A Comparison of Oral Chloral Hydrate and Sublingual Midazolam Sedation for Echocardiogram in Children

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Objective: *To compare the efficacy and safety of oral chloral hydrate and sublingual midazolam to sedate the children undergoing echocardiography.*
Material and Method: *A double-blind, randomized trial study in the children judged to require sedation prior echocardiogram were performed. Two hundred sixty-four patients between 6 months and 5 years of age were randomized to chloral hydrate or midazolam groups. Either 50 mg/kg of chloral hydrate orally or 0.3 mg/ kg of midazolam sublingually was given in each groups. If the child was not responded within 30 minutes after the first dose, another half dose of each drug for the second dose will be required. The action duration time, sedation score level and the ability to complete echocardiogram were collected.*
Results: *Both groups were comparable with respect to age, sex, body weight, underlying heart disease, baseline O_2 saturation and functional heart classification. The children in chloral hydrate group needed the second dose for sedation more than midazolam group (10.6%, 5.3% p = 0.111). The onset, action duration and total study time were significantly shorter in midazolam than in chloral hydrate group (p < 0.001). The number of the patients who had the action duration within the optimal time (< 45 min) were significantly more cases in midazolam than in chloral hydrate group (93.1%, 43.5% p < 0.001). Success rate of echocardiogram was 99.2% in each group. There was no difference in echocardiographic time performed in both groups. The children in chloral hydrate group had deeper in level of sedation (p < 0.001). Both groups showed no significant difference in term of the ability to complete echocardiographic examination. The reaction of the children to take the medication and the number of the patients who had systemic O_2 saturation change more than 5% from the baseline were higher in chloral hydrate group significantly (14.4%, 4.5% p = 0.006 and 9.9%, 3.1% p = 0.025).*
Conclusion: *Sublingual midazolam at the dose of 0.3 mg/kg can be used to sedate the children at age group between 6 months to 5 years who undergoing echocardiogram with comparable rate of success and safety as 50mg/kg of chloral hydrate orally. The less depth in the level of consciousness after sedation with midazolam compare to chloral hydrate may be advantage in a high risk patient to avoid deep sedation but may be disadvantage in case who need more comprehensive echocardiographic evaluation.*

Keywords: *Conscious sedation, Echocardiogram, Midazolam, Chloral hydrate, Heart disease, Congenital*

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Chloral hydrate has been used for hypnosis and sedation in children for more than a hundred years[1-3]. Mostly clinical used of the chloral hydrate is pre-medication for invasive and non-invasive procedures[1,4-8]. Due to time honorly, relative short action duration and rather safe from side effect, chloral hydrate has been used continuously for a long time in children. The disadvantage of chloral hydrate is difficult to take from a bitter taste, vomit and may cause respiratory depression especially in patients

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with severe congenital heart disease or compromised respiratory function[9-11].

Echocardiogram is very useful to confirm the clinical diagnosis of congenital heart disease. Accurate data from echocardiogram is very important for decision-making. This painless procedure can be performed on quiet, calm, non crying children; so many young children may need some sedation. Chloral hydrate has been used for this purpose with a low rate of adverse events. Most of the cases become to deep sedation after taken chloral hydrate[12-14], which may depress the consciousness more than needed for echocardiogram.

Midazolam is one of the effective drugs in benzodiazepine group, very fast onset and short action duration and widely used for sedation prior to many procedures in children[15-22]. Midazolam can be given by many paths with different doses up to the desired effect[19,20,23-27]. Wheeler DS showed the comparable results of using 0.5mg/kg of midazolam to chloral hydrate 75 mg/kg orally to sedate the children underwent an echocardiogram but the children who received chloral hydrate had deeper levels of sedation and longer periods of recovery[12]. Maxwell LG commented that the sedative level used for clinical procedure from chloral hydrate is mostly in the unconscious stage[28]. This stage of unconsciousness may depress the protective reflex of the children, which fell in deep sedation stage and may cause hemodynamics decompensation in some patients with severe heart disease. The safety level of sedation for an echocardiogram is in the conscious sedation stage, for which the self-protective reflex remains. Effect of midazolam is closest to the true stage of conscious sedation[29]. There may be another option to sedate children when undergone an echocardiogram. The intravenous route is not appropriated for the outpatient case and the intranasal route can cause irritating in children, the sublingual route is an interesting option for practical uses with lower dosage, when compared to orally[19,20,24,27,30,31].

Objectives

To compare the efficacy and side effect of 0.3 mg/kg midazolam sublingually and 50mg/kg chloral hydrate orally to sedate the children undergoing echocardiographic evaluation.

Material and Method

A randomized, double blinded clinical study was introduced at outpatient clinic of cardiology unit, Queen Sirikit National Institute of Child Health. The protocol was reviewed and approved by the institutional ethical committee. The study was started in October 2005 and completed in September 2006. The children scheduled for echocardiogram who met the inclusion criteria, the parents would be explained and invited to enroll the study. After the parents signed a consent form, the children were randomized to chloral hydrate or midazolam group according to the block of four by a study nurse. Baseline vital signs and oxygen saturation were taken. Pediatric cardiologist examined the child, evaluated cardiac condition, functional class and any exclusion criteria's before starting the procedure. The child was nil orally for at least 4 hours before the medication was started the medication, which was given according to the assigned group. Either 50 mg/kg of chloral hydrate orally or 0.3 mg/kg of midazolam sublingually was given by the first nurse who randomized and enrolled the patients. Intravenous preparation of midazolam was used for sublingual route. Pediatric cardiologist who performed the echocardiogram and the second nurse who monitored vital signs, oxygen saturation and conscious levels were blinded to the randomization. If the child was not sufficiently sedated for an echocardiogram within 30 minutes post medication, an additional half dose may be required. The maximum total dose should be less than 1 gm of chloral hydrate or 5 mg of midazolam. The ability to complete echocardiogram and the sedation level scores used in this presentation were according to the study by Wheeler[12]. Pediatric cardiologists who performed the echocardiograms determined the scores at the end of the study. The vital signs, oxygen saturation and conscious level were monitored until the child status showed full recovery.

Inclusion criteria

Children aged between 6 months to 5 years, who were not well adapted for an echocardiogram.

Exclusion criteria

Children who has upper airway obstruction, on-going respiratory tract infection, significant hepatic, renal or brain disease, a history of hypersensitive to either chloral hydrate or midazolam or had other problems, which a physician determines would not be a good candidate for the study.

Statistical analysis

Statistical analyses were performed using computer software. Data were described as percent,

mean, standard deviation, Chi-square tests or others where appropriate.

Results

Two hundred sixty-four children were enrolled and randomized either to chloral hydrate or midazolam group equally. Demographic data in each group were shown in Table 1. Both groups had comparable number of sex, age, body weight, baseline oxygen saturation and functional heart classification before sedation. The underlying heart diseases in both groups were not difference as shown in Table 2.

Table 1. Demographic characteristic of the children in both groups

	Chloral hydrate (n = 132)	Midazolam (n = 132)	p-value
Sex			
M (%)	77 (58.3)	62 (47.0)	0.064
F (%)	55 (41.7)	70 (53.0)	
Age (months)			
Mean (SD)	20.6 (12.9)	19.3 (11.6)	0.265
Median (min-max)	17 (7-69)	15.5 (6-61)	
BW (kg)			
Mean (SD)	9.4 (2.8)	9.3 (2.8)	0.669
Median (min-max)	9 (5.4-23.3)	9.1 (4-18.4)	
% initial O_2 sat			
Mean (SD)	92.5 (8.7)	92.7 (9.1)	0.120
Median (min-max)	96 (58-100)	96 (58-100)	
Functional class			
Class: I (%)	103 (78.0)	107 (81.1)	0.263
Class: II (%)	9 (6.8)	4 (3.0)	
Class: III (%)	8 (6.1)	13 (9.8)	
Class: IV (%)	12 (9.1)	8 (6.1)	

Table 2. The underlying heart disease and associated major anomalies in both groups

Diagnosis and associated anomalies	Chloral hydrate	Midazolam
Acyanotic CHD		
Ventricular septal defect	51	34
Patent ductus arteriosus	10	20
Atrial septal defect	2	8
Pulmonic valve stenosis	4	4
Others	6	9
Cyanotic CHD		
Tetralogy of fallot	13	9
Tricuspid atresia	5	1
Pulmonary atresia	1	2
Right isomerism complex	1	2
Total anomalous pulmonary venous return	0	2
Corrected transposition of the great arteries	0	2
Others	2	4
Kawasaki	17	16
Others	13	8
Normal heart	7	11
Down syndrome	5	2
Complete Heart Block	1	0

Table 3. The onset, duration, echocardiographic time, total recovery time and number of the patients who had duration time within optimum time

Time (minutes)	Chloral hydrate (n = 131)	Midazolam (n = 131)	p-value
Onset (minute)			
Mean (SD)	25.1 (20.2)	11.13 (8.6)	<0.001
Median (min-max)	20.0 (3-125)	10.00 (2-45)	
Duration (minute)			
Mean (SD)	54.6 (26.8)	30.50 (29.4)	<0.001
Median (min-max)	50.0 (10-150)	25.00 (10-335)	
Total recovery time (minute)			
Mean (SD)	78.9 (29.3)	40.10 (14.8)	<0.001
Median (min-max)	75.0 (20-170)	35.00 (15-90)	
No. of cases within optimal time			
Duration time < 45 min (%)	57.0 (43.5)	122.00 (93.1)	<0.001
Duration time > 45 min (%)	74.0 (56.5)	9.00 (6.9)	
Echocardiographic time (minute)			
Mean (SD)	10.6 (5.0)	10.20 (4.8)	0.478
Median (min-max)	10.0 (2-30)	10.00 (2-32)	

The mean of onset, duration and total recovery time were longer in chloral hydrate than in midazolam group significantly. ($p < 0.001$) The detail outcomes data were shown in Table 3. The children who had the duration time within the optimal time (< 45 min) were significantly higher in midazolam (93.1%) than in chloral hydrate group (43.5%) ($p < 0.001$). There was no difference in echocardiographic time between groups ($p = 0.478$).

The sedation level scores in Table 4 showed that most of the children (125/132 cases, 94.7%) in chloral hydrate group closed their eyes during echocardiogram (level 4), in contrast with the majority of the children (102 /132 cases, 77.3%) in midazolam group opened their eyes (level 3) during echocardiogram. The midazolam group also had more children (13.6%) in level 2 than chloral hydrate group (1.5%). One case in each group (0.8%) was crying (level 1) and failed the study.

The success rate of sedation means that the child can be sedated to level 2 or more when the echocardiogram was started. The success rate of sedation after the 1st dose of chloral hydrate was 89.4% compare to 94.7% of midazolam. The children in chloral hydrate group needed the second dose of sedation more than the midazolam group, but not significantly different ($p = 0.111$). After the 2nd dose, there was success in all, except one case in each group, so overall success rate was 99.2% in each group (Table 7).

The ability to complete echocardiogram in Table 5 showed that echocardiogram can be performed

Table 4. The sedation level score[12]

	Chloral hydrate n (%)	Midazolam n (%)	p-value
Level 1	1 (0.8)	1 (0.8)	<0.001
Level 2	2 (1.5)	18 (13.6)	
Level 3	4 (3.0)	102 (77.3)	
Level 4	125 (94.7)	11 (8.3)	

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
Level 4: Eyes closing spontaneously but response to minor stimuli

Table 5. The ability to complete echocardiogram[12]

	Chloral hydrate n (%)	Midazolam n (%)	p-value
Level 0	1 (0.8)	1 (0.8)	<0.001
Level 1	0 (0.0)	4 (3.0)	
Level 2	8 (6.1)	53 (40.1)	
Level 3	123 (93.1)	74 (56.1)	

Level 0: Unable to perform the study
Level 1: Important part of the study accomplished, but study shortened
Level 2: Complete study possible with coaxing
Level 3: Complete study easily accomplished

completely (more than level 2) in most of the children in both groups (99.2% vs. 96.2%) but more easily done (level 3) in chloral hydrate group (93.1% vs. 56.1%). The echocardiogram were incompletely performed in 4 cases (3%) of midazolam group and failed for the study in one case (0.8%) of both groups.

While performing echocardiogram, ten cases (8.5%) in midazolam group and two cases (1.6%) in chloral hydrate group had at least one difficult echocardiographic view. ($p = 0.034$) The most common difficult echocardiographic view noted was suprasternal notch; eight cases were in midazolam group and one case in chloral hydrate group. Two cases in midazolam and one case in chloral hydrate group had difficult echocardiographic view; noted were both suprasternal notch and subcostal views (Table 6).

In responding to taking the drugs, the children cried significantly more immediately after chloral hydrate (40.9%) than midazolam (19.7%) ($p < 0.001$). Vomiting and paradoxical reaction were noted more in chloral hydrate (13.6%) than in the midazolam group (2.3%) and hiccups were noted in 3 cases (2.3%) in midazolam group only. The overall side effects from chloral hydrate were significantly more often than midazolam ($p = 0.006$). There was no significant change in vital signs during the study from baseline in both groups. Nine cases (6.8%) in chloral hydrate group showed increase in more than 5% of systemic O_2 saturation from initially compared to four cases (3.0%) in the midazolam group. Four cases (3%) in chloral hydrate group showed a decrease of more than 5% of systemic O_2 saturation from initiation, but none in

Table 6. Difficult echocardiographic view to perform

ECHO view difficulty	Chloral hydrate n (%)	Midazolam n (%)	p-value
Difficult in some views	2 (1.5)	10 (7.6)	0.034
Suprasternal notch view	1	8	
Both suprasternal notch and subcostal views	1	2	
Not difficult	130 (98.5)	122 (92.4)	

Table 7. Doses, reactions and side effects of chloral hydrate and midazolam

	Chloral hydrate n (%)	Midazolam n (%)	p-value
Medication			
No need 2nd dose	118 (89.4)	125 (94.7)	0.111
Need the 2nd dose	14 (10.6)	7 (5.3)	
Crying			
No/mild	78 (59.1)	106 (80.3)	<0.001
Moderate to severe	54 (40.9)	26 (19.7)	
Side effects			
No side effect	113 (85.6)	126 (95.5)	0.006
Vomiting	14	1	
Paradoxical reaction	4	2	
Hiccup	0	3	
Others	1	0	
Total side effects	19 (14.4)	6 (4.5)	
Change in O_2 saturation			
No change	118 (90.1)	127 (96.9)	0.025
Increase > 5%	9	4	
Decrease > 5%	4	0	
Total O_2 sat change	13 (9.9)	4 (3.1)	

midazolam group. The data of doses, adverse reactions and side effects of both groups are shown in Table 7.

Discussion

The finding from this randomized clinical trial study shows that 0.3 mg/kg of midazolam sublingually has comparable efficacy to 50 mg/kg chloral hydrate orally for sedation in children who underwent the echocardiographic study at between 6 months to 5 years. Midazolam has fewer problems, which could be due to smaller volume and less bitter taste than chloral hydrate; vomiting and the need for additional doses occurred less often than with chloral hydrate.

When compare to chloral hydrate, midazolam has a shorter time of onset, duration and total recovery time as in the previous study[12]. There were 93.1% of the children in midazolam group and 43% in chloral hydrate group who had duration time of less than 45 min, which should be an optimum time or enough time for performing routine echocardiogram; more than half of the children in chloral hydrate group may have more than enough duration for usual echocardiogram.

The depth of sedation which was determined by sedation level score in this presentation shows that 77.3% of the children in the midazolam group had opened their eyes but not fighting (level 3) and only 8.3% closed their eyes (level 4) when compared to 94.7% of the chloral hydrate group who closed their eyes (level 4) during echocardiogram. Midazolam 0.3mg/kg sublingually shows less deep sedation than 50 mg/kg of chloral hydrate orally. In general, the ability to complete an echocardiogram depends on the depth of sedation. It is easier to complete echocardiogram in a sleeping child than in the conscious one. The more depth in the level of sedation, the more protective reflex of the child may be lost and can cause some degree of respiratory depression. In compromised cardiac patients, this may change to decompensation stage. Napoli[9] reported a decrease in O_2 saturation from chloral hydrate sedation, about 6% of the children who underwent an echocardiogram. In this present, most of our cases were in functional class I-II; no serious adverse events occurs in either group; the side effects from decrease in O_2 saturation was found 3% in chloral hydrate but none in midazolam group.

There seems to be more advantages in using sublingual midazolam than oral chloral hydrate in children with simple cardiac lesion cases; follow-up case in out patient clinic studies and probably in a high risk child with severe heart failure or compromised respiratory in whom respiratory depression is of concern. Because of the short duration of time and less deep sedation, midazolam had some disadvantages in cases that needed extensive echocardiographic evaluation, accurate Doppler evaluation and a comprehensive study in aortic arch evaluation from suprasternal notch view.

The onset time in midazolam is very fast and eyes opening almost of the time. This is contrast to chloral hydrate which the child usually goes to sleep and eyes closing, so the exactly beginning point of duration time when echocardiogram can be started is different from chloral hydrate, if the child can lays down, not crying and quiet play, the study should be started.

In summary, we found that the dose of 0.3 mg/kg of midazolam administered sublingually, used for sedation of the children between the ages of 6 months to 5 years old who undergo echocardiogram, has as good efficacy and safety as 50 mg/kg of chloral hydrate administered orally. Midazolam has been shown to be near conscious sedation stage more than chloral hydrate. The advantage and disadvantage used of midazolam compare to chloral hydrate have been discussed.

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การศึกษาเปรียบเทียบการใช้ยา chloral hydrate โดยการรับประทานกับยา midazolam ที่ให้ทางใต้ลิ้นในการทำให้เด็กสงบเพื่อการตรวจคลื่นเสียงสะท้อนหัวใจ

ธนะรัตน์ ลยางกูร, ชัยสิทธิ์ แสงทวีสิน, ธวัชชัย กิระวิทยา, วรการ พร้อมพันธุ์, อัญชลี อัตตชู, อมรรัตน์ เพชรดำรงค์สกุล, ญาณิศา อินทศร, ปริศนา หาญชัย, ชลีรัตน์ อุ่นเจริญ, พุทรา น้อยแสง

วัตถุประสงค์: *เพื่อเปรียบเทียบประสิทธิภาพและความปลอดภัยของการใช้ยา chloral hydrate ชนิดรับประทานกับยา midazolam ทางใต้ลิ้น ในการทำให้เด็กสงบเพื่อการตรวจคลื่นเสียงสะท้อนหัวใจ*

วัสดุและวิธีการ: *ศึกษาโดยการสุ่มแบบปกปิดทั้งสองด้านในเด็กที่จำเป็นต้องได้รับการทำให้สงบก่อนการตรวจด้วยคลื่นเสียงสะท้อนหัวใจ มีเด็กเข้าร่วมการศึกษาจำนวน 264 ราย อายุตั้งแต่ 6เดือนถึง 5 ปีเด็กได้รับการสุ่มให้อยู่ในกลุ่ม chloral hydrate และ midazolam กลุ่มละเท่าๆกัน โดยจะได้รับยา chloral hydrate ขนาด 50 มก. ต่อ กก. ทางปาก หรือ ยา midazolam ขนาด 0.3 มก.ต่อกก.ทางใต้ลิ้นขึ้นอยู่กับกลุ่ม ถ้ายังไม่สามารถให้เด็กสงบได้ภายหลังจากให้ยาครั้งแรกนาน 30 นาทีอาจให้ยาเพิ่มอีกครึ่งหนึ่งของครั้งแรก ทำการเปรียบเทียบโดยดูช่วงเวลาของการออกฤทธิ์ของยาทั้งสองชนิด เวลาการออกฤทธิ์ของยาที่น้อยกว่า 45 นาที คะแนนระดับความลึกของความรู้สึกตัว ระดับความสำเร็จจากการตรวจคลื่นเสียงสะท้อนหัวใจ และผลข้างเคียงของยาทั้งสองชนิด*

ผลการศึกษา: *เด็กทั้งสองกลุ่มไม่มีความแตกต่างกันในด้านอายุ เพศ น้ำหนัก ชนิดของโรคหัวใจ ค่าความเข้มข้นของออกซิเจนในเลือด และระดับความรุนแรงของโรคหัวใจขณะเข้าร่วมการศึกษา เด็กในกลุ่ม chloral hydrate จำเป็นที่จะต้องได้รับยาเพิ่มครั้งที่สองมากกว่าเด็กในกลุ่ม midazolam แต่ไม่แตกต่างกันอย่างมีนัยสำคัญ(10.6%, 5.3% p = 0.111) ช่วงเวลาก่อนยาออกฤทธิ์ ช่วงเวลาออกฤทธิ์ของยา และช่วงเวลาทั้งหมด ในเด็กกลุ่มที่ได้รับยา midazolam จะสั้นกว่ากลุ่มที่ได้รับยา chloral hydrate อย่างมีนัยสำคัญ (p < 0.001) พบว่ากลุ่ม midazolam มีเด็กที่มีช่วงเวลาการออกฤทธิ์ของยาน้อยกว่า 45 นาที ซึ่งน่าจะเป็นช่วงเวลาที่มากพอสำหรับการทำการตรวจคลื่นเสียงสะท้อนหัวใจ มีจำนวนมากกว่ากลุ่ม chloral hydrate อย่างมีนัยสำคัญ (93.1%, 43.5% p < 0.001) เด็กในกลุ่ม chloral hydrate มีระดับความลึกของการสงบมากกว่ากลุ่ม midazolam อย่างมีนัยสำคัญ(p < 0.001) อัตราความสำเร็จของการตรวจด้วยคลื่นเสียงสะท้อนหัวใจเท่ากับ 99.2% เท่ากันทั้งสองกลุ่ม เด็กกลุ่ม chloral hydrate มีปฏิกิริยาต่อการได้รับยาและการเปลี่ยนแปลงของค่าความเข้มข้นของออกซิเจนในกระแสเลือดที่มากกว่า 5% จากค่าเริ่มต้น มากกว่าเด็กในกลุ่ม midazolam อย่างมีนัยสำคัญ (14.4%, 4.5% p = 0.006 และ 9.9%, 3.1% p = 0.025)*

สรุป: *การให้ยา midazolam ขนาด 0.3 มก.ต่อกก.ทางใต้ลิ้น สามารถใช้ในเด็ก 6 เดือนถึง 5 ปี เพื่อทำให้เด็กสงบก่อนการตรวจคลื่นเสียงสะท้อนหัวใจ ได้ผลไม่แตกต่างจากการใช้ยา chloral hydrate ขนาด 50 มก.ต่อ กก. โดยมีระดับความลึกของความรู้สึกตัวตื้นกว่าการให้ยา chloral hydrate ในการศึกษานี้ไม่พบภาวะแทรกซ้อนที่รุนแรงจากยาทั้งสองชนิด ยา midazolam อาจมีข้อดีในการนำมาใช้ในเด็กกลุ่มเสี่ยงที่ไม่ต้องการให้เด็กหลับหรือหลับลึก แต่ก็อาจมีข้อเสียเปรียบในรายที่ต้องการตรวจอย่างละเอียดมากหรือต้องใช้เวลานานเมื่อเทียบกับ chloral hydrate*