



Original Article

Comparison of Efficacy of Chloral Hydrate and Midazolam as Sedative in Diagnostic Neuro-Imaging of Children

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Abstract

Objective: To compare the efficacy of chloral hydrate and midazolam as sedative in diagnostic neuro-imaging of children.

Methods: This Randomized Controlled study was carried out for duration of six months from 23-05-2023 to 23-11-2023 at the Department of Pediatrics, PGMI/ Sheikh Zayed Hospital Lahore. Total 60 patients (30 in each group) from inpatient department of pediatrics Medicine, PGMI/ Sheikh Zayed Hospital, Lahore, were included in the study after fulfilling inclusion criteria. Lottery method was used to divide all patients randomly. Group A: chloral hydrate as oral suspension (50mg/kg) and group B: injectable midazolam (1mg/kg). Ramsay sedation scale was noted for assessment of sedation level.

Results: A total of 60 (30 in each group) patients were included. Mean age was calculated as 7.96 ± 3.20 years in group A (42.9% (n=18) females while 66.7% (n=12) were male and 9.66 ± 2.4 years in group B (57.1% (n=17) were females while 33.3% (n=6) were male). This study showed a significant difference in both groups. Efficacy in group A was 73.7% (n=28) and 26.3% (n=10) in group B with a p-value of 0.001.

Conclusion: Chloral hydrate is more effective compared to midazolam as a sedative in diagnostic neuroimaging of children.

Keywords: Midazolam; chloral hydrate; hypnotics and sedatives; conscious sedation; sedatives.

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Introduction

Sedation is drug-induced consciousness depression ranging from wakefulness to anesthesia. It reduces anxiety, pain, and patient movement during procedures. Children can get apprehensive during medical treatments.¹ Pain and anxiety might make the procedure harder for the medical team due to patient movement or noncooperation.²

There is a great deal of variation in how patients react to the same dose of a sedative medication. When a patient is tranquil, a dose that is capable of putting them into a deep sleep may not be sufficient to settle them down if they are agitated, even if the patient is the same one. In addition, even a little increase in the sedative dose might result in a fast shift in the amount of drowsiness for the same patient. This change can range from mild to severe sedation, which carries the risk of the patient losing their airway protecting

reflexes. In the past, studies have demonstrated that chloral hydrate (CH) has been associated with a longer and deeper sedation as compared to midazolam (MD).³

MRI is emerging technology for neuroimaging in both neurology and psychiatry because of its exceptional anatomical tissue contrast, safety (absence of radiation), and the capability to explore both anatomy and function.⁴ Because the scanner is very loud and the enclosed "tunnel" can quickly make children feel scared and anxious, so this is a greater problem in younger children. It is unfortunate that children who are younger may be less susceptible to training. This is because they may not completely understand or recall the instructions that are provided to them. Such procedures are often difficult to perform successfully in infants and toddlers. The period from birth to four years is a crucial and rapidly

changing phase of brain development. Therefore, following brain development over time is important to understand normal maturation as well as the causes of neurodevelopmental problems.^{5,6}

Despite the fact that chloral hydrate has been utilized as a sedative for several decades, it is not usually acknowledged as a suitable agent for sedation. A further investigation revealed that the group treated with chloral hydrate had a 100% efficacy rate, but the group treated with midazolam had a 50% efficacy rate.

The purpose of this study is to compare the efficacy of chloral hydrate and midazolam as sedative in diagnostic neuroimaging. There is lack of evidence available in our setting literature. Through this study we will be able to compare cost, as well as route of administration of two drugs. So, the results of this study will put forward current scenarios on this important aspect to formulate suggestion and recommendations for the pediatricians, so that in future, we may be able to make a protocol for use of proper drug as sedative for children undergoing neuroimaging.

Methods

A randomized controlled trial study was conducted in the Paediatric Department, PGMI, Shaikh Zayed Hospital, Lahore, over a six months duration. A total of 60 children, aged 1 to 12 years, of both genders and planned to undergo neuroimaging for indications such as brain or spinal cord tumors, epilepsy, nasal, facial, or oropharyngeal tumors, were included. Children who had received sedatives or hypnotic agents within the past 48 hours, those with documented allergy to the study medications, or those presenting with respiratory distress were excluded. A non-probability consecutive sampling method was used. A total of 60 patients (30 in each group) were included. The sample size was calculated with 80% study power and a 5% significance level, assuming an expected efficacy of 100% for chloral hydrate and 50% for midazolam.

After approval from the hospital ethics committee, eligible patients were included in the study, and written consent was obtained from their parents or guardians. Patients were randomly divided into two groups using the lottery method. Group A received oral chloral hydrate (50 mg/kg), while Group B received injectable midazolam (1 mg/kg). Sedation was assessed at 30 minutes using the Ramsay sedation scale, which has a total score range of 0–6. Efficacy was labelled if the Ramsay score was greater than 4 at the specified time point. Throughout the

procedure, continuous monitoring of vital signs was performed to ensure patient safety. All relevant data were recorded in a predesigned proforma.

Data was analyzed using SPSS version 25. Quantitative data (e.g., age) were expressed as mean $\pm$ standard deviation, while qualitative data (e.g., gender and efficacy) were presented as frequencies and percentages. The chi-square test was used to compare efficacy between the two groups, and a p-value < 0.05 was considered statistically significant.

The data were further stratified for age, gender, and weight, and post-stratification chi-square test was applied to assess the significance of differences between the groups, again considering a p-value ≤ 0.05 as statistically significant.

Results

A total 60 children were enrolled in this randomized controlled experiment; the two groups were made up of an equal number of children, with thirty children in each group. The average age of the patients in Group A (chloral hydrate) was 7.96 ± 3.20 years, while the average age of the patients in Group B (midazolam) was 9.66 ± 2.24 years, which is slightly higher. The majority of the children in Group A, at 66.7 percent, were between the ages of one and six years old. On the other hand, 57.1 percent of the children in Group B were between the ages of seven and twelve years old.

The gender distribution in Group A was 66.7 percent male and 42.9 percent female, while in Group B, males made up 33.3 percent and females made up 57.1 percent. Consequently, there were more males than females in Group A, and there were more females than males in Group B.

A substantial difference was discovered between the two groups when the level of efficacy in each group was examined. A p-value of 0.001 was found. The sedation was obtained in 73.7 percent ($n = 28$) of the children in the chloral hydrate group (Group A). On the other hand, the required sedation was accomplished in only 26.3 percent ($n = 10$) of the children in the midazolam group (Group B). The fact that chloral hydrate was considerably more effective than midazolam for sedation in pediatric neuroimaging is indicated here.

The findings from the age stratification revealed that chloral hydrate was effective in 90.9 percent of children between the ages of one and six years, compared to just 9.1 percent of children treated with midazolam ($p = 0.006$). Similarly, in children ages 7–12 years, chloral hydrate continued to outperform midazolam with an efficacy of 66.7% against 33.3%

in the midazolam group, respectively ($p = 0.001$). Consequently, chloral hydrate was continuously more efficacious in both age groups as compared to other treatments.

An analysis that took into account both sexes produced results that were comparable. Among the males, 90.9 percent of those in Group A were successfully sedated, compared to only 9.1 percent of those in Group B ($p = 0.006$). Among females, the efficacy of chloral hydrate (66.7%) was found to be substantially higher than that of midazolam (33.3%), with a p -value of 0.001. These data demonstrate that the superiority of chloral hydrate over midazolam is not influenced by gender.

Table 1: Distribution of Age, Gender, and Efficacy ($N = 60$)

Variable	Category	Group A (n=30)	Group B (n=30)	Total (n=60)	p-value
Age group	1–6 years	12 (66.7%)	6 (33.3%)	18 (100.0%)	0.041
	7–12 years	18 (42.9%)	24 (57.1%)	42 (100.0%)	
Gender	Male	12 (66.7%)	6 (33.3%)	18 (100.0%)	0.115 (ns)
	Female	18 (42.9%)	24 (57.1%)	42 (100.0%)	
Efficacy	Yes	28 (73.7%)	10 (26.3%)	38 (100.0%)	<0.001
	No	2 (9.1%)	20 (90.9%)	22 (100.0%)	

When stratification was performed according to weight, substantial disparities were likewise seen. For children who weigh ≤ 30 kg, the efficacy of chloral hydrate was 80%, while the efficacy of midazolam was just 20% ($p = 0.003$). Among children weighing more than 30 kilograms, chloral hydrate proved to be more effective again, reaching efficacy in 66.7 percent of cases compared to 33.3 percent of cases with midazolam ($p = 0.001$). This substantiates the efficacy of chloral hydrate. Significant differences were observed for age distribution ($p=0.041$) and efficacy ($p<0.001$). No statistically significant Gender distribution difference was found ($p=0.115$).

Discussion

Techniques and drugs that are employed in order to reduce anxiety and pain associated with difficult or unpleasant operations are together referred to as pediatric procedural sedation (PPS). Painful or difficult operations are necessary at times, and when they are, PPS is employed. Physical, psychological, and pharmacological therapies are incorporated into PPS in order to minimize discomfort. PPS is not restricted to more significant painful operations that necessitate heavier levels of sedation in the young patient group. Pediatric children who undergo common medical procedures, such intravenous cannulation, venipuncture, urethral catheterization, and lumbar puncture, can experience a significant amount of discomfort or anguish as a result of these treatments. Pediatric patients may need to have anxiolysis in order to have imaging tests such as CT or MRI scans, ultrasounds, or echocardiograms. This is done to ensure that appropriate imaging is obtained

Table 2: Stratification of Efficacy with Respect to Age, Gender, and Weight ($N = 60$)

Variable	Category	Efficacy – Yes (n, %)	Efficacy – No (n, %)	Total (n)	p-value
Age group	1–6 years	A: 10 (90.9%) B: 1 (9.1%)	A: 2 (28.6%) B: 5 (71.4%)	18	0.006
	7–12 years	A: 18 (66.7%) B: 9 (33.3%)	A: 0 (0.0%) B: 15 (100.0%)	42	0.001
Gender	Male	A: 10 (90.9%) B: 1 (9.1%)	A: 2 (28.6%) B: 5 (71.4%)	18	0.006
	Female	A: 18 (66.7%) B: 9 (33.3%)	A: 0 (0.0%) B: 15 (100.0%)	42	0.001
Weight group	≤ 30 kg	A: 16 (80.0%) B: 4 (20.0%)	A: 2 (22.2%) B: 7 (77.8%)	29	0.003
	> 30 kg	A: 12 (66.7%) B: 6 (33.3%)	A: 0 (0.0%) B: 13 (100.0%)	31	0.001

and to reduce the amount of stress that the kid experiences.⁸

PPS can be conducted skillfully in a variety of situations and is no longer only the domain of anesthesiology practitioners. In the present day, a number of nurse specialists, emergency and critical care physicians, and other experts routinely perform PPS. A multidisciplinary consensus on unscheduled, time-sensitive procedural sedation was created by the American College of Emergency Physicians (ACEP) in 2019.^{9,10}

The age distribution showed that in Group A, most children were 1–6 years old (66.7%, n=12), while 42.9% (n=18) were 7–12 years old. In Group B, 33.3% (n=6) were in the 1–6 year group, and a higher proportion, 57.1%, were aged 7–12 years. The average age was 7.96 ± 3.20 years in Group A and 9.66 ± 2.4 years in Group B. The patients were divided into groups based on gender. In group A, 66.7% (n = 12) of the patients were male, and 42.9% (n = 18) were female. In group B, 33.3% (n = 6) of the patients were male, and 57.1% (n = 57.1) were female.

One study found that chloral hydrate has been used as a sedative for decades, it not widely accepted as valid choice for sedation. Another study found that the percentage of efficacy was 100% in chloral hydrate group and 50% in midazolam group.¹¹ This study showed a significant difference in both groups. Efficacy in group A was 73.7% (n=28) and 26.3% (n=10) in group B with a p-value of 0.001.

Chloral hydrate treats insomnia with mild hypnosis. Short-term use is advised since chloral hydrate tolerance develops quickly. Long-term use can cause physical dependence, withdrawal anxiety, and insomnia. Currently, it treats simple insomnia temporarily. Chloral hydrate can cause rash, fever, and eosinophilia. Oral anticoagulants, antidepressants, and alcohol interact heavily with chloral hydrate. Hepatic encephalopathy can be caused or worsened by chloral hydrate in cirrhosis patients.¹²

Chloral hydrate has remained the drug of choice for sedation of children at a number of clinics because it is inexpensive.¹³ It is difficult to decide best drug for sedation due to its efficacy and data conflict. There is a great deal of research that indicates that there are a variety of additional effective sedative drugs that have pharmacokinetic profiles that are more predictable than those of chloral hydrate, including oral or intranasal midazolam. Many studies have found that chloral hydrate is more effective sedative in children than other agents, and it can be used in

specific painless diagnostic procedures, like auditory brainstem response, neurological imaging, and echocardiography.^{13,14}

Nonetheless, a great number of further studies have demonstrated that a variety of alternative sedative medications, such as midazolam, result in less serious negative side effects. Costa et al. conducted a study on children who used a high dose of either oral chloral hydrate or oral midazolam during dental procedures. They found that, among 118 cases of neurologic injury or fatal outcomes reported to the FDA, 65% children was sedated with chloral hydrate. It was all due to high dose of chloral hydrate.¹⁵

Intravenous midazolam is used for treatment of seizures and also is helpful in induction of anesthesia. It can control status epilepticus when other intravenous medications is not an option. Dose of midazolam can be increased in order to sustain the therapeutic effect because it has a high tolerance rate.¹⁶

Propofol's response to the induction dose is less consistent than thiopental's response to the induction dose when it is used for anesthesia.¹⁷ Midazolam is a medicine which used in sleep induction during general anesthesia and relieve anxiety. It requires the administration of fewer additional medications and better than thiopental for anesthesia. Midazolam is used in regional and local anesthesia for different diagnostic and treatment procedures and is well-received by patients and physicians.¹⁸

Conclusion

This study showed a significant difference in both groups. Efficacy in group A was 73.7% (n=28) and 26.3% (n=10) in group B with a p-value of 0.001. Hence it is concluded that chloral hydrate is more effective compared to midazolam as a sedative in diagnostic neuroimaging of children.

Ethical Approval: The IRB/EC approved this study via letter no. 02-TERC/NHRC-SZH/INT-SC/112 dated January 20, 2023.

Conflict of Interest: None

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Authors' Contribution

HS: Conception.

FJ, MFAK: Design of the work.

MKI, SB, KM: Data acquisition, analysis, or interpretation.

HS, MKI, SB, KM: Draft the work.

FJ, MFAK: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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