ORIGINAL RESEARCH

A Comparative Analysis of Prehospital Emergency Treatments: Midazolam Intramuscularly, Diazepam Enema, and Chloral Hydrate Enema for Pediatric Convulsions

Yao Cheng, MM; Fujun Yao, MM; Yanling Chen, BM

ABSTRACT

Objective • This study aimed to compare the effectiveness of prehospital emergency treatments using midazolam (MDL) intramuscularly, diazepam (DZP) enema, and chloral hydrate (CH) enema in managing pediatric convulsions.

Methods • A comparative observational study was conducted, and a total of 140 children with acute convulsions treated with prehospital anti-convulsions at Qinhuangdao First Hospital's emergency department between June 2015 and May 2019 were included in this study. The children were categorized based on the prehospital anti-convulsion measures received: group M (n = 48) received MDL intramuscularly, group D (n = 46) received DZP enema, and group C (n = 46) received CH enema. The emergency effects of the three treatment groups were compared.

Results • 1. Group M showed significantly shorter treatment preparation time and total rescue time compared to groups C and D (both $P < .05$); no significant difference was observed between groups C and D (both $P > .05$), including convulsion control time in the effective cases (45 in group M, 42 in group C, and 43 in group D) (all $P > .05$ Group M had effective rates of 93.75%, while group C and group D had rates of 91.3% and 93.48%, respectively (all $P > .05$); Group M had more controlled cases at 1 min, 3 min, 5 min, and 10 min than group C and group D (all $P > .05$). Group M had significantly fewer relapses, cases requiring intravenous maintenance treatment, and faster convulsion control after intravenous maintenance compared to groups C and D ($P < .05$), with no significant differences between groups C and D in time to recovery of consciousness and length of hospitalization ($P > .05$). 4. Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory (R) frequency, and peripheral oxygen saturation (SpO_2) showed no significant differences before and 10 minutes after medication in all three groups ($P > .05$); SBP and DBP levels fluctuated within the normal range, while HR decreased, R frequency decreased, and SpO_2 increased significantly 10 minutes after medication compared to before treatment ($P < .05$). 5. No significant adverse effects were observed in the three patient groups.

Conclusions • MDL intramuscular injection, DZP enema, and CH enema were effective prehospital treatments for pediatric acute convulsions. MDL intramuscular injection demonstrated advantages such as fast onset, reliable efficacy, ease of use, and high safety, making it more suitable for the prehospital treatment of pediatric convulsions. (*Altern Ther Health Med.* 2023;29(8):121-127).

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INTRODUCTION

Convulsions represent a prominent neurological emergency and a serious childhood illness, ranking among the most prevalent pediatric neurological symptoms. Infants and children are particularly susceptible, with an incidence of approximately 4%-6% in children under the age of 6, significantly surpassing the incidence in adults by 10~15 times.[1,2] Prolonged convulsive episodes exceeding five minutes, if left untreated, pose a substantial risk of brain tissue damage and even fatality.[3,4] Thus, it becomes imperative to promptly and efficiently address pediatric acute convulsions to achieve the shortest possible convulsion control time and minimize brain tissue harm.

Effective interventions are crucial to safeguard the well-being of pediatric patients experiencing convulsions. Prehospital emergency care plays a crucial role in the management of pediatric acute convulsions. Children experiencing acute convulsions may still suffer from convulsions or recurrent seizures lasting over 5 minutes, posing a risk of permanent

neurological damage if not promptly controlled.[5-7] Hence, rapid and efficient prehospital anti-convulsion treatment is essential to mitigate brain injury and improve prognosis.

Diazepam (DZP) intravenous drugs are the preferred treatment for pediatric acute seizures in China. However, administering these treatments in a school's complex environment can be challenging due to difficulties establishing a vein circuit. The traditional method of static push administration of diazepam may prove difficult, and various constraints, such as drug storage conditions and dosage forms, further complicate prehospital treatment for children.[8,9] DZP is not ideal for the initial treatment of acute convulsions due to its slow and unstable intramuscular absorption. Therefore, selecting safe and effective anticonvulsive measures in prehospital treatment becomes imperative.[10]

Currently, most research on pediatric acute convulsions and persistent convulsions therapeutics in both China and abroad has focused on in-hospital treatments, with limited attention to prehospital care. In this study, we selected children requiring prehospital treatment for acute convulsions from Qinhuangdao First Hospital. We compared the clinical efficacy and safety of midazolam (MDL) intramuscular injection, chloral hydrate (CH) enema, and DZP enema to explore safer and more efficient prehospital treatment methods for pediatric acute convulsions. The study aims to provide prehospital clinicians with a basis for selecting appropriate drugs for treatment decisions.

METHODS

Study Design and Patients Selection

In this study, we included children with acute convulsions treated at the prehospital emergency department of Qinhuangdao First Hospital from June 2015 to May 2019. The children were categorized into three groups based on the anti-convulsive measures they received: the MDL intramuscular injection group (group M, 48 cases), the DZP enema group (group D, 46 cases), and the CH enema group (group C, 46 cases). Detailed information regarding the enrolled 140 children was recorded, including their names, contact information, sex, age, weight, history of previous illnesses, birth history, etiology, and type of convulsive attack.

Clinical Manifestations of Convulsions

Convulsions present with a sudden loss of consciousness (partial seizures may have clear consciousness or partial impairment). They are accompanied by sudden, systemic, or limited tonic or clonic facial and limb muscle convulsions. Additionally, patients may exhibit hanging, staring, or squinting perioral salivation and facial cyanosis and may or may not experience urinary incontinence or apnea.[11]

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) Children exhibiting clinical manifestations consistent with acute convulsions; (2) Patients with seizures persisting with muscle twitching or unconsciousness (typically lasting for more than 5 minutes) at the time of enrollment; (3) No prior use of other anticonvulsant medications during the convulsion episode; (4) Parents and children willing and able to comply with the current treatment plan; (5) Written informed consent obtained from the parents of all enrolled children.

Exclusion criteria were as follows: (1) Individuals with known allergies to the drugs used in the test; (2) Patients with primary liver, kidney, heart, or other organ diseases; (3) Individuals with hematological system diseases, autoimmune diseases, genetic metabolic diseases, and systemic metabolic disorders; (4) Patients with myasthenia gravis, myotonia, myotonic dystrophy, or other neuromuscular junction diseases.

Intervention Methods

Children experiencing convulsive seizures upon prehospital admission received immediate anti-convulsive treatment. Group M received intramuscular MDZ (2 ml: 10 mg, State Drug Administration H10980025, Jiangsu Enhua Pharmaceutical Co. Ltd.) at a dose of 0.2 mg/kg, with a maximum of 10 mg. In Group D, DZP 0.5 mg/kg (maximum dose 10 mg) was administered as an enema in 5~10 ml of saline. Group C received a 10% CH enema at a dose of 0.5 ml/kg, with a maximum of 10 ml. Throughout the intervention, vital signs such as respiration, heart rate, and blood pressure were monitored, and mental and muscle tone changes were observed.

Standardized Treatment and Follow-Up

In this study, all three groups received the same standard treatments. Upon prehospital admission, the child was immediately placed in the lateral position, with the collar loosened and the head tilted to the side to clear any foreign bodies, vomit, or secretions from the oral and nasal cavities. The airway was opened for oxygenation, and a quiet environment with reduced stimulation was maintained. For fever exceeding 38.0°C, a single acetaminophen bolus (0.15 g/pc, State Drug Administration H13020458, North China Pharmaceuticals Hebei Huanuo Co., Ltd.) was administered anally to lower the temperature.

In cases of persistent peripheral oxygen saturation (SpO_2) decrease despite oxygenation, prompt tracheal intubation, breathing balloon, or ventilator-assisted ventilation was provided. Urgent transfer to the hospital was ensured. Upon admission, all children in both groups received identical treatment. Those with unremitting or recurrent convulsions were maintained on continuous midazolam therapy at a rate of 1 μg/(kg-min) and increased by 1 μg/(kg-min) every 15 minutes until seizure control was achieved (maximum dose ≤5 μg/(kg-min)). If the maximum effective dose was maintained for 24 hours without convulsion recurrence, the dose was gradually reduced by 1 μg/(kg-min) every 15 minutes to 2 hours until complete discontinuation.

Observation Indexes

The following observation indexes were recorded for the three groups: (1) Treatment preparation time: The time elapsed from the arrival of medical personnel to the child's

location until the start of medication administration; (2) Convulsion control time: The duration from the initiation of medication administration to the cessation of convulsions; (3) Total rescue time: The overall time span from the arrival of medical personnel to the child's location until the cessation of convulsions after medication administration.

Convulsion Control and Treatment Efficacy at Different Time Intervals. The number of cases where convulsions were controlled within specific time intervals was documented. Specifically, the number of children in each group whose convulsions were controlled within 1 minute, 3 minutes, 5 minutes, and 10 minutes after drug administration was recorded. Convulsion control within 10 minutes after drug administration was considered effective, while children who still experienced convulsions or showed persistent convulsions after 10 minutes of drug administration were considered ineffective treatment responses.

Treatment Outcomes and Maintenance Need Assesment. In this study, treatment outcomes were evaluated, and the number of cases with ineffective treatment, convulsion relapse, and the need for maintenance treatment were recorded for each group. (1) Ineffective treatment: children who continued to experience convulsions or showed persistent convulsions after 10 minutes of medication administration were classified as having ineffective treatment; (2) Convulsion relapse: children who experienced recurrent convulsions during the course of treatment were categorized as having convulsion relapse; (3) Maintenance treatment: children who exhibited unremitting convulsions or experienced recurrence after 10 minutes of medication administration and required further maintenance treatment were included in this category.

Vital Sign Monitoring. In this study, vital signs were closely monitored before and after medication administration in the three groups of children. The following parameters were observed: (1) Consciousness level; (2) Blood pressure (BP); (3) Respiration rate (R); (4) Heart rate (HR); (5) Peripheral oxygen saturation (SpO_2); (6) Body temperature; (7) Muscle strength; and (8) Muscle tone.

The blood pressure, respiration rate, heart rate, and peripheral oxygen saturation data were recorded both before medication administration and 10 minutes after drug administration.

Incidence of Adverse Reactions in Three Study Groups. This study assessed the incidence of adverse reactions in the three groups after treatment. The following adverse reactions were closely monitored: (1) blood pressure changes; (2) heart rate variations; (3) respiratory rhythm changes; (4) urinary retention; and (5) decreased blood oxygen saturation.

These adverse reactions were observed and recorded to determine their occurrence and potential impact on the study outcomes in each group.

Statistical Analysis

Statistical analysis was conducted using Statistical Product and Service Solutions (SPSS) 21.0 (IBM, Armonk, NY, USA). Normally distributed measures were presented as mean ± standard deviation ($\bar{x} \pm s$). One-way ANOVA was employed to compare the three groups, followed by the SNK-q test for multiple comparisons. Count data were expressed as the number of cases (%) and analyzed using the chi-square test or Fisher's exact probability method for group comparisons. The significance level was set at $\alpha = 0.05$, indicating that $P < .05$ represented a statistically significant difference.

Table 1. Comparison of basic information of children in the three groups

Item	Group M (n = 48)	Group C (n = 46)	Group D (n = 46)	F/χ^2 value	*P* value
Gender (%)				0.379	.827
Boy	28 (58.33)	26 (56.52)	24 (52.17)		
Girl	20 (41.67)	20 (43.48)	22 (47.83)		
Age (years; Mean, SD)	2.86 ± 1.96	2.84 ± 2.11	2.91 ± 1.93	0.015	.985
Etiology (%)				1.655	.949
Febrile Convulsions	29 (60.42)	26 (56.52)	28 (60.87)		
Epilepsy	7 (14.58)	6 (13.04)	4 (8.70)		
Intracranial Infection	6 (12.50)	6 (13.04)	5 (10.87)		
Other	6 (12.50)	8 (17.39)	9 (19.57)		
Seizure Type (%)				0.535	.765
Generalized Seizures	38 (79.17)	39 (84.78)	37 (80.43)		
Focal Seizures	10 (20.83)	7 (15.22)	9 (19.57)		

Note: n: Number of cases; SD: Standard deviation; F: F-statistic for analysis of variance (ANOVA); χ^2: Chi-square test statistic; Gender: The percentage of boys and girls in each group is shown in parentheses; Age: Mean age with standard deviation (SD) is given for each group; Etiology: The distribution of different etiologies in each group is shown; Seizure Type: The percentage of cases with generalized seizures and focal seizures in each group is presented.

RESULTS

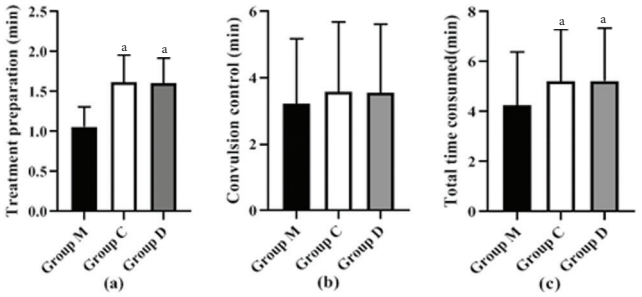
Comparison of Basic Information

Detailed information about the 140 enrolled children, including their names, parents' contact information, sex, age, weight, birth history, etiology, and seizure type, were recorded and compared. The results indicated no statistically significant differences in gender, age, etiology, and seizure type among the three groups ($P > 0.05$). Refer to Table 1 for details.

Comparison of Emergency Care

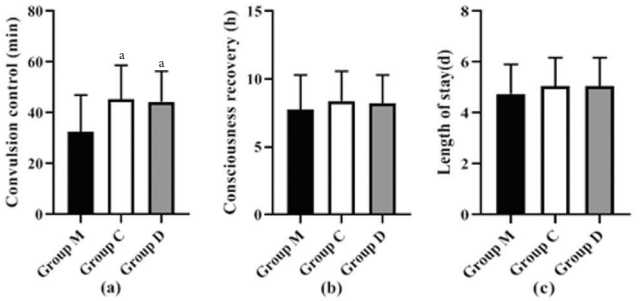
The prehospital emergency situations, including treatment preparation time, convulsion control time, and total rescue time, were recorded and analyzed in the three groups. The results revealed that Group M exhibited significantly shorter treatment preparation time and total rescue time compared to Groups C and D (both $P < .05$). However, there was no statistically significant difference in convulsion control time among the three groups for effective cases (45 in Group M, 42 in Group C, and 43 in Group D) (all

Figure 1. Comparison of emergency care for children in the three groups [n, (Mean, SD)]. (A) represents treatment preparation time; (B) represents convulsion control time; (C) represents total treatment time.



[a]$P < .05$, Comparison with group M.

Figure 2. Comparison of the effects of maintenance treatment among the three groups of children [n, (Mean, SD)] (A) represents convulsion control time; (B) represents the time to regain consciousness; (C) represents hospitalization time.



[a]$P < .05$, Comparison with group M.

Table 2. Comparison of children's convulsion control in the three groups at different times [n (%)]

Group	1 Min After Dosing (%)	3 Min After Dosing (%)	5 Min After Dosing (%)	10 Min After Dosing (%)
Group M (n = 48)	5 (10.42)	24 (50.00)	38 (79.17)	45 (93.75)
Group C (n = 46)	4 (8.70)	19 (41.30)	34 (73.91)	42 (91.30)
Group D (n = 46)	4 (8.70)	21 (45.65)	35 (76.09)	43 (93.48)
χ^2 value	0.111	0.716	0.364	0.252
P value	.946	.699	.833	.882

Note: The table presents the percentage of children with convulsion control at various time points after dosing in each group. The effective rate 10 minutes after dosing is also provided as a percentage. The χ^2 value and *P* value represent the statistical analysis of the data. No statistically significant differences were observed among the three groups at different time points ($P > .05$).

Table 3. Comparison of the effects of maintenance treatment among the three groups of children [n (%)]

Group	Treatment ineffective (%)	Relapses (%)	Maintenance Treatment (%)
Group M (n = 48)	3 (6.25)	5 (10.42)	8 (16.67)
Group C (n = 46)	4 (8.70)	12 (26.09)[a]	16 (34.78)[a]
Group D (n = 46)	3 (6.52)	14 (30.43)[a]	17 (36.96)[a]
χ^2 value	0.252	6.078	5.669
P value	.882	.048	.059

[a]Statistically significant difference ($P < .05$)

$P > .05$). Additionally, no significant difference was observed between Group C and Group D in comparing treatment preparation time and total rescue time (both $P > .05$). Please refer to Figure 1A-1C for detailed data.

Comparison of Convulsion Control at Different Times

Group M demonstrated 45 effective cases with an efficiency of 93.75%, Group C had 42 effective cases with an efficiency of 91.30%, and Group D showed 43 effective cases with an efficiency of 93.48%. The differences in convulsion control efficiency among the three groups were not statistically significant (all $P > 0.05$). Moreover, Group M exhibited more controlled cases at 1 minute, 3 minutes, 5 minutes, and 10 minutes compared to Groups C and D, but none of these differences were statistically significant (all $P > 0.05$). Refer to Table 2 for detailed data.

Comparison of Maintenance Treatment Effects

Group M exhibited significantly fewer relapses and cases requiring intravenous maintenance treatment compared to Groups C and D ($P < .05$). However, there was no statistically significant difference between Groups C and D in the number of relapses and cases requiring intravenous maintenance ($P > .05$).

All three groups achieved convulsion control after repeated dosing and continuous intravenous midazolam pumping. Group M demonstrated a shorter time to control convulsions after intravenous maintenance treatment compared to Group C and Group D, with statistically significant differences ($P < .05$). However, there were no statistically significant differences in the time to recovery of consciousness and hospitalization time among the three groups ($P > .05$). Refer to Table 3 and Figure 2A-2C for detailed data.

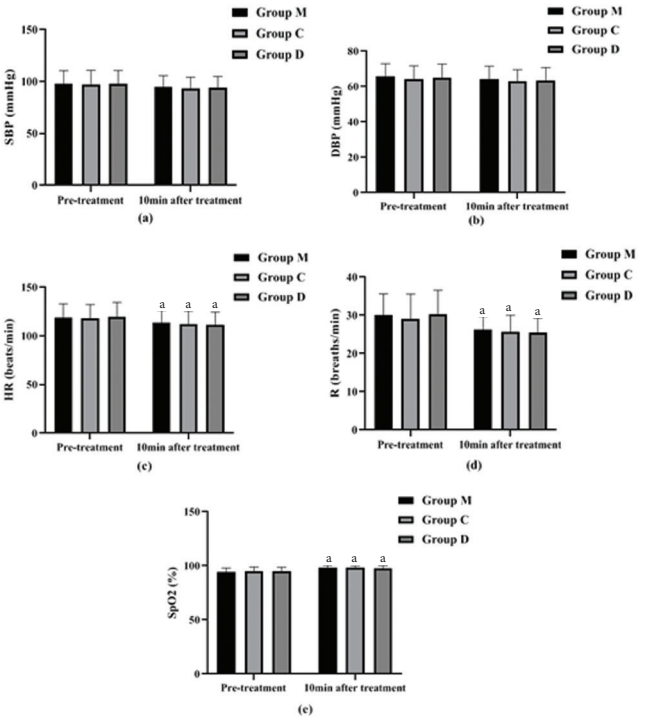
Vital Signs and Adverse Reactions Comparison

Before and 10 minutes after drug administration, the SBP, DBP, HR, respiratory frequency (R), and SpO_2 of the children in all three groups were similar, with no statistically significant differences ($P > .05$).

At 10 minutes after drug administration, SBP and DBP levels in the three groups showed fluctuations compared to before treatment, but they remained within the normal range ($P > .05$). The HR level and R frequency decreased significantly 10 minutes after medication, but the fluctuations were within the normal range, and thus, discontinuation of medication or treatment was unnecessary ($P < .05$). Furthermore, the SpO_2 levels of children in all three groups increased significantly at 10 minutes after drug administration compared to before treatment, reaching normal levels within the groups ($P < .05$). Refer to Figure 3A-3C for detailed data.

There were no abnormal changes in respiration, heart rate, blood pressure, and oxygen saturation during the medication period in the three groups of children. Four children in group C and three children in group D had defecation after medication, all of which occurred after stopping the convulsions and did not affect the efficacy, nor did they require re-infusion.

Figure 3. Comparison of vital signs and adverse reactions of children in the three groups before and 10 min after drug administration [n, (Mean, SD)]. (A) represents SBP level; (B) represents DBP level; (C) represents HR level; (D) represents R level; (E) represents SpO_2 level.



[a]$P < .05$, Comparison with group M.

DISCUSSION

Pediatric patients experiencing acute convulsions commonly manifest body or limb convulsions and tonic episodes, which typically subside within 2-3 minutes and do not necessitate specific treatment. However, if the convulsions persist frequently and the patient undergoes intermittent periods of non-recovery of consciousness, there is a risk of brain tissue damage.[12,13] Studies have demonstrated that convulsive seizures lasting 5-10 minutes can result in irreversible impairment of neurogenic function.[14] When the duration of an epileptic seizure exceeds 30 minutes, the brain loses its ability for systemic autoregulation and becomes hyperexcitable.[13-14]

Prolonged seizures are challenging to control and pose a higher risk of permanent brain damage.[15] Consequently, the definition of the convulsive state duration has been shortened to 5 minutes in recent years, emphasizing the significance of early management. Rapid and efficient prehospital anti-convulsive treatment has become crucial in reducing brain damage and enhancing the prognosis of children with convulsions.[16,17] Intravenous administration has traditionally been the primary method for controlling convulsive seizures; however, in prehospital settings, establishing intravenous access can be challenging, particularly in pediatric patients. As a result, rectal administration combined with intramuscular administration has emerged as a practical and clinically valuable alternative.[18]

This study compared the emergency effects of three non-intravenous routes: MDL intramuscular injection, DZP enema, and CH enema. The rectal administration of the DZP solution proves to be beneficial in promptly controlling convulsive seizures, especially in situations where venipuncture is difficult or during out-of-hospital convulsions. Nonetheless, it is worth noting that DZP is ineffective in approximately 12% of convulsive seizures and carries a potential risk of respiratory depression.[19]

Chloral hydrate exhibits rapid absorption into the bloodstream following rectal administration, bypassing the first-pass effect of the liver and avoiding the influence of the stomach and small intestine on the drug. Its high lipid solubility allows it to easily cross the blood-brain barrier, leading to widespread distribution in all organ tissues. The liver quickly metabolizes CH into active trichloro ethanol, effectively inhibiting the upstream activation system of the human brainstem reticular structures to induce sleep-like effects, thereby exerting fast sedative, hypnotic, and antispasmodic effects.[20,21] The advantages of CH include its rapid onset of action, effective anti-convulsive properties, ease of administration, affordability, and minimal discomfort for children. As a result, it is widely utilized in clinical practice as the initial anti-convulsive treatment for children with outpatient emergency convulsions.[22]

Chang et al.[22] conducted a study on intranasal fentanyl and midazolam for providing analgesic and anti-anxiety effects in children aged 3 years and younger. However, further prospective studies are necessary to evaluate better the safety and efficacy of these treatments in younger populations. The probable reason for the effectiveness of MDL could be attributed to its classification as a new class of benzodiazepines, acting as a complete agonist of benzodiazepine receptors, thereby exhibiting potent anticonvulsants and antiepileptic effects. Furthermore, MDL possesses a short half-life, approximately 1.5 to 2.5 hours, leading to minimal drug

accumulation and fewer adverse effects, making it well-tolerated by children during treatment.[22,23]

In this study, the group treated with MDL intramuscularly (group M) showed significantly shorter treatment preparation time, total rescue time, and time to control convulsions after maintenance treatment compared to group C (treated with CH enema) and group D (treated with DZP enema). Additionally, group M had fewer recurrences and fewer cases requiring intravenous maintenance treatment compared to groups C and D ($P < .05$). However, there were no statistically significant differences among the three groups in terms of time to convulsion control, time to recovery of consciousness after maintenance treatment, length of hospitalization, treatment efficiency, and vital signs (SBP, DBP, HR, R frequency, and SpO_2) after 10 minutes of medication ($P > .05$).

These results suggest that MDL intramuscular, CH enema, and DZP enema are equally safe and effective in treating prehospital pediatric acute convulsions, but MDL intramuscular is easier to administer and has better stability. The analysis of the reasons for this may be that more factors affect the enema. Firstly, the route of administration plays a significant role in the effectiveness of the treatment. Intramuscular injection is a direct method of delivering medication into muscle tissue, which is more straightforward and simpler than rectal administration. Rectal administration involves the insertion of a rectal tube, controlling the flow rate of the liquid, and positioning, while intramuscular injection only requires inserting a needle into the muscle tissue, making it more convenient.

The second factor to consider is the pharmacokinetics of MDL. Midazolam is a benzodiazepine medication known for its rapid absorption and quick onset of action. Muscle tissue has a fast medication absorption rate, allowing midazolam to enter the bloodstream quickly and achieve therapeutic effects. In contrast, rectal administration may require more time to reach the same drug concentration, making the therapeutic effects of intramuscular midazolam more stable and rapid.

The third factor is the presence of fewer interfering factors. Rectal administration involves multiple factors, including positioning, temperature, and the depth of insertion of the rectal tube, which may influence the effectiveness of the treatment. In contrast, intramuscular midazolam administration is relatively straightforward, with fewer interfering factors, leading to more stable therapeutic effects. Therefore, intramuscular midazolam should be prioritized in prehospital emergencies or when intravenous access is unavailable. This approach ensures a simpler and more reliable method of drug delivery.[24,25]

In this study, 4 cases in group C and 3 in group D experienced stool passage after medication, occurring after the cessation of convulsions, without affecting the efficacy or requiring additional irrigation. To prevent bloody defecation after enema, the enema solution can be diluted with an equal amount of normal saline to reduce intestinal mucosa stimulation by the drugs. After administration, parents can be advised to gently pinch the anus for 3-5 minutes and raise the child's hips to the left decubitus position, facilitating the entry of enema fluid into the deep colon due to gravity. This method avoids direct stimulation of the anal sphincter and rectum, reducing the urge for immediate defecation and prolonging the retention time of the enema fluid to ensure efficacy.[25] These findings support the safety and effectiveness of MDL, CH, and DZP as treatment options for prehospital pediatric acute convulsions.

Study Limitations and Future Implications

The study has certain limitations that should be acknowledged. Firstly, the sample size was relatively small, which may limit the generalizability of the findings to a larger population. To enhance the reliability and validity of future research, larger and more diverse samples should be considered. Secondly, the study only focused on prehospital emergency care and early treatment stages, lacking long-term follow-up data.

Future studies should incorporate longer follow-up periods to assess the sustained effects of different treatment methods and evaluate indicators such as long-term prognosis and recurrence rates. More rigorous randomized controlled trials should be designed to evaluate the effectiveness of different treatment methods better to compare the efficacy and safety of various pharmacological treatments. Additionally, the introduction of supplementary interventions, such as supportive care and other adjunctive therapies, can be considered to improve patient outcomes further. Despite these limitations, the current study provides valuable insights into the efficacy and safety of various treatment approaches for pediatric acute convulsions, laying the groundwork for more comprehensive investigations in the future.

CONCLUSION

In conclusion, this study demonstrates that MDL intramuscular injection, CH enema, and DZP enema are all safe and effective treatments for prehospital pediatric acute convulsions. However, MDL intramuscular injection emerges as a more convenient and stable option for prehospital emergency care. While the study included 140 cases, the sample size remains limited, and no significant adverse reactions were observed during the study. However, due to the strict dosage limitations and short duration of use, the relationship between drug dose and adverse reactions was not fully explored. To gain a more comprehensive understanding, future research should consider expanding the scope, increasing the sample size, and conducting further investigations to improve the study's overall outcomes.

DATA AVAILABILITY

The data can be obtained from the author upon reasonable request.

CONFLICTS OF INTEREST

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHORS' CONTRIBUTION

Yao C and Yanling C designed the study and performed the experiments, Yao C and Fujun Y collected the data, Yanling C and Fujun Y analyzed the data, and Yao C and Yanling C prepared the manuscript. All authors read and approved the final manuscript.

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ETHICS STATEMENT

The ethics committee of The First Hospital of Qinhuangdao approved this study.(EA2015089)

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