



# Efficacy and Safety of Intranasal Midazolam Versus Chloral Hydrate as Sedation for Quality Computed Tomography Imaging in Children

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## ABSTRACT

**Aim:** The purpose of this study was to compare the efficacy and safety of aerosolized intranasal midazolam (INM) compared to oral chloral hydrate (OCH) as procedural sedatives in pediatric patients undergoing computed tomography (CT) imaging.

**Materials and Methods:** A prospective, randomized, double-blind clinical trial was utilized in children aged 1 to 8 years who presented to the ED with minor head trauma and were scheduled to undergo brain CT scan. One hundred and sixty children were randomized to receive INM 0.3 mg/kg with oral placebo or 75 mg/kg OCH with intranasal placebo. If the patient was not adequately sedated 20 minutes after the initial dose, a second dose of the same medication at one-third of the initial dosage was given. The sedation level of patients after drug administration was assessed using the Ramsay sedation scale.

**Results:** Both groups were comparable with respect to age, male to female ratio, weight, and baseline vital signs. Sixty two children (77.50%) in the INM group and 59 children (73.42%) in the OCH groups reached a Ramsay score of four, respectively ( $p=0.55$ ). There was no significant difference in regards to the time to become adequately sedated ( $21.32\pm 6.54$  vs  $23.62\pm 7.40$ ,  $p=0.173$ ) and time for completing CT scan ( $30.37\pm 7.18$  vs  $32.96\pm 7.85$ ,  $p=0.185$ ). However, the time to recovery was shorter for the INM group ( $72.52\pm 10.17$  vs  $88.10\pm 10.27$ ,  $p=0.001$ ). No serious side effects were seen in the study groups ( $p=0.836$ ). The majority of parents were somewhat to very satisfied, 83.54% and 81.25% in the OCH and INM groups, respectively ( $p=0.928$ ).

**Conclusion:** INM can be used to sedate children between 1 to 8 years who are to undergo CT imaging of brain with a comparable rate of efficacy and safety to OCH.

**Keywords:** Chloral hydrate, computerized tomography, conscious sedation, intranasal midazolam

## Introduction

In order to obtain useful data from accurate imaging without excessive radiation exposure, a child needs to be laid down during the scanning procedure. The imaging tests that are affected negatively by motion [computed

tomography (CT) or magnetic resonance imaging] are the most common procedures for which children undergo sedation (1-3). Imaging can often be performed without sedation in older cooperative children and young infants (up to six months of age) who are swaddled and recently fed (1-4). It is difficult to keep younger children still during

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the time they need to get a scan. For CT, the child needs to lie still for 10-15 mins (3). There are several methods that can be used to limit the movement of a child during scanning.

Sedation has become more common for children undergoing imaging procedures. Adequate procedural sedation (PS) reduces patient's anxiety, reduces parental emotional distress and facilitates the ease, accuracy and the completion of the procedure (1,4). When a child is kept still long enough to obtain the necessary imaging, a successful sedation is assumed (5). A wide range of sedative medications are available for pediatric procedural sedation and analgesia (PSA) (6,7). The choice of drug and the targeted depth of sedation depends on the type of procedure and the patient's underlying medical condition (1-4). The ideal PSA agent should be one that has a quick onset of action, rapid recovery, few side effects, short and sufficient duration of action, provides airway protection, and has minimal effects on hemodynamics (8,9). Effective sedation may be given by several routes: Intravenous (IV) and oral, rectal, intranasal, transcutaneous, intramuscular and inhalation.

Oral chloral hydrate (OCH) is one of the first synthetic sedative agents, which has been considered as a sedative agent in pediatric patients for imaging, and it has been successfully given with other sedative agents (10-12). OCH produces effective sedation in 80-90% of patients (13). No significant adverse effects on cardiovascular or respiratory function have been reported at therapeutic doses (12,14). The main disadvantage is gastric irritation, which can lead to vomiting.

Midazolam has become the benzodiazepine of choice in PSA, with a more rapid onset and offset of effect (15,16). Midazolam is approved for many routes, including oral, IV, IM, rectal and intranasal (15-17). Intranasal Midazolam (INM) has got some advantages. INM can be rapidly absorbed through the highly vascularized nasal mucosa, resulting in a rapid and reliable onset of action. The shorter half-life, ease of administration, predictability and increased bioavailability by circumventing first-pass metabolism makes it a useful drug in the ED setting (17-21).

The dose of INM used in different studies range between 0.2 mg/kg and 0.5 mg/kg. The most common adverse effects reported following INM are burning or irritation in the nose and a bitter taste in the mouth (17-23). Aerosolized administration of midazolam on mucosal surfaces may enhance drug delivery. Aerosolized rather than drip administration of INM may decrease discomfort and improve tolerance of this route (24,25).

In this study, we compared the efficacy, safety, and recovery time of aerosolized INM and OCH as procedural sedatives in pediatric patients undergoing CT imaging. We evaluated the successful sedation rate, time to achieve sedation, sedation duration, and side effects.

## Materials and Methods

### Study Design and Setting

This study was designed as a prospective, randomized, parallel group, double-blinded placebo-controlled clinical trial. The study was conducted between September 2017 and June 2018 at Al-Zahra and Kashani Hospitals, two university hospitals in Isfahan/Iran. This study was approved by the ethics committee of Isfahan University of Medical Sciences (approval number: IR.MUI.REC.1396.3.516) and was registered in the Iranian Registry of Clinical Trials under the number (IRCT20180129038549N4). Informed written parental consent was obtained before enrolling children into the study.

### Participants

We enrolled a appropriate sample of children aged 1 to 8 years who presented to the ED with minor head trauma, were scheduled to undergo brain CT scan and who were determined by their physicians to require sedation. A complete history and physical examination determined all enrolled children as American Society of Anesthesiology class 1 (a normally healthy patient) or 2 (a patient with mild systemic disease e.g. mild asthma, controlled diabetes mellitus).

Children with any of the following criteria were excluded from the study: A history of developmental delay, underlying neurologic abnormality or autism; receiving a sedative hypnotic agent within the previous 48 hours; presence of gastritis or any other serious systemic disease; nasal allergy to drugs; obesity (body mass index >30), known contraindications to the use of the study drugs (e.g. hypersensitivity).

### Study Protocol

We used a computer-generated random number table, which maintained allocation concealment, to randomize children into two groups. Randomization and double blinding of medication use was done by an independent investigator who was concealed from the study investigators. Neither the patients who received the drugs nor their parents, nor any of the investigators who administered the drugs, nor the health care providers knew the active component of the study medication. Data collectors and data analysts were all kept blinded to the allocation.

After ensuring informed consent, the patient's demographics (weight, height, age, gender) were recorded. The patient's initial vital signs including respiratory rate (RR), heart rate (HR), and pulse oximetry (O<sub>2</sub> saturation) were documented.

The children were randomly divided into two groups: Namely the OCH group and the INM group. The OCH group received 75 mg/kg OCH (100 mg/mL, Merck KGaA Company, Germany) with 0.3 mg/kg of intranasal placebo and the INM group received 0.3 mg/kg INM (5 mg/mL, Tehran Shimi Company, Iran) with an oral 75 mg/kg placebo. The sedation level of the patients after drug administration was assessed using the Ramsay sedation scale (RSS) (5,9,10,19). A score of four is considered as adequately sedated. If the patient was not adequately sedated 20 minutes after the initial dose, a second dose of the same medication at one third of the initial dosage was given. In case of failure to create an adequate sedation within 40 minutes, the patient was excluded from the study.

The RSS and vital signs (oxygen saturation, HR and RR) were examined at 10, 15, 20, 25, 30, 40, 60 and up to 180 minutes as needed in the studied patients.

Placebos were prepared for INM and chloral hydrate syrup. Every child received both a spray and a syrup so that the chance of receiving either drug was equal. The drugs were prepared and packed by the pharmacist. Each package contained a nasal spray and syrup. The packets were marked A or B following the codes according to the randomization. In one packet, there were INM and oral placebo, and in another packet, there were an equal volume of chloral hydrate syrup and the intranasal placebo. The patients and their parents, nurses, health care providers, researchers, data collectors, and outcome assessors and data analysts were blind to the allocation.

### Outcome

The primary outcome measurement was the efficacy to induce adequate sedation to complete the CT scan. Adequate sedation was determined by the study nurse or physician.

A secondary outcome was the side effects (oxygen saturation of less than 90%, the need for assisted ventilation, vomiting, intractable irritability and agitation, laryngospasm, bradycardia and paradoxical agitation). The time from administration of the sedative drugs until adequate sedation, complete imaging and recovery criteria for discharge were also

recorded. Recovery criteria included the return to baseline alertness, ability to maintain a patent airway, and the ability to sit up for 10 seconds or longer.

Parent satisfaction on a Likert scale (very satisfied, somewhat satisfied, unsure, somewhat dissatisfied, very dissatisfied) was evaluated by a study team member (19).

### Statistical Analysis

Statistical analysis was performed using the SPSS 20.0 (IBM, Chicago, IL, USA). Chi-square test or Fisher exact test was used for data analysis of qualitative variables and mean values were compared using the independent t-test. All demographic and clinical variables were summarized using count and percentage n (%) for categorical variables and means plus or minus standard deviations for continuous variables. P<0.05 was determined to indicate statistical significance.

### Results

One hundred and sixty children were entered into the study and 159 patients were analyzed. The patients of the two groups (INM and OCH) had comparable age, male to female ratio, weight, and baseline vital signs (Table I). Sixty-two children (77.50%) in the INM group and 59 children (73.42%) in the OCH groups reached a Ramsay score of four, respectively (p=0.55). The acquired Ramsay sedation score was 3.95±0.618 and 3.82±0.655 in the INM and OCH groups respectively (p=0.648) (Table II).

All children received an initial dose of medication, 33 (41.25%) patients in the INM group and 29 (36.71%) patients in the OCH group required a second dose (p=0.627).

No difference was noted between the 2 study groups in regards to the time to become adequately sedated (p=0.173) and time to completion of CT scan (p=0.185). However, the

Characteristics	Midazolam, n=80	Chloral hydrate, n=79	p value
Age (y)	3.8500±1.72913	3.8354±1.7572	0.958
<b>Sex</b>			
Male (%)	53 (66.25%)	51 (64.56%)	0.932
Female (%)	27 (33.75%)	28 (35.44%)	
Weight (kg)	14.7750±3.63518	14.2911±3.77628	0.878
Heart rate, bpm	105.33±16.84	103.58±16.91	0.513
Respiratory rate	22.38±1.97	23.24±2.04	0.645
Oxygen saturation, %	98.63±0.93	98.46±1.03	0.334

time to recovery was shorter for the INM group ( $p=0.001$ ) (Table II).

No serious side effects were seen in our study groups. Side effects including a decrease in O<sub>2</sub> saturation  $\geq 10\%$  below baseline, vomiting, and paradoxical agitation were the same between the two groups ( $p=0.836$ ). The majority of parents were very to somewhat satisfied, 83.54% and 81.25% in the OCH and INM groups, respectively ( $p=0.928$ ) (Table II).

There was no need for any invasive resuscitation. Oxygen saturation, HR and RR showed no significant differences before and after sedation in both groups (Table III).

Outcomes	Midazolam	Chloral hydrate	p value
Adequately Sedated <sup>1</sup>	62 (77.50%)	59 (73.42%)	0.55
Second dose <sup>1</sup>	33 (41.25%)	29 (36.71%)	0.627
Acquired Ramsay sedation score <sup>2</sup>	3.95±0.62	3.82±0.66	0.648
Time to sedation (minimum) <sup>2</sup>	21.32±6.54	23.62±7.40	0.173
Time to completion of CT scan (min)	30.37±7.18	32.96±7.85	0.185
Time to recovery (minimum) <sup>2</sup>	72.52±10.17	88.10±10.27	0.001
Side effects <sup>1</sup>	10 (14.28%)	8 (10.12%)	0.836
Vomiting	6 (7.6%)	6 (7.6%)	-
Decreased O <sub>2</sub> saturation	2 (2.5%)	2 (2.5%)	-
Paradoxical agitation	2 (2.5%)	0 (0%)	-
Parental satisfaction <sup>1</sup>	-	-	0.928
Very satisfied	25	27	-
Somewhat satisfied	40	39	-
Unsure	12	10	-
Somewhat dissatisfied	3	2	-
Very dissatisfied	0	1	-

<sup>1</sup>Number (%), <sup>2</sup>Mean ± standard deviation

## Discussion

Appropriate sedation for children undergoing imaging in the ED is an important attribute for providing quality care and parental satisfaction. In this double blinded, placebo controlled randomized clinical study, the clinical effectiveness, safety, and potential side effects of OCH versus INM for pediatric sedation for brain CT scan were compared. The findings from this study show that 0.3 mg/kg of INM has comparable efficacy to 75 mg/kg chloral hydrate orally for sedation in children between the ages of 1 year and 8 years who underwent imaging.

Adequate sedation was achieved in 77.50% of the children who used INM compared with 73.42% for those who were given OCH. As in our study, Mekitarian Filho et al. (26) showed that the use of Aerosolized INM produced sedation in 76% of children within 20 minutes. Dallman et al. (27) showed an equal efficacy between INM (0.2 mg/kg) and chloral hydrate (62.5 mg/kg), although the latter caused longer sedation. However, Fallah et al. (5) showed that OCH was more effective than INM (93.3% vs 40%) in sedation induction in uncooperative children undergoing CT scan. The lower efficacy of midazolam in that study may be related to the low dose of 0.2 mg/kg. Stephen et al. (21) concluded successful sedation leading to completion of procedure was achieved in 95% of children with chloral hydrate compared with 51% for INM. Probably the differences between individuals, race and age range of the patients led to these differences.

Our study demonstrates a faster recovery time with INM versus chloral hydrate, similar to studies by Wheeler et al. (28), and Dallman et al. (27) while in contrast to Stephen et al. (21) Dallman et al. (27) and Wheeler et al. (28) showed that patients sedated with INM slept less and recovered more quickly than patients sedated with OCH, but Stephen et al. (21) showed that a significant difference in time to recovery was noted in the chloral hydrate group (78 minutes) versus the INM group (108 minutes).

The time to become adequately sedated and time to completion of CT scan was comparable between the 2

Parameter	Before sedation			After sedation		
	Midazolam	Chloral hydrate	p value	Midazolam	Chloral hydrate	p value
Heart rate, bpm	105.33±16.84	103.58±16.91	0.513	104.38±15.12	101.96±15.09	0.313
Respiratory rate	22.38±1.97	23.24±2.04	0.645	21.95±1.69	22.74±1.78	0.462
Oxygen saturation, %	98.63±0.93	98.46±1.03	0.334	98.12±0.80	97.91±1.25	0.523

Bpm: beats per minute, values presented as mean ± standard deviation

groups in our study similar to the study by Wheeler et al. (28) Stephen et al. (21) demonstrated a faster onset of sedation with chloral hydrate versus INM. However, Fallah et al. (5) showed a faster onset with INM. These differences in studies can be due to differences in drug dosage or how they were administered. Midazolam by oral or intranasal routes achieves successful sedation in only 50 to 87 percent of patients undergoing CT, with higher efficacy in patients receiving it by the intranasal route (15,16). Primosch and Guelmann (24), suggested that the use of a commercially available atomizer improved patient acceptance of INM administration but did not influence agent efficacy compared to drops administration for 2- to 3-year-old dental patients in an office setting.

Hijazi et al. (29), showed that chloral hydrate (75 mg/kg) compared to midazolam (0.5 mg/kg) had a higher sedation success rate, shorter time to achieve sedation, shorter length of stay in the hospital, and a longer sedation duration. Of course, oral midazolam has been compared in this study. Klein et al. (25), compared the administration of midazolam by 3 routes to facilitate pediatric laceration repair in the ED. They showed that 0.3 mg/kg INM produced superior sedation to identical doses via the buccal and oral routes with respect to time to onset, quality, and efficacy.

The dosages of medications used in this study were based on previous clinical literature and practice (5,7,10,16). Several clinical trials report satisfactory sedation with either of these dosages (5,21,29). Tsze et al. (18), determined the optimal volume of administration of INM sedation with escalating volumes of administration (0.2, 0.5, and 1 mL) during laceration repair in children in an ED. A volume of administration of 0.5 mL was associated with a statistically shorter time to onset of minimal sedation compared with a volume of administration of 1 mL or 0.2 mL, but all 3 volumes of administration produced comparable clinical outcomes. The effectiveness of INM at a dose of 0.5 mg/kg in the conscious sedation of Iranian children was reported in another study (30).

Parents' average satisfaction with the sedative effect of INM in children was 81.25% and with the sedative effect of OCH, it was equal to 83.54%. Stephen et al. (21), and Fallah et al. (5) showed parents to be more satisfied with chloral hydrate ( $p < 0.01$ ), while Wood (31) reported a higher score for INM.

In this study, INM and OCH were both found to be safe and effective drugs for sedation in children undergoing CT scan of the brain. No serious side effects were seen in our study groups.

### Study Limitations

There are limitations to the study design that may have impacted the outcomes. The limitations of this study were the small number of patients enrolled and the short duration of follow up, further studies are needed to prove the effectiveness and compare the effects of these drugs.

This study was limited by the use of convenience sampling when the research team was available.

Increased nasal secretion due to the crying of the child following the drugs being sprayed into their nostrils could have diluted the effective dose of the delivered midazolam, thereby causing lower absorption rates. Also, it was observed that some of the drug is lost due to coughing, or dripping from the nares. Therefore, it is not possible to definitively determine the volume and dosage of INM that was delivered intranasally.

To make sure enough concealment, the study pharmacist prepared nasal midazolam using the IV dosage form of midazolam for all patients in the INM group. The effective dosage may not be comparable with available commercial intra nasal midazolam.

### Conclusion

A dose of 0.3 mg/kg of INM, used for the sedation of those children between the ages of 1 to 8 years old who are to undergo CT imaging of brain, has as good an efficacy and safety profile as 75 mg/kg of OCH. Compared with chloral hydrate, INM showed an earlier recovery. This study demonstrated that INM and OCH are equally effective for pediatric sedation and have comparable parental satisfaction.

### Ethics

**Ethics Committee Approval:** This study was approved by the ethics committee of Isfahan University of Medical Sciences (approval number: IR.MUI.REC.1396.3.516).

**Informed Consent:** Informed written parental consent was obtained before enrolling children into the study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: F.H., S.M., M.N.E., Concept: F.H., Design: F.H., Data Collection or Processing: F.H., M.N.E., S.M., M.N.E., Analysis or Interpretation: F.H., M.N.E., H.S., Literature Search: F.H., M.N.E., S.M., M.N.E., Writing: F.H., M.N.E.

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