Chloral hydrate versus midazolam as sedative agents for diagnostic procedures in children

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ABSTRACT

الأهداف: مقارنه تأثير المسكن ل الكلورال هيدرات(CH) و الميدازولام (MD) عند استخدامهما في حال القيام بإجراءات تشخيصية للأطفال.

الطريقة: أجريت دراسة مستقبلية، عشوائية التوزيع ومزدوجة التعمية في وحدة العناية اليومية لطب الأطفال (DCU) في مدينة الملك عبد العزيز الطبية، الرياض، المملكة العربية السعودية خلال الفترة من يوليو 2005م حتى اكتوبر 2006م. بعد التأكد من مطابقة المشارك لمعايير الاشتراك في الدراسة والحصول على الموافقة الخطية المسبقة المبنية على المعرفة من الوالدين، تم توزيع المشاركين عشوائياً لأخذ أحد أدويه الدراسة ثم تمت مراقبة نتائج المسكنات.

النتائج: في هذه الدراسة تم إدراج 275 طفل من الذين يحتاجون إلى مسكن من أجل عمل إجراءات تشخيصية. أجريت 292 حالة تشخيصية. نظراً لوجود فقدان في البيانات تم ادرج 286 حالة في عملية التحليل النهائي. يتضمن هذا التحليل 144 في مجموعة CH و 142 في مجموعة MD. لم يكن هناك فارق بين المجموعتين من حيث الخصائص الديموغرافية والصفات الرئيسية. وجدنا أن مجموعه CH مقارنة بمجموعة MD حصلت على معدل نجاح أعلى بالنسبة إلى عملية التسكين، وقت أقصر لحصول التسكين ووقت أقصر في وحدة العناية اليومية بالإضافة إلى ذلك مدة التخدير كانت أطول. في كلا مجموعتي الدراسة المرضى اللذين احتاجوا إلى جرعة ثانية من الدواء كانوا أكبر سناً ووزناً. لم يتم رصد أي آثار جانبية بالغة في كلا المجموعتين. كان متوسطات درجات تسكين أعلى لدى الأطفال في المجموعة CH و بشكل ملحوظ في الأوقات 15، 30، 45، 60 دقيقة بعد إعطاء الجرعة.

خاتمة: وجد أن CH مقارنة ب MD يملك وقت أقصر لتحقيق التسكين ومعدل أعلى لنجاح التسكين وأقل حاجة لاستخدام جرعة تخدير ثانية، بالإضافة إلى ذلك وجد أن الوقت الذي يقضيه الطفل في وحدة العناية اليومية كان أقصر. الأطفال الأكبر سناً ووزناً يحتاجون في الغالب لأخذ جرعه ثانية من المسكن لإتمام عملية التسكين.

Objectives: To compare sedation outcomes for chloral hydrate (CH) and midazolam (MD) as sedative agents for diagnostic procedures in children.

Methods: A prospective, randomized, double-blind study conducted between July 2005 and October 2006, at the Pediatric Day Care Unit (DCU), King Abdulaziz Medical City, Riyadh, Saudi Arabia. After meeting the inclusion criteria and getting informed consent, patients were randomized, given the study drug, and monitored for sedation outcomes.

Results: Two hundred and seventy-five patients who had 292 sedation sessions for diagnostic procedures were included in the study. Due to missing data, 286 sedations were included in the final analysis; 144 in the CH and 142 in the MD group. Both groups were comparable with respect to demographic and baseline characteristics. The CH compared to MD group, had a higher sedation success rate, shorter time to achieve sedation, shorter length of stay in DCU, and longer sedation duration. In both study groups, patients who required a second dose tended to be older and heavier. No major side effects were encountered. The CH group had a significantly higher mean sedation scores at 15, 30, 45, and 60 minutes.

Conclusion: Chloral hydrate compared to MD, had a shorter time to achieve sedation, a higher success rate, less need for a second dose, and decreased the time spent in the DCU. Older and heavier patients are more likely to require a second dose of the study drug to be sedated.

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Sedating children for diagnostic and therapeutic procedures continues to be a challenge.[1-3] Sedation is needed to decrease patients' anxiety, movement, radiation exposure, and to improve the procedure outcome. The response to a certain dose of sedative agent varies from one patient to another. Even in the same patient, a dose that can put the patient into deep sleep when he is quiet may not be sufficient to calm him down if he is irritated. Furthermore, in the same patient, a small increment in the sedative dose can suddenly change the level of sedation from moderate to deep with the risk of a loss of airway protective reflexes. In previous reports, chloral hydrate (CH) compared to midazolam (MD) showed a deeper and longer sedation.[4] These features could be either an advantage or disadvantage based on the procedure that mandated the sedation.[1,4-7] The literature reports variable success rates of sedation and incidence of adverse effects as well as the use of different dosing regimens of CH.[1,5,7-14] Midazolam has been used for the same purpose in many studies.[10-12,15-23] There is no consensus on which drug, route, and dosing should be used for sedating children. Furthermore, none of the available drugs is risk-free. The fear of side effects related to these medications leads some physicians to avoid using them.[24] Currently, different regimens are used for sedation. This includes using a single sedative agent,[4-8,20] combined sedative agents,[1,12,22,23,25] and/or adding another drug when the first agent fails.[3,26] The use of combined sedative drugs has declined because of the higher risk of side effects.[27] Oral CH is a non-benzodiazepine, non-barbiturate hypnotic agent. It is well absorbed from the gastrointestinal tract with an onset of action between 0.5-1 hour, and duration of action between 4-8 hours. Chloral hydrate has no available specific antidote.[28] Oral CH was the most commonly used drug in many studies on sedation.[1,5-9,13,14,25,29] Although rectal CH has been tried, it was found to be less effective.[30] Midazolam a benzodiazepine and is a well-known anxiolytic agent. Its onset of action is variable based on the route used, ranging from 3-5 minutes for intravenous use to 10-20 minutes for oral routes.[15] Oral MD is rapidly absorbed with a bio-availability of approximately 36%, time to peak concentration of 0.17-2.6 hours and half-life between 2-6 hours.[31] Compared with CH, MD has a specific reversal agent and shorter time to achieve sedation.[15,28] Having rapid onset, short duration of action, and available reversal agent, made health care provider shift from the old CH to the new MD as sedative agent. However, the reports on MD were not always positive. Some previous studies reported lower sedation success rates with MD compared with CH.[4,8,9] As mentioned, children sometimes need sedation to optimize their care. Chloral hydrate and MD are in use for this purpose. No large prospective studies are available to help compare the sedation outcomes of these drugs. The aim of this prospective, double-blind, randomized study is to compare the sedation outcomes for oral MD with CH as sedative agents for diagnostic procedures in children. Our primary outcome is the successful sedation rate, and our secondary outcomes include time to achieve sedation, sedation duration, and side effects. Additionally, the sedation score at different times is our tertiary outcome.

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Methods. This is a prospective, randomized, double-blind study. It was approved by the Institution Review Board (IRB). The IRB approval number was 2005.03. The study was conducted between July 2005 and October 2006 at the Day Care Unit (DCU), King Abdulaziz Medical City, Riyadh, Saudi Arabia. King Abdulaziz Medical City is an approximately 900 bed tertiary care center with pediatric beds representing approximately 30% of the total hospital capacity. Patients included in the study were all pediatric patients ≤12 years of age who were judged to need sedation for diagnostic or therapeutic procedures, and whose guardians signed the study informed consent forms.

Exclusion criteria included having respiratory, renal and/or hepatic impairment, hypotension, gastric ulcer,current use of anticoagulants, allergy to the study drug, American Society of Anesthesia (ASA) class III & IV, and those who received sedation in the past 48 hours prior to the procedure. Randomization of the study drugs was performed by an independent pharmacist using a computer-generated random number program and was concealed from the study investigators. Neither the patient, nor any of the investigators, nor the health care providers knew the active component of the study medication.

Preparation of the study medications. Oral MD was not available on our formulary at the time of starting our study, we prepared a color- and volume-matched oral MD preparation using the intravenous dosage

form of Midazolam® (intravenous infusion injection in a glass vial intended for single use only) (Hikma Pharmaceuticals, Amman, Jordan). The chemical we use in preparing MD for oral use to match the same color of CH is cherry syrup (Homco, Texas, USA). The ready-made cherry flavored syrup at a concentration of 100 mg/mlCH (Pharmascience, Inc., Montreal, Canada). The final concentration of extemporaneously prepared MD was 0.66 mg/ml to match the dose volume of CH. This preparation was stable for 30 days. Validation of the prepared study medication was performed by administering 5 volunteers a blinded medication to determine if there was any difference between the 2 medications. The assigned medication was prepared daily, drawn up in 10-mL syringes, and placed into a plastic bag by the dedicated pharmacist. Each syringe clearly stated the study sample number along with the time and date of administration, the latter of which was monitored by the principle investigator in a blinded fashion. The pharmacy kept the study medicine with a code for each drug.

Study protocol. Patients determined to require sedation for a diagnostic or therapeutic procedure were assessed by the DCU nurse and physician for the need and readiness for sedation. To assure the patient's safety during the procedure, we followed our institution sedation policy, which is in compliance with the American Society of Anesthesia (ASA) and other, related sedation guidelines.[32] Patients were kept nil per os (NPO) before the procedure as per the ASA guidelines. The DCU medical staff members were certified in Pediatric advanced Life Support (PALS) and moderate sedation courses. The PALS course is taught at our postgraduate education center in affiliation with the American Heart Association. The moderate sedation course is a one-day course taught by anesthesiologist for non-anesthesia health care providers who are expected to provide mild to moderate sedation. After ensuring the appropriateness of sedation by the physician, and receiving the signed informed consent form, the patients were placed in the monitoring area. The DCU physician sent the order to enroll the patient in the study to the pharmacy. The pharmacist assigned the patient to either CH or MD group based on the randomization protocol mentioned earlier. Next, the pharmacist sent the appropriate dose of medication based on the patient's weight in an oral syringe labeled with the patient's study number and the desired dose in milliliters. Demographic data, the procedure that mandated sedation, baseline vital signs and sedation score were collected. In our protocol, both study drugs were given orally. Based on product information and doses used in previous studies, the initial first dose of the study drug was either CH (75 mg/kg, maximum dose of 2 gm.) or prepared MD (0.5 mg/kg, maximum dose of 10 mg).[4,8,16,31] If vomiting occurred within 15 minutes of taking the medication, the same first dose was repeated. If the patient was not adequately sedated 30 minutes after the initial dose, a second dose of the same drug was given. The second dose was 30 mg/kg for the CH group and 0.25 mg/kg for the MD group. After receiving the study drug, the bedside nurse recoded the patient's vital signs and sedation score over time, the time of drug administration, the study drug sample number, time to achieve sedation, need for a second dose, and the recovery time. The Ramsay Sedation Score[33] was used to document the patient's sedation score throughout the procedure (**Appendix 1**). The original Ramsay score of 3 (patient drowsy but responds to commands) was modified to drowsy because it might not be relevant for young infants. The occurrence of the following complications was also recorded: a decrease in oxygen saturation by ≥10% from baseline, the need for assisted ventilation, a decrease in mean arterial blood pressure ≥25% of baseline, vomiting, nausea, and paradoxical agitation (excessive limb movement, head thrashing, hysterical crying or hyperactivity). The patients were observed in the unit for at least one hour after full recovery. Time to achieve sedation was defined as the time between receiving the first dose of the study drug and the onset of sedation. Sedation duration was defined as the time between sedation onset and full recovery. Time to recovery was defined as time between receiving the first dose of the study drug and full recovery. This would be a reflection of length of stay in DCU. The sedation was defined as successful if the patient was sedated enough to tolerate the procedure within 2 hours of receiving the first dose of the study drug. Failure of sedation was defined as patient had insufficient sedation to tolerate the procedure 2 hours after receiving the first dose of the study drug. Full recovery was defined as the ability to maintain an open airway, return to baseline cardiopulmonary function, normal hydration and the ability to sit up for 10 seconds or longer. Patients were observed in the unit for one hour after full recovery. The sedation scores were recorded at different time points (0, 15, 30, 45, 60, 75, 90, and up to 180 minutes) as needed on a 6-point ordinal scale, ranging from 1-6. Post-sedation instructions were given to the patients' guardians upon discharge. The patients' guardians were

instructed to call our contact number if there were delayed side effects of the sedative drug.

Statistical analysis. Sample size calculations were based on a 40% failure rate for the MD group and a 22% failure in rate using CH. A sample size of 140 for each arm was needed for a 90% probability of rejecting the null hypothesis of equal proportion if the alternative holds. Thus, we targeted recruitment of a total of 290 subjects. All demographic and clinical characteristics were summarized using count and percentage n (%) for categorical variables and means plus or minus standard deviations (mean ± SD) for continuous variables across the treatment groups (CH and MD). To examine if the treatment groups were comparable at baseline, differences in baseline characteristics such as age, weight, systolic/diastolic blood pressure, heart rate, body temperature, oxygen saturation, time to achieve sedation, sedation duration, time to recovery, and respiratory rate were assessed using independent 2-sample t-tests. If any of the above variables is not normally distributed within each of the 2 groups, then Mann-Whitney U test was used instead of the independent 2-sample t test. The relationship between treatment across gender, side effects, sedation adequacy, and sedation assessment were assessed using Chi-square tests. When 20% of the expected frequencies are less than 5, we used Fisher's exact test instead of the Chi-square test. The impact of age and weight on the need for a second dose of the study drug was investigated by Mann-Whitney U test. Our interest was to evaluate the similarities and differences between the 2 drugs in sedation score at different time intervals. The random intercept model was employed to assess the relationship between the sedative agents and the sedation scores over time. We assumed that sedation scores between different patients were independent but correlated within the same patients. The results were considered significant at a level less than 0.05. All analyses were conducted using SAS® versions 9.2 (SAS Institute Inc., Cary, NC, USA).

Results. Two hundred seventy-five patients were enrolled in the study. These patients had a total of 292 sedation procedures. Six procedures were excluded due to incomplete data collection. Thus, 286 sedation procedures were included in the data analysis. Fourteen (4.9%) patients had more than one sedation procedure. These 14 patients had a total of 31 sedation procedures that were performed on different dates more than 48 hours apart. Of the 286 sedation procedures included in the analysis, 144 used CH and 142 used MD for sedation. Of our patients, 33% were under one year of age, 60% were under the age of 2, and 74% were under the age of 3 years. Seventy-five percent of patients were equal to or less than 14.2 kg in weight. Both study groups, were comparable with respect to demographic data, the diagnostic procedure mandating sedation, baseline vital signs, and baseline sedation scores (p>0.05), **Table 1**. At baseline, the percentage of anxious and agitated patients (Ramsay sedation score 1) was similar in both groups, 99.26% in the MD group compared to 100% in the CH group (p=0.4910). In our study, the levels of sedation for our subjects ranged from Ramsay score of one (patient is anxious and agitated or restless, or both) to Ramsay score of 4 (patient exhibits brisk response to light glabellar tap or loud auditory stimulus). None of our subjects reached Ramsay score of 5 or 6. **Table 1** shows that the time to achieve sedation (p<0.0001) and the time to recovery (p=0.0386) were both shorter in the CH group. However, the sedation duration was shorter for the MD group (p=0.0006). Our subjects needed sedation for different diagnostic procedures. However, there was no statistically significant difference between the 2 treatment groups in regards to the diagnostic procedure that mandated sedation (p=0.4722). No difference between the 2 study groups in regards to the need for a repeat dose within 15 minutes of the first dose due to vomiting (p=0.6633). However, 23 (16%) of the patients in the CH group versus 104 (73.2%) in the MD group were not sufficiently sedated at 30 minutes after receiving the first dose (p=0.0001). These patients were given a second dose of the study drug. Successful sedation was higher in the CH 136 (94.4%) compared to MD group 88 (62%) (p=0.0001).

No major side effects were observed in our study groups. Side effects including a decrease in O_2 saturation ≥10% below baseline, the need for assisted ventilation, a decrease in mean arterial BP ≥25% of baseline, and paradoxical agitation occurred in 8 (5.6%) patients in the CH and 9 (6.3%) in the MD groups (p=0.6586). However, paradoxical agitation occurred in 0 (0%) in the CH and 8 (5.6%) in the MD groups (p=0.0039). Four (2.8%) patients in the CH group had decreased in the mean arterial BP ≥25% of the baseline compared to 0 (0%) in the MD group, (p=0.0455) (**Table 2**).

Table 3 shows the impact of age and weight on the need for second dose of the study drug. In the CH group, the age of patients who did not require a second dose was 24.53±18.53 months versus 36.83±23.40 months for those who required a second dose (p=0.0090). This observation was not limited to CH, in both groups;

Table 1 - The distributions of demographic and baseline characteristics across the treatment groups (N=286).

Characteristics	Chloral hydrate n=144	Midazolam n=142	*P*-value
Age (months)	26.49±19.82	26.21±22.58	0.9096+
Weight (kg)	11.15±3.76	11.90±5.84	0.1988+
Gender (male%)	80 (55.6)	87 (61.3)	0.3271#
SBP (mm Hg)	101.50±12.01	100.30±11.17	0.4097+
DBP (mm Hg)	61.31±11.74	61.52±11.86	0.8826+
Heart rate (minute)	121.5±18.38	123.7±19.18	0.3325+
Temperature (°C)	36.44±0.46	36.38±0.42	0.3188+
Respiratory rate (minute)	28.81±5.73	29.22±5.94	0.5604+
Oxygen saturation (%)	97.45±1.31	97.77±1.23	0.0764*
Time to sedation (minute)	24.30±16.96	53.12±40.94	0.0001*
Sedation duration (minute)	75.90±38.37	58.98±35.05	0.0006*
Time to recovery (minute)	99.41±39.65	112.67±47.82	0.0386*
Baseline sedation (%)			
Ramsay sedation score 1	141 (100.0)	135 (99.3)	0.4910#
Ramsay sedation score 2	0 (0.0)	1 (0.7)	
Diagnostic procedure (MRI) (%)	50 (34.7)	56 (29.4)	0.4722#
Computerized tomography	56 (38.9)	46 (32.4)	
DTPA	23 (16.0)	23 (16.2)	
ABR	2 (1.4)	7 (4.9)	
Eye exam	11 (7.6)	8 (5.6)	
Others	2 (1.4)	2 (1.4)	
Repeat dose after 15 min (yes) (%)	3 (2.1)	2 (1.4)	0.6633#
Second dose after 30 min (yes) (%)	23 (16.0)	104 (73.2)	0.0001#
Successful sedation (yes) (%)	136 (94.4)	88 (6.2)	0.0001#
Side effects (yes) (%)	8 (5.6)	9 (6.3)	0.6586#

+*p*-values from 2-sample t test, *p*-values from Mann-Whitney U test, #*p*-values from Fisher's/Chi square test. DTPA - diethylene triamine pentaacetic acid renal scan, ABR - auditory brainstem response, SBP - systolic blood pressure, DBP - diastolic blood pressure

Table 2 - Occurrence of side effects by treatment groups.

Side effects	Chloral hydrate n=144 n (%)	Midazolam n=142 n (%)	*P*-value
Decrease O_2 saturation by ≥10% from baseline	1 (0.1)	0 (0.0)	1.0000
Need assisted ventilation	3 (2.1)	1 (0.1)	0.6224
Decrease BP (MAP) ≥25% from baseline	4 (2.3)	0 (0.0)	0.0455*
Paradoxical agitation	0 (0.0)	8 (5.6)	0.0039*

p-values from Fisher's/Chi square test, *statistically significant at alpha = 0.05, BP - blood pressure, MP - mean arterial pressure

Table 3 - The impact of age and weight on the need for second dose of the study drug.

Drug	Characteristics	Second dose after 30 min		*P*-value
		Yes	No	
Chloral Hydrate (A)	Age (months)	36.83±23.40	24.53±18.53	0.0090*
	Weight (kg)	13.05±3.83	10.78±3.65	0.0070*
Midazolam (B)	Age (months)	27.38±21.08	22.99±26.32	0.0070*
	Weight (kg)	12.01±5.10	11.59±7.56	0.0320*

p-values from Mann-Whitney U test, *statistically significant at alpha = 0.05

Table 4 - Tukey-Kramer multiple comparison adjustment of mean sedation scores with 95% confidence intervals (CI).

Drugs	Time	Drugs	Time	Estimate	SE	Pr > |t|	Adj P	Adj lower	Adj upper
Chloral hydrate	0	Midazolam	0	0.01	0.09	0.9071	1.0000	-0.293	0.314
Chloral hydrate	15	Midazolam	15	0.83	0.10	0.0001	0.0001	0.493	1.166
Chloral hydrate	30	Midazolam	30	0.94	0.10	0.0001	0.0001	0.616	1.257
Chloral hydrate	45	Midazolam	45	0.83	0.10	0.0001	0.0001	0.492	1.169
Chloral hydrate	60	Midazolam	60	0.44	0.11	0.0001	0.0033	0.082	0.807
Chloral hydrate	75	Midazolam	75	0.19	0.12	0.1189	0.9557	-0.215	0.589
Chloral hydrate	90	Midazolam	90	-0.04	0.13	0.7785	1.0000	-0.465	0.393

*Statistically significant at alpha = 0.05. Pr > |t| - *p*-value, Adj P - multiple comparison adjustment for the *p*-values, Adj lower - adjusted lower CI for the differences of least squares mean (LS-mean), Adj upper - adjusted upper CI) for the differences of LS-mean.
If the 95% CI does include 0, means there is evidence of similarity between chloral hydrate and midazolam

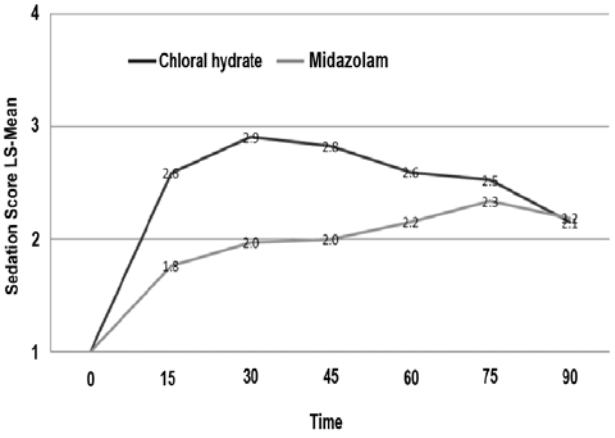

Figure 1 - Similarities and differences over time between chloral hydrate and midazolam. The mean sedation scores were not significantly different at time 0, 75, and 90 minutes. The patients in the chloral hydrate group had a higher degree of sedation at 15, 30, 45, and 60 minutes.

patients who required a second dose of the study drug were older and heavier.

Table 4 shows that the interaction between time and drugs is significant and shows that there is a difference between CH and MD over time. The 2 groups baseline mean sedation scores had no significant difference (p=0.000). However, the sedation scores of both groups were different at 15 minutes (p<0.0001), 30 minutes (p<0.0001), 45 minutes (p<0.0001), and 60 minutes (p=0.0033). The sedation scores of both groups had no differences at 75 minutes (p=0.9557) and 90 minutes (p=1.0). Furthermore, sedation scores at 105 minutes or more were similar between the 2 groups. **Figure 1** shows that there are differences and similarities over time between CH and MD sedation scores. The mean sedation scores appears to be higher in CH group as compared to MD group at time 15, 30, 45, and 60 minutes. Children who received CH had a higher degree of sedation at faster rates than MD. The mean sedation scores for both groups were similar at 0, 75, and 90 minutes where the graph does not show a large gap between the 2 drugs.

Discussion. Following our study protocol, CH compared to MD achieved a higher successful sedation rate and shorter time between receiving the first dose of the study drug and sedation onset. Other authors had similar findings. Wheeler et al[4] reported success rate of 90% for CH and 48% for MD. D'Agostino et al[8] reported a sedation success rate of 100% for CH and 50% for MD. McCarver-May et al[9] found CH to be more efficacious than MD in a crossover study of 7 neonates. The above studies recruited a small number of subjects. In our study, the CH group had a significantly higher sedation scores at 15, 30, 45, and 60 minutes compared to the MD group. For example, at 30 minutes, the children administered CH with mean Ramsay sedation scores of 2.9, compared to a sedation score of 2.0 for children administered MD. We observed that as time increases, both drugs show similar effectiveness at sedating the patient. At 0, 75, and 90 minutes, the mean sedation scores for both groups were similar. For example, at 90 minutes, there was no significant difference in mean sedation scores between the 2 groups (2.15 in CH group versus 2.18 in MD group). The sedation score over time was not clearly reported in the previous studies as in our study. However, previous studies reported deeper and more successful sedation with CH compared to MD.[4,8,34] In our study, time

to sedate was shorter in in the CH group. This was observed in other previous reports.[1,34] While others such as Wheeler et al,[4] did not find a difference in time to sedate between CH and MD. The longer time to sedate in the MD group in our study can be explained by the fact that 73.2% of the MD versus 16% of the CH group (p=0.0001) needed a second dose of the study drug to be sedated. The need for a second dose increased the time to sedate and time to recovery. In a recent report,[34] CH compared to other sedation regimens was found to have faster onset, higher success rate (>90% for CH versus 66% for MD), and lower cost. Previous studies reported different results with regards to side effects of sedation using MD and CH. Wheeler et al[4] reported no adverse effects for either drug, while Costa et al[11] reported a higher incidence of side effects for CH; 3.9% hallucinations and 41.9% excessive sleep versus none for MD group. Similar to previous studies, no major side effects were observed in our study for either drug.[4,5,8,9,13,14,35] In a study using CH as sedative agent for auditory brain response testing, Avlonitou et al[36] reported paradoxical agitation in 8% of their subjects. In our study, paradoxical agitation was observed only in the MD group. As above, there were no major side effects in both groups after giving the second dose of the study drug. With high failure rates with MD, 0.5 mg/kg as a first dose, this supports consider making the initial oral dose for MD as 0.75 mg/kg rather than 0.5 mg/kg with. Bed occupancy in our DCU, which was reflected partially by time to recovery, was longer for patients in the MD group (112.67±47.82 minutes) compared to (99.41±39.65 minutes) CH group (p=0.0386). Not only did the CH group have a higher sedation success rate, but the CH sedated group also had a higher sedation score at different times after the first dose of study drug compared with the MD group. Similar to previous studies[1,4,6,8,9,29,34] we had a high sedation failure rate in the MD group (38%) compared with the CH group (5.5%). Higher sedation success rates mean more diagnostic procedures successfully performed in the CH group (94.4%) compared with the MD group (62%). Similar to a previous study, in this study the duration of sedation was shorter in the MD group compared to CH group (58.97±35.04 versus 75.90±38.36) respectively p=0.0006. However, the time to recovery, which reflects the length of stay at our day care unit, was shorter in the CH group (99.4±39.65 versus 112.7±47.2). Therefore, the use of CH as per our study protocol and previous studies[1,9,34] was not only more effective than MD, but also tended to save more time for patients and the nursing staff. In a previous study,[14] we reported that CH sedation effect is age and weight dependent. In a recent report, Lee et al[37] reported that the CH sedation success and complication rate for MRI is age and weight dependent. Success was better for patients <18 months of age and those weighing <11.4 kg. Adverse effects occurred in 10% of patients at 18 months of age and increased to 20% for those >36 months of age. Bracken et al[38] in a recent retrospective study reported that CH successfully sedated 96.7% of young children aged 1-36 months. Children less than one year of age had a higher success rate of 98.3% and less need for an augmentation dose. Similar to the previously mentioned studies,[14,37,38] in this study, the response to CH was age and weight dependent. This applies not only for CH, in this study, for both CH and MD, patients who required a second dose were older and weighed more compared to those who did not. When we used a random intercept model, it was found that CH was more effective than the MD at sedating a patient at 15, 30, 45, and 60 minutes. However, the 2 drugs were similar at the baseline, 75, and 90 minutes. These findings can be observed in **Figure 1**. In our study, we described the sedation score over time for the 2 groups that was not clear in previous reports. The aforementioned studies using MD and CH as sedatives for diagnostic procedures had smaller sample size, covered selected age groups and were each emphasized on one or few procedures. The results of this study support the use of 0.75 mg/kg as an initial oral dose for MD that is higher than the dose that we used based on previous studies. This study also showed that not only CH, but also both CH and MD have weight and age dependent effects.

In conclusion, sedating children with CH or MD for diagnostic procedures according to sedation guidelines is safe. As per our protocol, sedation with CH compared to MD has a higher success rate, less need for a second dose, shorter time to achieve sedation, and a shorter length of stay in the day care unit. Additionally, the CH group reached better sedation at 30 minutes. In both groups, older and heavier patients are more likely to need a second dose of the study drug to be sedated. Children who received CH had a higher sedation score at faster rates than MD. It may be more effective to have the initial oral dose of MD for sedation as 0.75 mg/kg rather than 0.5 mg/kg. Further studies may be indicated to examine the efficacy and safety of using 0.75 mg/kg for MD, and 75 mg/kg for CH as initial doses for sedation.

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Appendix 1 - Ramsey sedation assessment scale.

Score	Responsiveness
1	Patient is anxious and agitated or restless, or both
2	Patient is cooperative, oriented and tranquil
3	Patient drowsy but responds to commands
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response