RESEARCH BRIEF

Oral Chloral Hydrate *vs.* Intranasal Midazolam for Sedation During Computerized Tomography

***Razieh Fallah, #Mohammad Hosein Ataee Nakhaei, †Shekofah Behdad, $Reza Nafisi Moghaddam and **Ali Shamszadeh**

*From the *Department of Pediatrics, Research Center of Pain and #Department of Pediatrics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; †Anesthesia and Intensive Care and **Department of Computer Engineering, Engineering and Basic Sciences Faculty, Islamic Azad University, Sari Branch, Sari, Iran.*

Correspondence to:
Mohammad Hosein Ataee Nakhaei, Shahid Sadoughi Hospital, Ave - Sina Blvd, Shahid Ghandi Blvd, Yazd, IR Iran. DrAtaii@yahoo.com
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We conducted this single blind randomized clinical trial to compare the efficacy and safety of oral chloral hydrate and intranasal midazolam for induction of sedation for computerized tomography scan of brain in children. Participants aged 1-10 years (*n*=60) were randomized to receive 100 mg/kg chloral hydrate orally with intra nasal normal saline OR intranasal midazolam 0.2 mg/kg with oral normal saline. Adequate sedation (Ramsay sedation score of four) was obtained and CT scan completed successfully in 76.7% of chloral hydrate group and in 40% of midazolam group (*P*=0.004). No significant difference was seen for side effects frequency between the two drugs (10% in chloral hydrate , 3.3% in midazolam group; *P*= 0.34). We conclude that oral chloral hydrate can be considered as a safe and effective drug for sedation in children undergoing CT scan of brain.

Key words: *Chloral hydrate, Computerized tomography, Intranasal midazolam.*

Good quality CT scan needs sufficient immobility of children during the procedure and sedation and anesthesia is often used for this purpose [1]. Different sedation regimens are used for sedation. Chloral hydrate is a non-opiate, non-benzodiazepines sedative-hypnotic drug which has been used for pediatric sedation induction [2]. But , there are concerns about its long duration of action, obstruction of airway, respiratory depression, oxygen desaturation and its potential for carcinogenicity [3].

Midazolam is a water-soluble benzodiazepine which can be used by different routes (oral, intravenous, intramuscular, rectal, sublingual, aerosolized buccal and intranasal) for pediatric sedation induction [4-7]. Intranasal midazolam is a nonparenteral route that does not cause pain of injection and is a useful and effective alternative to oral route in children [6]. We conducted this study to compare the efficacy of oral chloral hydrate and intranasal midazolam in children for sedation during an elective brain CT scan.

Methods

We followed a randomized single-blind study design. Thirty children were required in clinical, open-label, parallel group study conducted on the each group to detect a 20% difference in efficacy between the two drugs with type one error (alpha) of 0.05 and 80% power.

Eligible participants included children aged 1-10 years , referred to CT center for elective brain CT scan. These children were in American Society of Anesthesiology (ASA) class 1 (a normally healthy patient) or 2 (a patient with mild systemic disease eg, mild asthma, controlled diabetes mellitus) [8]. Exclusion criteria consisted of presence of gastritis or any other serious systemic disease, severe systemic reaction, head injury and receiving a sedative hypnotic agent within the past 48 hours.

The trial used computer generated equal randomization and allocation ratio was 1:1 for the two groups. Randomisation and blinding was done by an investigator with no clinical involvement in the trial. Data collectors, outcome assessors and data analysts were all kept blinded to the allocation.

The children were randomized to receive either single dose of 100 mg/kg oral chloral hydrate with one milliliter of intranasal normal saline as placebo (Group I) or 0.2 mg/kg intranasal midazolam with oral normal saline as placebo (Group II). Ramsay sedation scale was used for assessment of sedation level [9]. A score of four was

considered as adequately sedated. The primary outcomes were efficacy in adequate sedation and completing of CT scan.

Secondary outcomes included clinical side effects , serious adverse events (hypotension, hypoxia and cyanosis, severe vomiting, intractable irritability and agitation , apnea, laryngospasm, and bradycardia), time from administration of the drug to adequate sedation, caregiver's satisfaction on a likert scale (1-5), and total stay time in CT center. Respiratory depression requiring assisted ventilation, oxygen saturation of less than 90%, or a 25% or greater decrease in pre sedation mean arterial blood pressure were considered as serious side effects.

Failure to achieve adequate sedation (patient awakened or moved, interfered with completion of CT scan, inadequate sedation and need to administration of other sedative drug) and procedure abortion due to serious adverse events, were considered as failure of sedation regimen. The developmental status of the patient was assessed by a pediatric neurologist based on Denver II Developmental screening test.

The data were analyzed using SPSS 15 statistical software. Chi-square test or Fisher exact test was used for data analysis of qualitative variables and mean values were compared using independent t-test. Differences were considered significant at $P < 0.05$. Informed consent was taken from patients' parents and the study has been approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. This study is registered in Iranian clinical trials with registration number IRCT201107082639N4.

RESULTS

Sixteen children (24 girls) with mean age of 2.75± 2.3 years were evaluated **(*Table* I)**. Ramsay sedation score of four was achieved in 12 children (40%) in intranasal midazolam and in 28 children (93.3%) in CH groups, respectively ($P<0.001$). Brain CT scan was successfully completed in 40 % of Group II (95% CI. 0.23- 0.57) and in 76.7% of Group I (95% CI: of 0.62- 0.92) ($P<0.05$).

TABLE I DEMOGRAPHIC CHARACTERISTICS OF CHILDREN IN STUDY SUBJECTS

	Chloral hydrate (n = 30)	*Midazolam (n = 30)*	*P value*
Female	11	13	0.59
Delayed development	18	14	0.30
Age (y)*	2.68 ± 1.62	2.81 ± 1.63	0.83
Weight (kg*)	12.08 ± 5.7	11.66 ± 4.34	0.29

** (mean ±SD); #midazolam by intranasal route.*

***Table* II** shows comparison between the outcome in the two groups. Mild side effects such as vomiting occurred in 3 (10%) children in Group I and transient agitation in 3.3% of Group II. No serious adverse events were seen in any of the study subject.

DISCUSSION

Oral chloral hydrate was more effective than intranasal midazolm in sedation induction in uncooperative children undergoing CT scan. Dallman, *et al.* [7] in an earlier study, could not demonstrate any significant differences in behavior assessments (crying, movement, sleep) of 0.2 mg/kg intranasal midazolam and 62.5 mg/kg chloral hydrate with 12.5 mg promethazine. Layangool, *et al*. [10] demonstrated a comparable success rate of 99.2% for echocardiography with 50 mg/kg chloral hydrate or 0.3 mg/kg of sublingual midazolam. Our results are in agreement with another study with oral midazolam [11]. However, Schulte-Uentrop concluded that in sedation induction for MRI, chloral hydrate, pentobarbital and midazolam are not proper and dexmedetomidine may be a more effective drug in sedation induction in children without cardiac risk [12].

The lower efficacy of midazolam in sedation induction of children in present study may be related to the low dose of 0.2 mg/kg. Effectiveness of intranasal midazolam in dose of 0.5 mg/kg in conscious sedation of Iranian children was reported in another study [13].

TABLE II COMPARISON OF OUTCOME VARIABLES (MEAN ±SD) IN THE TWO GROUPS

Characteristics	*Chloral hydrate*	*Intranasal Midazolam*	*P value*
Acquired Ramsay sedation score	4.53 ± 1.19	2.93 ± 2.21	0.0001
Time from drug administration to adequately sedated (min)	23.75 ± 15.09	10.92 ± 4.23	0.02
Time after taking the drug to completing CT scan (min)	35.01 ± 12.6	35.14 ± 14.05	0.929
Caregiver's satisfaction scale	4.1 ± 1.28	2.4 ± 1.62	0.001
Total stay time in CT center (min)	56.06 ± 23.05	50.8 ± 15.3	0.56

WHAT THIS STUDY ADDS?

- Chloral hydrate is more effective than intranasal midazolam in sedation induction of uncooperative children undergoing CT scan.

Therefore, further boluses of intranasal midazolam, upto its maximum dose and its combination with other sedative drugs may be more effective in sedation of Iranian children and its usage as a premedication before anesthesia may be logical.

The limitations of this study were its small sample size and short duration of follow up. Therefore, it is suggested that further studies be conducted with larger sample sizes, longer follow up periods and different dosages of the drugs.

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REFERENCES

1. Wachtel RE, Dexter F, Dow AJ. Growth rates in pediatric diagnostic imaging and sedation. Anesth Analg. 2009;108:1616-21.
2. Avlonitou E, Balatsouras DG, Margaritis E, Giannakopoulos P, Douniadakis D, Tsakanikos M. Use of chloral hydrate as a sedative for auditory brainstem response testing in a pediatric population. Int J Pediatr Otorhinolaryngol. 2011;75:760-3.
3. Haselkorn T, Whittemore AS, Udaltsova N, Friedman GD. Short-term chloral hydrate administration and cancer in humans. Drug Saf. 2006;29:67-77.
4. Chiaretti A, Barone G, Rigante D, Ruggiero A, Pierri F, Barbi E, *et al*. Intranasal lidocaine and midazolam for procedural sedation in children. Arch Dis Child. 2011;96:160-3.
5. Singh R, Kumar N, Vajifdar H. Midazolam as a sole sedative for computed tomography imaging in pediatric patients. Paediatr Anaesth. 2009;19:899-904.
6. Klein EJ, Brown JC, Kobayashi A, Osincup D, Seidel K. A randomized clinical trial comparing oral, aerosolized intranasal, and aerosolized buccal midazolam. Ann Emerg Med. 2011;58:323-9.
7. Dallman JA, Ignelzi MA Jr, Briskie DM. Comparing the safety, efficacy and recovery of intranasal midazolam vs. oral chloral hydrate and promethazine. Pediatr Dent. 2001;23:424-30.
8. Cote CJ, Wilson S. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. Pediatrics. 2006;118: 2587-602.
9. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J. 1974;2:656-9.
10. Layangool T, Sangtawesin C, Kirawittaya T, Prompan W, Attachoo A, Pechdamrongsakul A, *et al*. A comparison of oral chloral hydrate and sublingual midazolam sedation for echocardiogram in children. J Med Assoc Thai. 2008;91:S45-52.
11. D'Agostino J, Terndrup TE. Chloral hydrate versus midazolam for sedation of children for neuroimaging: a randomized clinical trial. Pediatr Emerg Care. 2000;16:1-4.
12. Schulte-Uentrop L, Goepfert MS. Anaesthesia or sedation for MRI in children. Curr Opin Anaesthesiol. 2010;23:513-7.
13. Mazaheri R, Eshghi A, Bashardoost N, Kavyani N. Assessment of intranasal midazolam administration with a dose of 0.5 mg/kg in behavior management of uncooperative children. J Clin Pediatr Dent. 2008;32:95-9.