration from November 2017 to November 2018.

Children between 1 month and 16 years old were admitted to the hospital with all kinds of seizures. Patients with history of allergy to benzodiazepines, respiratory depression, acute diarrhea and status epilepticus were excluded. The seizure was classified as a criterion of treatment failure if it was not discontinued 5 min after midazolam IM or rectal diazepam administration. Parents received informed consent to continue working. The list of randomization sequences was generated using random generated computer number. Participants were given to 1 or 2 types of treatment among groups. From the investigators, allocation sequence is concealed who registered their patient's number wise on sealed envelopes. After participants completed all the basic assessments, the envelopes were opened and it was time to determine the type of intervention. Until total data entry was done, random codes were saved. After patients randomization rectal diazepam or IM midazolam was given randomly. Subjects were given IM midazolam at 0.2 mg / kg a dose, which was gently given into the vastus lateralis muscle or gluteal muscle. The other experiment was given 0.5 mg / kg of rectal diazepam given in the lying on one side or recovery position and inserting gently the applicator back tip and then looking down. Using a stopwatch (second) immediately when anticonvulsants started until the seizures were stopped; time was calculated. Until one hour after seizure patient was kept under observation. The seizure was classified by the doctor. The drug efficacy was determined by observing the cessation of seizures within five minutes. All data were saved in a parametric statistics. Using the Kolmogorov Smirnov test; normality data were tested. By using SPSS 17; statistical analysis was done. $P < 0.001$ was significant statistically.

RESULTS:

There were 69 subjects who participated in the study. Three people were discarded because of diarrhea and status epilepticus.

management.

TABLE 1: Baseline characteristic of the subjects

Characteristic	Intramuscular Midazolam n (%)	Rectal Diazepam n (%)	*p*
Sex			0,083
- Male	22 (66,7)	15 (45,5)	
- Female	11 (33,3)	18 (54,5)	
Age*			
- < 1 year	19	27	0,255
- 1-5 year	9	4	
- > 5 year	5	2	
Nutritional status ·			
- Severe malnourished	3 (9,1)	0	0,215
- Moderate malnourished	3 (9,1)	2 (6,1)	
- Well nourished	25 (75,8)	29 (87,9)	
- Overweight	1 (3)	1 (3)	
- Obesity	1 (3)	1 (3)	
History of seizure			
- Yes	14 (42,4)	13 (39,4)	
- No	19 (57,6)	20 (60,6)	0,802
Type of seizures			
- General	25 (75,8)	27 (81,8)	
- Partial	8 (24,2)	6 (18,2)	0,547

Statistically significant if p<0,05
* *Mann-Whitney* test
**Data in median (range) (bulan)
‡Uji Chi squaretest

Table 1 presents the basic characteristics of variables such as age, gender, nutritional status, previous seizure history, seizure type of the subjects before treatment. He was 12. The basic characteristics were homogeneous between the two groups. Thirty-two patients underwent intramuscular midazolam and 33 patients underwent rectal diazepam. Two groups were analyzed together. The median withdrawal period for midazolam IM group was found to be 45 (28.1 - 61.8) seconds and 180 (67.4 - 292.5) for rectal diazepam group p <0.001.

TABLE 2: Time to seizure cessation in IM midazolam compared to rectal diazepam

Variabel	Intramuscular Midazolam (n=33)	Rectal Diazepam (n=33)	*p*
Time to seizure cessation (Median + range)	45 (28,1 - 61,8)	180 (67,4 – 292,5)	<0,0001

There was a statistically significant time since the interruption of the seizure between the two groups. IM midazolam had a shorter duration than rectal diazepam to stop the seizures. In the last study, 5 people were observed to have more than 5 minutes (300 s) of seizures. Treatment was classified as failure criteria (Table 3).

TABLE 3. Failure to treatment

Administration	Time so seizure Cessation (second)	Diagnosis	Status Epilepticus
Intramuscular Midazolam	400	Encephalitis	Yes
Rectal Diazepam	452	Encephalitis	Yes
Rectal Diazepam	400	Encephalitis	Yes
Rectal Diazepam	367	Meningoencephalitis	Yes
Rectal Diazepam	360	Febrile seizure	No

This analysis determines the midazolam tolerability given IM and rectal diazepam given within 24 hours after onset. There were no variations significantly in the side effects incidence and complications between the two groups. Hypoxia occurred in 2 people who received midazolam with IM and in 2 people receiving diazepam rectally and improved with oxygen delivery. None of this was thought to require secondary intubation in respiratory depression caused by midazolam or diazepam.

DISCUSSION:

Seizures may lead to increased muscle activity leading to anaerobic metabolism and tissue deterioration, as well as increasing the cerebral metabolic rate beyond the oxygen and glucose supply to non-muscular ischemia and neuronal death[11]. Therefore, it is important to quickly check for seizures to minimize systemic and cerebral damage. Seizure can be a special challenge to deal with. An ideal anticonvulsant should be safe, effective, easy to manage, fast effective and cost effective. Diazepam has been used in the treatment of epilepsy and other convulsive syndromes in the last forty years and in the control of seizures in 60-80% of cases[12]. Several controlled studies have demonstrated the safety and efficacy of rectal diazepam when administered outside the hospital setting by non-medical caregivers[13]. Dreiffuss et al. Performed a randomized study of parallel diazepam treatment groups in which she gives placebo of 0.2 to 0.5 mg / kg rectal diazepam to 91 adults and children at home. Patients treated with rectal diazepam had fewer seizures and longer recurrences than those in the placebo group ($p < 0.001$)[14]. Therefore, intravenous or rectal preparations of diazepam are generally used in acute seizures, but it is difficult to obtain intravenous access in children with seizures and rectal administration of medications can be improved. Midazolam, a benzodiazepine, is the first water-soluble benzodiazepine. It offers many advantages over water, such as solubility in water, less pain in injection, faster onset of action, predictable and shorter time of action, lack of accumulation and lack of active metabolite. Midazolam is highly lipophilic in physiological PH, rapidly dispersed into tissues and central nervous system, and has a very rapid onset of action. This lipophilic trait explains the short duration of action, with active hepatic metabolism, eliminating the half-life of 1.17 (0.34) hours in pediatrics. From the body, it is eliminated much faster than diazepam (T1 / 2 30-56 hours), and, in contrast, midazolam has no long-term metabolites[15]. The volume of the distribution is not related to age or gender. No significant negative impact was recorded in this trial. The relationships between the dose of benzodiazepine, respiratory problems and the need for subsequent endotracheal intubation are not well known. McMullan stated that respiratory depression had an acceptable effect of benzodiazepine drugs and this meta-analysis showed that midazolam was as safe as diazepam in terms of respiratory complications. In this study, we found that intramuscular midazolam was effective in controlling seizures, similar to those reported in another study. We have shown that midazolam IM is more effective than acute rectal diazepam in acute exacerbations. Our data were consistent with the finding of midazolam IM's statistical superiority. The meta-analysis of McMullan et al. Revealed that midazolam in any path was superior to diazepam to ensure that the crises stopped in pooled analysis.

CONCLUSION:

Midazolam is safe and effective to seize seizures in children and works faster than rectal diazepam. It can be used as an alternative treatment for acute seizures in patients with intravenous or rectal difficulties. This innovative therapy offers interesting possibilities especially in pediatric emergency medicine and pre-hospital care, especially in developed countries. The use of midazolam for pre-hospital treatment with

local physicians and general practitioners is promising. This trial supports the clinical decision to use a more pramatic intramuscular approach in the hospital and to use pre-hospital treatment of acute attacks.

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