

A COMPARATIVE STUDY ON THE SEDATIVE EFFECT OF ORAL MIDAZOLAM AND ORAL CHLORAL HYDRATE MEDICATION IN LUMBAR PUNCTURE

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Objective: Lumbar puncture (LP) is usually associated with anxiety and apprehension in children and their parents. This study was performed for controlling children's anxiety before and during LP and increasing the success of LP due to relaxation of the child following the use of sedative drugs and to compare the efficacy and side effects of oral midazolam and oral chloral hydrate. **Method:** This prospective randomized controlled clinical trial included 160 children aged 2-7 years, candidates for LP. They were divided into two randomized groups of 80 children each: group I received 80 mg/kg oral chloral hydrate and group II received 0.5 mg/kg oral midazolam before LP.

Results: The results indicated that the mean sedation grade was 3.8 ± 1.0 in chloral hydrate group and 2.3 ± 0.9 in midazolam group ($P < 0.001$). The mean onset of sedative effect was 30.9 ± 8.8 min in midazolam group and 16.5 ± 5.8 min in chloral hydrate group ($P < 0.001$). Prolonged sedation was the most common side effect in oral midazolam group (94.4%) versus 22.2% in chloral hydrate group.

Conclusion: Based on the level of sedation, side effects, time to onset of sedation and recovery time from sedation, oral chloral hydrate is a better sedative medication than oral midazolam.

Key words: lumbar puncture, chloral hydrate, midazolam, anxiety, premedication

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INTRODUCTION

Chloral hydrate was the first therapeutic agent introduced as a synthetic central nervous system (CNS) depressant (1). It has been described as a safe and efficient medication (2,3). Midazolam is a short-acting benzodiazepine shown to be safe and effective when used for sedated pediatric procedure (4-6).

Lumbar puncture (LP) is indicated for both diagnostic and therapeutic purposes. It is used to obtain a cerebrospinal fluid (CSF) sample. Analysis of CSF is useful in the diagnosis of infectious processes and neurologic diseases. Therapeutically, LP can be used for injection of chemotherapeutic agents, anesthetic drugs and antibiotics in the subarachnoid space (7).

LP is a very painful procedure and causes severe anxiety and distress (8-10) that can persist for months after the procedure in some children (11).

The three main modalities reported to reduce preoperative anxiety in children include behavioral preparation programs of various kinds, parental presence during induction of anesthesia, and sedative premedication (12,13). Due to some limitations of behavioral preparation programs (14) and some findings about parental presence during induction (14,15), these options do not appear as suitable substitutes for sedative premedication.

The aim of this study was to compare the sedative effects of oral chloral hydrate versus oral midazolam and

assess their complications. We prescribe these drugs in common doses for patients.

METHODS

This prospective randomized controlled clinical trial was conducted at Emergency Department of Mofid Children's Hospital in Tehran. The study was carried out from June 2010 to November 2010.

Study design was approved by the Mofid Children's Hospital Ethics Committee. Study group consisted of 160 children older than 2 years examined by an Emergency Medicine resident and presented for LP. The children were completely conscious. The parents of all patients gave their written informed consent before inclusion in the study.

Patients were randomly divided into two groups. Group I patients received oral chloral hydrate syrup 80 mg/kg and if after 20 min this dosage was not effective, an additional dose of 20 mg/kg up to 2 g was administered (1). Group II patients received oral midazolam syrup 0.5 mg/kg 50 minutes before LP (14). An additional dose of up to 8 mg was administered to the children with inadequate sedation (16).

Patients with hypersensitivity or known idiosyncrasy to the study medications or having a history of psychiatric disease and those aged <2 years were excluded.

The children should be monitored during sedation because the accumulation of chloral hydrate can cause some complications such as excessive CNS, respiratory and vasomotor depression (1).

The Wheeler's sedation level score was used to assess the level of patient sedation (4,5), as follows:

Level 1: agitated, clinging to parents and/or crying;

Level 2: alert, awake but willing to leave parent with coaxing;

Level 3: calm and not fighting, but eyes open most of the time; and

Level 4: eyes closing spontaneously but response to minor stimuli.

The heart rate (HR), respiratory rate (RR), blood pressure (BP) and oxygen saturation were monitored during sedation.

An expert nurse was responsible to record any side effects in patients of either group.

Upon data collection, statistical analysis was performed by SPSS-18 and independent t-test used to compare the groups. The level of significance was set at $P < 0.05$.

RESULTS

The mean patient age was 3.4 ± 1.9 (2.2-6.5) years in the chloral hydrate group and 3.6 ± 2.6 (2.1-6.8) years in the midazolam group ($P < 0.778$). The mean weight was 16.8 ± 5.1 (11.0-29.3) kg in the chloral hydrate group and 18.1 ± 4.2 (10.8-32.1) kg in the midazolam group ($P < 0.123$). There were 42 girls and 38 boys in the chloral hydrate group as compared with 48 girls and 32 boys in the midazolam group ($P < 0.473$). The two groups were similar with respect to age, gender and weight. Also, there was no significant between-group difference according to baseline HR, RR, BP and O_2 saturation (Table 1).

The mean onset of sedation was 30.9 ± 8.8 (12-50) min in the midazolam group and 16.50 ± 5.8 (6-29) min in the chloral hydrate group ($P < 0.001$). Total recovery time was 68.9 ± 15.6 in the chloral hydrate group and 92 ± 20.9 in the midazolam group ($P < 0.012$).

Successful sedation (patient falling asleep or remaining calm enough (4) to complete the LP procedure was 92.5% (74/80) in the chloral hydrate group and 72.5% (58/80) in the midazolam group, which was significantly different ($P < 0.045$).

Five percent (4/80) of children in the chloral hydrate group and 10% (8/80) in the midazolam group needed an extra dosage of the drug ($P < 0.089$). The sedation level scores are shown in Table 2.

There was no significant change from baseline in vital signs and O_2 saturation during sedation in either group.

The most frequent side effect seen in children was prolonged sedation (75% in the midazolam group and 20% in the chloral hydrate group), yielding a statistically significant between-group difference ($P < 0.001$) (Table 3).

Table1.

The basal amount of vital signs

Vital sign	Chloral hydrate group	Midazolam group	P value
HR	120.7+16.7	120.1+12.3	<0.368
RR	27.0+4.9	25.8+7.3	<0.802
Systolic BP	98.8+16.9	100.7+21.3	<0.216
Diastolic BP	60.3+14.4	58.1+16.3	<0.070
O2 Sat	98.1+2.4	97.4+2.0	<0.407

Table2.

The sedation level score in two groups

	Chloral hydrate group %(n)	Midazolam group %(n)	P value
Level 1	5(4)	10(8)	<0.001
Level 2	5(4)	25(20)	
Level 3	13.75(11)	50(40)	
Level 4	76.25(61)	15(12)	

Table3.

Side effects in 2 groups

	Chloral hydrate group %(n)	Midazolam group %(n)	P value
Vomiting	2.5(2)	2.5(2)	<0.141
Headache	2.5(2)	1.25(1)	<0.087
Agitation	12.5(10)	16.25(13)	<0.208
Prolonged sedation	20(16)	75(60)	<0.001
Without side effects	62.5(50)	5(4)	<0.015

DISCUSSION AND CONCLUSION

Pharmacological advantages observed in the present study included rapid onset of action and shorter recovery from sedation, which can accelerate patient recovery. These results were in contrast with those reported by Layangool *et al.* in 2008 and D'Agostino and Terndrup in 2000 (5,17). They concluded that the duration of sedation was shorter in children who were sedated by midazolam. Layangool *et al.* also report a shorter onset of sedation for midazolam; however, they used the intravenous form of midazolam sublingually (5).

Results of some other studies showed that midazolam needed shorter time to the onset of sedation compared with some other medications such as promethazine and chloral hydrate (11,18). On the contrary, another study found no significant difference between chloral hydrate and midazolam according to the onset of sedation or side effects, but just like our study, chloral hydrate was found to provide more suitable sedation than midazolam (4).

As in Wheeler *et al.* and Layangool *et al.* studies, we found that most of the children in the chloral hydrate group had a deeper level of sedation compared with those in the midazolam group (4,5).

According to Vade *et al.*, the children's level of sedation should be higher than in adults because of their separation anxiety and fear, and this is in line with our results (3).

Similar to Wheeler *et al.*, no significant hemodynamic changes occurred in our study groups (4). On the other hand, Layangool *et al.* report an O₂ saturation reduction by more than 5% in the chloral hydrate group (5).

The overall side effects from midazolam were recorded significantly more often than with chloral hydrate, mostly related to prolonged sedation. This finding is in contrast to Layangool *et al.* (5), but their findings included vomiting and it should be noted that they prescribed a different route of drug administration (sublingual midazolam) and initially used a lower dose of chloral hydrate than our study.

D'Agostino and Terndrup found no significant relation of side effects in the two groups (17).

The main advantage of our study in comparison with other studies was that our population were not candidates for surgery and did not need induction of general anesthesia. Therefore, we assessed the actual amount of

sedation medications without the interfering effect of anesthetic drugs.

However, there were several limitations to our study. Our sample size was small. In addition, we only studied children older than 2 years because chloral hydrate has a contraindication for children younger than 2 years. Thus, our findings cannot apply to children younger than 2 years.

Similar to Wheeler *et al.* and D'Agostino and Terndrup, we found that the deeper level of sedation with chloral hydrate compared to midazolam may suggest the former as a successful and safe medication to sedate children over 2 years of age (4,17). In addition, our findings showed less adverse effects for chloral hydrate compared to midazolam. In a recent study conducted in Iran by Fallah *et al.*, they report chloral hydrate as a safe and effective medication in some procedures like LP in children (19). In addition, some studies demonstrated a combination of promethazine and chloral hydrate to be better than midazolam for children sedation at pediatric intensive care unit (20,21).

On the other hand, Layangool *et al.* report that chloral hydrate and midazolam can be used equally in young children (5). However, a multicenter study in a larger population with more varieties of sedative drugs is obviously warranted.

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S A Ž E T A K

USPOREDNA STUDIJA O SEDATIVNOM UČINKU PERORALNO PRIMIJENJENIH MIDAZOLAMA I KLORAL HIDRATA KOD LUMBALNE PUNKCIJE

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Cilj: Lumbalna punkcija (LP) je obično povezana s anksioznošću i nemirom djece i njihovih roditelja. Ova je studija provedena u cilju svladavanja anksioznosti djece prije lumbalne punkcije i u njenom tijeku te da se poveća uspješnost LP zahvaljujući opuštenosti djeteta nakon uporabe sedativnih lijekova, kao i da se usporede učinkovitost i nuspojave peroralno primijenjenih midazolama i kloral hidrata.

Metoda: Ova prospektivna randomizirana klinička studija provedena je na 160 djece u dobi od 2 do 7 godina kojima je trebalo učiniti lumbalnu punkciju. Podijeljeni su u dvije jednake randomizirane skupine po 80 ispitanika. Prva je skupina prije LP primila 80 mg/kg kloral hidrata peroralno, a druga skupina istim putem 0,5 mg/kg midazolama.

Rezultati: Pokazalo se da je prosječna razina sedacije iznosila $3,8 \pm 1,0$ u skupini koja je primila kloral hidrat, a $2,3 \pm 0,9$ u skupini koja je dobila midazolam ($P < 0,001$). Produžena sedacija bila je najčešća nuspojava nakon primjene midazolama (94,4%), a nakon primjene kloral hidrata uočena je u 22,2% djece.

Zaključak: S obzirom na razinu sedacije, nuspojave, vrijeme početka sedacije i vrijeme oporavka, kloral hidrat u peroralnoj primjeni je bolji sedativ od midazolama u istoj primjeni.

Ključne riječi: lumbalna punkcija, kloral hidrat, midazolam, anksioznost, premedikacija