Comparative Effectiveness of Intranasal Dexmedetomidine–Midazolam versus Oral Chloral Hydrate Targeting Moderate Sedation during Pediatric Transthoracic Echocardiograms

Jordan Fett[1] Richard Hackbarth[1,2] Brian M. Boville[1,2] Anthony D. Olivero[1,2] Alan T. Davis[3] John W. Winters[1,2]

[1] Michigan State University College of Human Medicine, East Lansing, Michigan, United States
[2] Division of Critical Care, Department of Pediatrics, Helen DeVos Children's Hospital, Grand Rapids, Michigan, United States
[3] Department of Surgery, Michigan State University College of Human Medicine, Grand Rapids, Michigan, United States

Address for correspondence John W. Winters, MD, Department of Pediatrics, Critical Care Medicine, Helen DeVos Children's Hospital, MC 117, 100 Michigan Street NE, Grand Rapids, MI 49503, United States (e-mail: johnw.winters@helendevoschildrens.org).

J Pediatr Intensive Care 2017;6:182–187.

Abstract

Objective To compare efficacy and safety of two moderate sedation regimens for transthoracic echocardiography (TTE): intranasal dexmedetomidine–midazolam (DM) versus oral chloral hydrate (CH) syrup.

Method This was a retrospective cohort of 93 children under 4 years of age receiving moderate sedation with either DM or CH for TTE from January 2011 through December 2014.

Measurements and Main Results Forty-nine patients received oral CH and 44 received the intranasal combination of DM. The demographics between groups were similar except the DM patients were slightly older and heavier (each $p < 0.05$). Failure rate between groups did not reach statistical significance (CH 14.3% vs. DM 6.8%; $p = 0.324$). Total sedation to discharge time was similar between groups (CH 89.4 minutes vs. DM 89.6 minute; $p = 0.97$). Cardiopulmonary data did reveal a significantly lower heart rate (101.9 vs. 91.7; $p < 0.001$) and respiratory rate (23.4 vs. 21.0, $p = 0.03$) in the DM group, but no difference in blood pressure measurements or echo determined shortening fraction.

Conclusion These data support the use of intranasal DM as a safe and efficacious method of moderate sedation for children undergoing TTE.

Keywords
- intranasal dexmedetomidine–midazolam
- chloral hydrate
- transthoracic echocardiography

Introduction

Pediatric patients often require sedation for diagnostic studies. Procedural sedation and analgesia facilitates the ability to complete these tasks by minimizing motion, anxiety, and discomfort. Many noninvasive pediatric procedures do not require deep sedation. An infant or toddler in need of brainstem auditory evoked responses (BAERs), magnetic resonance imaging (MRI), or transthoracic echocardiography (TTE) does not always need monitored anesthesia care to lie sufficiently still to complete the process. In some cases, deep sedation may be contraindicated in terms of the effect on myocardial contractility, vascular tone, or airway stability.

received
September 3, 2016
accepted after revision
November 21, 2016
published online
December 26, 2016

DOI https://doi.org/10.1055/s-0036-1597696.
ISSN 2146-4618.

Table 1 University of Michigan Sedation Scale

Sedation level	Description
0	Awake and alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleepy, easily arousable with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation
4	Unarousable

Source: Malviya S, Voepel–Lewis T, Tait AR, Merkel S, Tremper K, Naughton N. Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS). Br J Anaesth 2002;88(2):241–245.

Historically at our institution, chloral hydrate (CH) was used to induce moderate sedation (University of Michigan sedation scale [UMSS] sedation level 2 [►**Table 1**])[1] for toddlers undergoing nonpainful procedures (BAER, MRI, nuclear medicine studies). Production of commercially formulated CH was discontinued in 2012; therefore, a locally compounded product had to be formulated. Additionally, the taste of the CH was not palatable and often the children would spit out an unmeasurable portion of the dose.

In recent years, the intranasal route of administration of sedative agents has become more common.[2] The nasal mucosa is easily accessible and highly vascularized, which facilitates rapid absorption of medications and eliminates the first-pass metabolism of enterally administered medications. Plasma concentrations of many medications given intranasally routinely have similar pharmacokinetic properties as those given intravenously.[3–6]

Dexmedetomidine, an α_2 agonist with central sedative effects and spinal cord (dorsal horn) analgesic properties, has been used in pediatric patients through the intranasal route to facilitate preinduction patient separation from parents as well as intravenous (IV) insertion.[7–10] Intranasal midazolam has also been used as a preinduction sedative[11] as well as monotherapy sedation for short imaging situations.[12] Additionally, several groups have reported using intranasal dexmedetomidine with or without intranasal midazolam as a complete sedation regimen to attain moderate sedation for longer pediatric procedures.[13–15]

In 2014, we began using a sedation regimen of intranasal dexmedetomidine–midazolam (DM) supported by data from published literature,[13] abstracts,[14,15] and local expertise. This change was induced by several factors: Institute for Safe Medication Practices recommendations that commercially available medications be used whenever possible and cardiologist opinion that inadequate levels of sedation were being attained with CH sedation. This paper reports a comparison of efficacy and safety between patients given DM or CH to induce moderate sedation to facilitate TTE.

Methods

After Institutional Review Board approval, we performed a single center retrospective review of patients less than 4 years of age admitted to the sedation unit at Helen DeVos Children's Hospital (HDVCH) who were sedated for complete TTE between January 2011 and December 2014. Informed consent for sedation was obtained on all patients prior to sedation. Data were extracted from the electronic medical record (EMR; Cerner Millennium PowerChart, Cerner Corporation, Kansas City, Missouri, United States).

Prior to April 2012, commercially formulated CH syrup (500 mg per 5 mL) was used to induce moderate sedation in the pediatric patients at HDVCH. Once the production of the CH syrup was discontinued, local pharmacists at HDVCH compounded a CH solution by dissolving a crystalline product (Fagron Inc., St Paul, Minnesota, United States) in water and diluting with simple syrup to a concentration of 250 mg per 5 mL. Typical CH dosing was 75 mg/kg (to a maximum of 1,000 mg).

As of January 2014, our moderate sedation protocol was changed; intranasal dexmedetomidine (100 mcg/mL, Mylan N.V., Hatfield, United Kingdom) plus midazolam (5 mg/mL, Hospira, Lake Forest, Illinois, United States) were mixed and delivered through a nasal atomizer (LMA MAD Nasal, Teleflex Medical, Research Triangle Park, North Carolina, United States). The typical dexmedetomidine dosing was 3 to 4 mcg/kg (no maximum dose) while that for midazolam was 0.25 to 0.4 mg/kg (to a maximum of 5 mg).

Once sedation was given, each patient was monitored by a dedicated sedation nurse per institutional policy until mental status, hemodynamics, and respiratory status returned to baseline. The sedation nurse documented in the EMR the time of medication delivery and the time at which moderate sedation was attained.

The primary outcome measured was sedation failure, which was defined as the inability to obtain images acceptable to the cardiologist without additional intranasal or IV sedatives. Any patient who did not reach an acceptable level of sedation to complete the TTE had an IV catheter placed and was transitioned to a deep sedation protocol. The secondary outcomes included safety measures (vital signs, myocardial shortening fraction, cardiorespiratory intervention), sedation times, parental satisfaction (based on a hospital-wide post-admission yes/no survey), and image quality (as graded by a group of five cardiologists).

Quantitative data are expressed as the mean ± standard deviation, while nominal data are expressed as a percentage. Quantitative data were compared between groups using the *t*-test, while nominal data were compared using the chi-square test or Fisher's exact test, as appropriate. Statistical significance was defined as a $p \leq 0.05$. Analyses were performed using IBM SPSS Statistics v. 22 (Armonk, New York, United States).

Table 2 Demographic and baseline clinical data

	Chloral hydrate	Dexmedetomidine–midazolam	*p*-Value
N	49	44	
Age (mo)	11.1 ± 5.2	16.2 ± 7.5	<0.001[a]
Weight (kg)	8.3 ± 1.6	9.7 ± 2.3	0.001[a]
Sex (male/female)	21/28	20/24	0.801[b]
ASA (I/II/III)	4/36/8	1/37/6	0.48[c]
Echo time (min)	35.4 ± 11.7	32.1 ± 9.3	0.132[a]
Presentation vital signs			
Heart rate	121.2 ± 17.9	119.7 ± 13.5	0.669[a]
Respiratory rate	27.8 ± 4.6	27.1 ± 9.0	0.714[a]
Systolic BP	99.4 ± 19.1	101.8 ± 21.9	0.67[a]
Mean BP	72.3 ± 15.8	71.5 ± 17.4	0.878[a]
Diastolic BP	62.5 ± 16.0	57.6 ± 17.4	0.291[a]

Abbreviations: BP, blood pressure (mm Hg); ASA, American Society of Anesthesiologists.
[a]*t*-test.
[b]Chi-square test.
[c]Fisher's exact test: quantitative data expressed as mean ± standard deviation.

Results

During the time period of January 2011 to December 2013, 49 patients were sedated with oral CH (interquartile dose range: 66.5–77.1 mg/kg) to facilitate TTE, whereas from January to December 2014, the regimen of intranasal dexmedetomidine (interquartile dose range: 3.4–3.9 mcg/kg) and midazolam (interquartile dose range: 0.35–0.4 mg/kg) was used in 44 patients.

The demographic and baseline clinical data from the two groups are outlined in ►**Table 2**. Gender, ASA (American Society of Anesthesiologists) class, procedure time, and baseline vital signs were found to be similar in both groups. Of note, the age and weight of the DM group was slightly higher ($p = 0.001$).

A comparison of the indications for TTE in the CH and DM groups is shown in ►**Table 3**. Complex cardiac defects comprised 57% in each group (CH 28/49 vs. DM 25/44). No significant differences between the two groups were seen.

Each patient was monitored by a dedicated sedation nurse and felt to be at a level of moderate sedation based on patients responding to foot touch, blood pressure cuff activation, and other light-stimulating activities. No patients were felt to reach UMSS sedation level 3.

Table 3 Indication for transthoracic echocardiography

	Chloral hydrate	Dexmedetomidine–midazolam	p-Value
Congenital heart disease	39	36	0.786[a]
Noncongenital heart disease	10	8	

[a]Chi-square test.

The results of the primary and secondary measures are summarized in ►**Table 4**. There was a lower overall failure rate in the DM group, though this difference did not reach statistical significance. In addition, the patients who received DM did take longer to reach level 2 sedation, but the time from medication administration to discharge was not significantly longer.

In terms of the hemodynamic effects of the two regimens, the DM group did experience a statistically greater decrease in heart rate after receiving the sedative agent (CH 9.1% vs. DM 16.7%), but none of the patient heart rates fell outside of an acceptable range for age.[16] Neither blood pressure nor echocardiogram determined shortening fraction measurements differed significantly, and no interventions were required for chronotropic or hemodynamic stabilization. Patients in the DM group had a lower average respiratory rate that was statistically significant, but this value remained within the normal limits for age, and no supplemental oxygen or airway manipulations were required except in those patients from both groups who transitioned to a deep sedation protocol.

Parental satisfaction was measured during a phone survey on the day after sedation. In the DM group, 63.6% of the families were able to be contacted, compared with 75.5% of the families from the CH group. The percentage of families that were satisfied with their sedation experience was 96.5% in the DM group (one parent preferred the shorter sedation duration associated with a previous deep IV sedation) and 100% in the CH group. There were no reports of prolonged sedation or nausea/vomiting from either group.

Echocardiogram quality was classified as poor, adequate, good, or very good by the cardiologist interpreting the study. Only one patient in each group had a study that was graded as poor quality. These differences did not reach statistical significance, though there was a tendency toward better echo quality in the DM group (►**Table 4**).

Table 4 Results

	Chloral hydrate	Dexmedetomidine–midazolam	p-Value
Sedation failure rate (%)	7 (14.3)	3 (6.8)	0.324[a]
Sedation Onset time (min)	26.5 ± 15.1	37.8 ± 16.8	0.001[b]
Total sedation time[c] (min)	89.4 ± 28.4	89.6 ± 27	0.97[b]
Shortening Fraction (%)	40.6 ± 5.2	39.1 ± 5.5	0.219[b]
Sedation vital signs			
Heart rate: low	101.8 ± 13.0	91.7 ± 11.6	<0.001[b]
Heart rate: mean	110.2 ± 13.0	99.8 ± 12.7	0.001[b]
Respiratory rate: low	23.4 ± 4.2	21.1 ± 4.4	0.032[b]
Respiratory rate: mean	32.7 ± 17.8	26.5 ± 5.0	0.045[b]
Systolic BP: low	85.5 ± 16.8	82.8 ± 14.5	0.655[b]
Systolic BP: mean	92.3 ± 15.1	85.9 ± 13.0	0.233[b]
Diastolic BP: low	43.3 ± 14.4	37.2 ± 17.2	0.374[b]
Diastolic BP: mean	46.0 ± 14.0	39.8 ± 13.9	0.261[b]
Echo quality			
Good/very good (%)	80.9	90.7	0.184[a]

Abbreviation: BP, blood pressure (mmHg).
[a]Chi-square test.
[b]*t*-test.
[c]Time from medication administration to discharge: quantitative data expressed as mean ± standard deviation.

Discussion

This study compared two options for moderate, non-IV sedation for patients undergoing TTE. Difference in the primary outcome variable, sedation failure, did not reach statistical significance between the two groups, although there was a trend toward lower failure rate in the DM group. Success rates from other groups[13,15,17,18] studying the use of intranasal dexmedetomidine (2–3 mcg/kg) showed varying success rates between 60 and 89%. Greenberg et al[14] added intranasal midazolam (0.3 mg/kg) to the intranasal dexmedetomidine (2.8 mcg/kg), attaining a success rate of 87.4%. Finally, Miller et al[19] prospectively compared a regimen of CH (70 mg/kg orally) to dexmedetomidine (2–3 mcg/kg intranasally), finding no difference in success rates between these groups (96–100%). Of note, the average echo times for this cohort were 8 to 11 minutes, which is much shorter than the time required for our typical complete TTE, suggesting less complex imaging requirements. These reports, in conjunction with our data, support the hypothesis that intranasal dexmedetomidine ± midazolam can provide an adequate level of sedation for pediatric patients for TTE. The variable success rates between these studies is likely multifactorial, including differing sedation expectations, or medication combinations and dosing. We propose a trend toward better success for more complex and stimulating procedures with the higher dose of dexmedetomidine and a synergistic effect when midazolam was added to the regimen.

The second aspect of the efficacy topic is time. There was a statistically significant difference in time required for the DM patients to fall asleep compared with the CH patients. This difference is difficult to explain since intranasal medication delivery should have a more rapid onset. Though the intranasal medications were delivered through an atomizer, there may have been some unmeasurable portion of the medication that was swallowed resulting in delayed effect. There was no statistical association between the age of the patient and the onset time, but with the wide range of onset times (range: DM 11–79 minutes vs. CH 9–66 minutes), there must be interindividual differences affecting sedation onset. Other studies[14,15,17–19] looking at patients dosed with intranasal dexmedetomidine showed shorter intervals to onset of adequate sedation (13–32 minutes), but similar intervals of sedation-to-discharge (82.3–95 minutes). Some of these studies[18,19] compared intranasal dexmedetomidine with CH, which showed a time to onset of adequate sedation to be 14 to 30 minutes, and a sedation-to-discharge time of 96 minutes. These metrics are difficult to standardize since the determination of when a patient is ready to be imaged or discharged is somewhat subjective.

Most children have some component of anxiety associated with being in an unfamiliar setting prior to sedation and therefore it is not surprising to see a difference in vital signs between presedation and intrasedation measurements. Additionally, dexmedetomidine is known to cause bradycardia in a portion of those patients who receive it. This study reveals that the DM regimen has a greater impact than the CH regimen on heart rate and respiratory rate. Although these findings were statistically significant, they did not extend beyond normal limits for age. Both groups had similar decreases in

blood pressure measurements, none of which crossed the threshold for sedation related hypotension,[20] and no cardiopulmonary interventions were required in any of the moderately sedated patients from either group. Li et al[17] described an average decrease in heart rate of 17.2% compared with our decrease of 16.6%. Based on the data available at this time, the higher dose of dexmedetomidine and the addition of midazolam do not cause a greater effect on patient heart rate.

In terms of other metrics, parent satisfaction with both sedation regimens, based on phone calls made on the day after the sedation, revealed no difference between the DM and CH groups. Additionally, echocardiogram quality was statistically similar between groups; however, in poststudy discussions, most technologists preferred the level of sedation provided in the DM group, expressing that the patients were more compliant.

There are limitations to the study design that may have impacted the outcomes. Single-institution patient enrollment limited sample size; a larger cohort may have allowed for more statistical differences to be determined. Yet, there have been more than 600 patients sedated at HDVCH with this DM regimen for other procedures (MRI, nuclear medicine scans, BAER) with similar success rates and safety profiles (data not yet published). The retrospective, nonblinded nature of any study weakens its impact; a prospective design would have assured more consistent documentation of predetermined data to be collected on all patients. A prospective study would have allowed for creation of a specific postsedation survey that might have documented differences between the sedation regimens. Finally, two different formulations of CH were used during the study period. Hill et al[21] recently presented data suggesting that the reconstituted crystalline CH was less effective in sedating pediatric patients for TTE; we did not find this difference in our population. We encountered failure to sedate adequately in 6/31 (19.4%) patients using the commercial syrup and only 1/18 (5.6%) patients who received the reconstituted crystalline product ($p = 0.238$).

Conclusion

This study is the first peer-reviewed publication showing that the intranasal delivery of DM provides an efficacious and safe moderate sedation regimen and that this combination compares favorably with our historical control group of CH patients as well as the other pediatric data available in present literature. These data suggest a greater success rate for complete/complex TTE with a higher dose of dexmedetomidine and a synergistic effect of midazolam without increasing bradycardic effects. Future studies may need to focus on optimal dosing of medications as well as other medication combinations that might mitigate unwanted side effects while continuing to improve efficacy.

Ethics Approval

This study was approved by the Institutional Review Board of Helen DeVos Children's Hospital.

Funding

None.

Conflict of Interest

None.

Acknowledgments

The authors thank Denise Katerberg (RN), Kimberly Winterhalter (MD), and Akunne Ndika (MD) for assistance with study design.

References

1 Malviya S, Voepel-Lewis T, Tait AR, Merkel S, Tremper K, Naughton N. Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS). Br J Anaesth 2002;88(2):241–245
2 Wolfe TR, Braude DA. Intranasal medication delivery for children: a brief review and update. Pediatrics 2010;126(3):532–537
3 Miller JL, Ashford JW, Archer SM, Rudy AC, Wermeling DP. Comparison of intranasal administration of haloperidol with intravenous and intramuscular administration: a pilot pharmacokinetic study. Pharmacotherapy 2008;28(7):875–882
4 Wermeling DP, Miller JL, Archer SM, Manaligod JM, Rudy AC. Bioavailability and pharmacokinetics of lorazepam after intranasal, intravenous, and intramuscular administration. J Clin Pharmacol 2001;41(11):1225–1231
5 Veldhorst-Janssen NM, Fiddelers AA, van der Kuy PH, Neef C, Marcus MA. A review of the clinical pharmacokinetics of opioids, benzodiazepines, and antimigraine drugs delivered intranasally. Clin Ther 2009;31(12):2954–2987
6 Fösel T, Hack C, Knoll R, Kraus GB, Larsen R. Nasal midazolam in children, plasma concentrations and the effect on respiration. Paediatr Anaesth 1995;5(6):347–353
7 Yuen VM, Hui TW, Irwin MG, et al. A randomised comparison of two intranasal dexmedetomidine doses for premedication in children. Anaesthesia 2012;67(11):1210–1216
8 Cimen ZS, Hanci A, Sivrikaya GU, Kilinc LT, Erol MK. Comparison of buccal and nasal dexmedetomidine premedication for pediatric patients. Paediatr Anaesth 2013;23(2):134–138
9 Gyanesh P, Haldar R, Srivastava D, Agrawal PM, Tiwari AK, Singh PK. Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI: a double-blind, randomized, placebo-controlled trial. J Anesth 2014;28(1):12–18
10 Jia JE, Chen JY, Hu X, Li WX. A randomised study of intranasal dexmedetomidine and oral ketamine for premedication in children. Anaesthesia 2013;68(9):944–949
11 Baldwa NM, Padvi AV, Dave NM, Garasia MB. Atomised intranasal midazolam spray as premedication in pediatric patients: comparison between two doses of 0.2 and 0.3 mg/kg. J Anesth 2012;26(3):346–350
12 Mekitarian Filho E, de Carvalho WB, Gilio AE, Robinson F, Mason KP. Aerosolized intranasal midazolam for safe and effective sedation for quality computed tomography imaging in infants and children. J Pediatr 2013;163(4):1217–1219
13 Ambi US, Joshi C, Ganeshnavar A, Adarsh E. Intranasal dexmedetomidine for paediatric sedation for diagnostic magnetic resonance imaging studies. Indian J Anaesth 2012;56(6): 587–588
14 Greenberg B, Schoonover J, Graf A, et al. Intranasal Combination Dexmedetomidine and Midazolam for Pediatric Procedural Sedation. Available at http://www2.pedsanesthesia.org/meetings/2010winter/syllabus/pdfs/abstracts/wapd/P134.pdf. Accessed August 29, 2016

15 Miller JW, Loepke A, Bernard P. Nasal dexmedetomidine sedation for pediatric transthoracic echocardiography. World J Ped and Cardiovasc Surg 2015;6:154–154
16 Kleinman ME, Chameides L, Schexnayder SM, et al. Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122(Suppl 3): S876–S908
17 Li BL, Ni J, Huang JX, Zhang N, Song XR, Yuen VM. Intranasal dexmedetomidine for sedation in children undergoing transthoracic echocardiography study–a prospective observational study. Paediatr Anaesth 2015;25(9):891–896
18 Reynolds J, Rogers A, Medellin E, Guzman JA, Watcha MF. A prospective, randomized, double-blind trial of intranasal dexmedetomidine and oral chloral hydrate for sedated auditory brainstem response (ABR) testing. Paediatr Anaesth 2016;26(3): 286–293
19 Miller J, Xue B, Hossain M, Zhang MZ, Loepke A, Kurth D. Comparison of dexmedetomidine and chloral hydrate sedation for transthoracic echocardiography in infants and toddlers: a randomized clinical trial. Paediatr Anaesth 2016;26(3): 266–272
20 Nafiu OO, Voepel-Lewis T, Morris M, et al. How do pediatric anesthesiologists define intraoperative hypotension? Paediatr Anaesth 2009;19(11):1048–1053
21 Hill GD, Walbergh DB, Frommelt PC. Efficacy of reconstituted oral chloral hydrate from crystals for echocardiography sedation. J Am Soc Echocardiogr 2016;29(4):337–340