DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Tuesday March 8, 2016
1800 HOURS

LOCATION:
Curry Original
253 Ontario Street

PRESENTING ARTICLES:
Dr. Anthony Ho & Dr. Jordan Leitch

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants, who will be expected to contribute pending suspension of bar privileges.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?
3. Was the food and wine up to the high standards expected by self-respecting anesthesiologists?

Pediatric Anesthesia

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ORIGINAL ARTICLE

A prospective, randomized, double-blind trial of intranasal dexmedetomidine and oral chloral hydrate for sedated auditory brainstem response (ABR) testing

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What is already known about the topic

- Oral chloral hydrate has been used for many years for sedating children undergoing nonpainful procedures such as auditory brain stem response (ABR) testing.
- High-dose dexmedetomidine by intravenous and intranasal routes is effective in sedating children undergoing CT scans and echocardiograms, but there are limited studies with direct comparison of the efficacy and side effects of the two drugs.

What new information this study adds

- This prospective, controlled, randomized, double-blind, double-dummy study showed that high-dose intranasal dexmedetomidine was associated with a greater rate of satisfactory sedation with a single dose, a shorter time to the start the procedure, and a higher rate of return to baseline activity on the day of the procedure compared to oral chloral hydrate in children undergoing ABR testing.
- There were no differences in the time from administration of sedation to completion of the ABR testing and discharge.

Keywords
administration; intranasal; chloral hydrate; dexmedetomidine; evoked potentials; auditory; brainstem; hypnotics and sedatives

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Summary

Background: Dexmedetomidine is increasingly used by various routes for pediatric sedation. However, there are few randomized controlled trials comparing the efficacy of dexmedetomidine to other commonly used sedatives.
Aim: To compare the efficacy of sedation with intranasal dexmedetomidine to oral chloral hydrate for auditory brainstem response (ABR) testing.
Methods: In this double-blind, double-dummy study, children undergoing ABR testing were randomized to receive intranasal dexmedetomidine 3 mcg·kg^{-1} plus oral placebo (Group IN DEX) or oral chloral hydrate 50 mg·kg^{-1} plus intranasal saline placebo (Group CH). We recorded demographic data, times from sedative administration to start and completion of testing, quality of sedation, occurrence of predefined adverse events, discharge times, and return to baseline activity on the day of testing.
Results: Testing completion rates with a single dose of medication were higher in the IN DEX group (89% vs 66% for CH, odds ratio with 95% confidence intervals 4.04 [1.3–12.6], $P = 0.018$). The median [95% CI)] time to successful testing start was shorter (25 [20–29] min vs 30 [20–49] min for IN DEX and CH, respectively, log rank test $P = 0.02$) and the proportion of children whose parents reported a return to baseline activity on the day of

testing was greater for the IN DEX than the CH group (89% vs 64%, OR [95% CI] 4.71 [1.34–16.6], $P = 0.02$). There were no major adverse events in either group and no significant differences in the incidence of minor events.
Conclusion: Intranasal dexmedetomidine is an effective alternative to oral chloral hydrate sedation for ABR testing, with the advantages of a higher incidence of testing completion with a single dose, shorter time to desired sedation level, and with significantly more patients reported to return to baseline activity on the same day.

Introduction

Dexmedetomidine is effective in anesthetic care as a preinduction anxiolytic medication, general and regional anesthetic adjunct, a component of postoperative pain management and for sedation in patients undergoing mechanical ventilation (1). The benefits of a relative preservation of airway tone and respiratory drive and the potential as a neuroprotective agent make dexmedetomidine an attractive choice as a sedative agent in children (2,3). Although there are many observational studies of sedation with this drug, there are few randomized clinical trials that compare important clinical outcomes with dexmedetomidine to other commonly used sedative drugs such as chloral hydrate (4).

The auditory brain stem response (ABR) is the preferred noninvasive screening test for hearing loss in children who cannot cooperate for audio-booth testing (5). Although it is not painful, it does require cooperation, and sedation is usually necessary in children above 6 months of age. For many years this has been accomplished with oral chloral hydrate, a drug widely considered to be a safe, effective sedative/hypnotic for pediatric procedures (6). However, chloral hydrate can result in profound respiratory depression with death or severe neurologic injury reported even when the usually recommended doses were administered (7). Oral chloral hydrate has been in short supply in the USA since 2013 when its manufacture was discontinued in this country for business reasons. Compounding pharmacies can prepare the drug but concerns about costs and quality control limit access to this option leading to a search for alternative sedative regimens (8).

Dexmedetomidine is a potent and highly selective alpha-2 receptor agonist with sedative, anxiolytic, and analgesic effects in children (9). Intravenous dexmedetomidine has become well established for procedural sedation in children, particularly for noninvasive imaging (2,10,11). However, the process of obtaining venous access in an awake child can be an unpleasant experience for all, including the child, families, and health care providers, even when local anesthetic patches are used.

Dexmedetomidine by the intranasal route has been used as the sole sedative to provide satisfactory conditions for successful completion of computed tomography (CT) scans, echocardiograms, and ABR testing, when given in doses based on pharmacokinetic data (12–14). In a recent editorial, Cravero *et al*. described the limitations of these observational studies and specifically identified the need for information on 'the efficiency of dexmedetomidine as a sedative (e.g., time to produce the desired state)', 'the quality of the sedation in meeting patient and provider needs for the procedure', and 'the relative recovery time with this drug compared to others using validated, objective, measures that are reproducible from one institution to another' (4).

This study was designed as a randomized, double-blind, double-dummy prospective comparison of intranasal dexmedetomidine and oral chloral hydrate for sedation for ABR testing.

Methods

The Institutional Review Board approved this study and an Investigational New Drug approval was obtained from the Food and Drug Administration as dexmedetomidine has not been approved for this indication or route of administration in children (IND 110586). The study was registered with clinicaltrials.gov (ID NCT01255904). Patients scheduled for sedation for ABR testing in the audiology clinic were screened for inclusion in the study. They were excluded if they were <6 months or >8 years, <5 kg or >25 kg in weight, had a history of a previous failed sedation, a body mass index (BMI) above 30 $kg{\cdot}M^{-2}$, or a diagnosis of attention deficit hyperactivity disorder, cardiac disease, or obstructive sleep apnea. Written informed consent from the legal guardians and child assent (when appropriate) were obtained after physician review of the presedation assessment.

The study was designed as a randomized, double-blind, double-dummy trial where patients were assigned to one of two groups based on a computer-generated random number. One group received intranasal dexmedetomidine and oral saline placebo (IN DEX

group), while the other group received oral chloral hydrate and intranasal saline placebo (CH group). The pharmacy prepared the oral medication/placebo and delivered them to the clinic in amber oral syringes labeled 'Study drug for oral use only' so that color differences between chloral hydrate and saline were not visible and the specific drug was not identified.

The intranasal medication/placebo was placed in a syringe labeled 'Study drug for intranasal use only' and attached to the laryngeal mask airway MAD Nasal™ needle-free intranasal drug delivery system (Teleflex Medical, Research Triangle Park, NC) (15). This device is 41.9 mm long, has a tip diameter of 4.3 mm, a dead space of 0.07 ml, and delivers a typical particle size of 30–100 μm. Air was added (0.2 ml) to the syringe so that the entire dose would be administered. The pharmacy also provided another set of similarly labeled syringes in case a second dose was required as described below. Nasal medications were administered to both nares with no more than 0.5 ml of medication/placebo placed in a single nostril.

The IN DEX group received a placebo dose of oral saline followed by 3 $mcg \cdot kg^{-1}$ of intranasal dexmedetomidine (drawn directly from the manufacturer vial in a concentration of 100 $mcg \cdot ml^{-1}$). This dose was chosen based on previous report of the bioavailability of dexmedetomidine delivered across the nasal mucosa (16). Given that the reported bioavailability is between 35% and 93%, this should provide blood levels comparable to IV doses of 1.05–2.79 $mcg \cdot kg^{-1}$, with a peak effect at 38 min (16). This is well within the reported safe range of IV administration (11). The CH group received a single oral dose of 50 $mg \cdot kg^{-1}$ chloral hydrate, with saline placebo for intranasal administration. This is in keeping with our current practice and within the published dose range for pediatric sedation for nonpainful procedures (17).

Adequate sedation to start testing was defined as a state that allowed the audiologist to place ABR electrodes. If this was not achieved by 30 min, the patient was considered a sedation failure and received a second dose of oral and nasal medications. Patients in the IN DEX group received a second dose of oral saline placebo with a second intranasal dexmedetomidine dose of 1 $mcg \cdot kg^{-1}$. Total dose of dexmedetomidine (sum of amount given for the first and second administration) was not to exceed 100 mcg. Patients in the CH group received a second dose of oral chloral hydrate (25 $mg \cdot kg^{-1}$) and intranasal saline placebo. Total dose of chloral hydrate (sum of amount given in first and second administration) was not to exceed 2 g.

In order to maintain blinding, the patient, parents, their health care providers, and the observers were not informed which administration (oral or intranasal) contained active medication or placebo. All efforts were made to administer the oral and intranasal medications within 60 s of each other. Patients who were unable to complete the exam after a second dose were rescheduled for sleep deprived sedation (with standard chloral hydrate protocol) in the Audiology clinic or general anesthesia in keeping with standard practice in the Audiology clinic.

The Audiology sedation nurse monitored the patient throughout the duration of their exam and monitoring was consistent with Hospital Policy and Procedures and the American Academy of Pediatrics/American Academy of Pediatric Dentistry (AAP/AAPD) guidelines on monitoring of pediatric patients during and after diagnostic and therapeutic procedures (18). This included continuous monitoring of pulse oximetry, heart rate, and respiratory rate. Blood pressure was obtained prior to administration of medication and repeated as possible during the period of sedation including at onset, at 5-min intervals, at the completion of the exam, and every 5 min thereafter until the patient met discharge criteria. This is in keeping with standard sedation practice in the Audiology clinic. A sedation physician or anesthesiologist remained present in a supervisory role until the exam was completed and was immediately available until the patient was discharged.

ABR completion was defined as the time that the audiologist terminated collection of data. If the child woke up during the procedure, the ABR testing was interrupted and the parent was asked to try to soothe the child back to sleep as would be done at home (e.g., patting on the back, singing to the child, etc.). If this was unsuccessful, the sedation was considered a failure and the procedure was rescheduled as described above. After the ABR testing was completed or abandoned, the patient entered the recovery phase, which occurred in the same location under the care of the same sedation nurse. Per hospital policy, discharge criteria include a patent airway without respiratory depression, return to baseline vital signs, return to baseline level of consciousness and motor function, adequate hydration without nausea or vomiting, adequate pain control, and return to presedation modified Aldrete score.

Data collected in both groups included age, gender, weight, doses and time of administration of sedative drugs, along with the time of the start and end of ABR testing. We noted if the testing was canceled for any reason (e.g., NPO violation, presence of wax or middle ear fluid) and categorized the efficacy of sedation into testing completed without interruptions, completed with interruptions, or as inadequate for testing. We recorded the occurrence of adverse events (bradycardia,

hypotension, hypoxia, or other), interventions required, time to awakening, and time to discharge. A follow-up phone call was made to determine if there were any complications and if the child returned to baseline activity on the same day of the procedure. Major complications were predefined as aspiration, death, cardiac arrest, unplanned hospital admission or level-of-care increase, or emergency anesthesia consultation (19). Cardiorespiratory adverse events were defined in keeping with consensus-based recommendations for standardized terminology in reporting adverse events (20). This included the criteria that minor events were defined as only those that require intervention or a change in disposition.

Statistics

The primary end point of the study was the time from the administration of the first dose of sedation to the completion of ABR testing.

Sample size

The sample size was based on a two group comparison of means, assuming that: (i) the mean ± SD time for study completion would be similar to that in an IRB approved retrospective study (108 ± 31 min) (14); (ii) A reduction in mean time of 20 min would be of clinical relevance as it would permit one additional case to be reliably completed in a 10 h shift; (iii) Standard deviation in both groups would be the same as in the retrospective study (31 min); (iv) Power = 80% at the 0.05 level of significance. Based on these assumptions, a group size of 39 was calculated. We enrolled a total of 90 subjects with 45 in each group to allow for a 15% loss from incomplete data.

Data were summarized using descriptive statistics of number of patients and percentages for categorical data. Continuous data are presented as mean and standard deviation if normally distributed and as median with 95% confidence intervals if not normally distributed, after testing for normality with the Wilk–Shapiro test. Student's *t*-tests were used for comparisons of continuous data that were normally distributed and by nonparametric Mann–Whitney tests for data not normally distributed. For categorical data we used chi-square tests or Fisher's exact test as appropriate and calculated the odds ratio with 95% confidence intervals. Separate Kaplan–Meier survival curves were constructed for the time from administration of the first dose of sedative drugs to the satisfactory start and completion of the procedure, with log rank tests for comparisons of median values. P values < 0.05 were considered statistically significant.

Results

Two hundred and sixteen patients were evaluated for enrollment in the study. Seventy-four patients did not meet eligibility criteria and 52 declined to participate. The remaining 90 were assigned into two groups of 45 each. After randomization, four patients in the CH group and one patient in the IN DEX group did not receive the allocated medication for reasons mentioned in the CONSORT diagram. In the chloral hydrate group, this included one patient with ear infection, one with impacted wax, one with an NPO violation, and one who on review did not qualify as the child had a previous sedation failure for ABR testing. In the dexmedetomidine group, this included one child with impacted wax. This left 41 patients in the CH group and 44 in the IN DEX group who received the allocated medication. Demographic characteristics are presented in Table 1 for both groups.

Kaplan–Meier curves for time from administration of the first dose to successful start and completion of ABR testing are presented in Figures 1 and 2, respectively. The time satisfactory sedation was established to enable that the start of the ABR procedure was shorter in the IN DEX group (median [95% CI] 25 [20–29] min vs 30 [20–49] min for IN DEX and CH groups, respectively, log rank test $P = 0.02$). ABR testing could be accomplished with a single dose of medication more often in the IN DEX group (39/44 [89%] vs 27/41 [66%] for IN DEX and CH groups, respectively, OR [95% CI] 4.04 [1.30–12.6], $P = 0.018$). However, there were no statistically significant differences in the proportion of patients, where both doses of sedation failed to produce satisfactory conditions for the start of ABR testing or where patients woke during testing but testing was still able to be completed (Table 2). There were also no statistically significant differences in the time to completion of ABR testing between the two groups (median [95% CI] 98.5 [80–110] vs 110 [85–119] min for IN DEX and CH groups, respectively, log rank test $P = 0.21$).

We could not contact seven (16%) and eight (20%) of patients in the IN DEX and CH groups, respectively the next day. In the patients we could contact, the proportion of children reported returning to baseline

Table 1 Demographic data presented as numbers, mean (95% CI)

	Intranasal dexmedetomidine	Oral chloral hydrate
n	44	41
Age (months)	23.3 (19.5–27.2)	25.6 (22.0–29.0)
Weight (kg)	12.3 (11.2–13.4)	12.8 (11.8–13.9)
Sex (Male/Female)	23/21	27/14

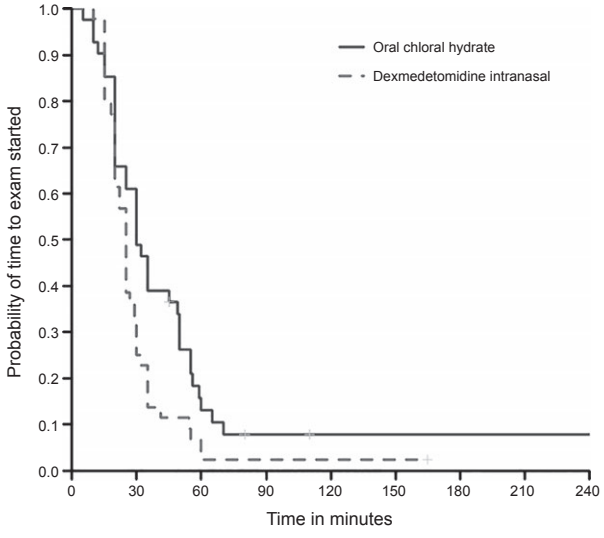

Figure 1 Kaplan–Meier survival curve showing probability of time to start ABR testing. This represents the time (in minutes) from administration of dose #1 to the start of testing. Solid line (——) represents oral chloral hydrate group. Dotted line (**- - -**) represents intranasal dexmedetomidine group.

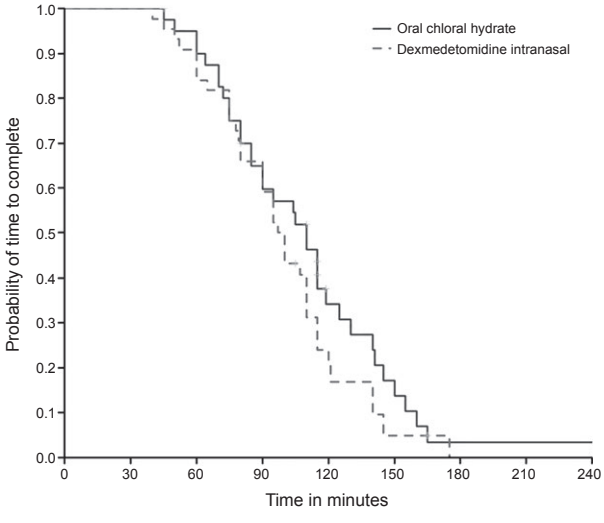

Figure 2 Kaplan–Meier survival curve showing probability of time to complete ABR testing. This represents the time (in minutes) from administration of dose #1 to completion of testing. Solid line (——) represents oral chloral hydrate group. Dotted line (**- - -**) represents intranasal dexmedetomidine group.

activity on the procedure day was higher in the IN DEX group (33/37 [89%] vs 21/33 [64%] for IN DEX and CH groups respectively, OR [95% CI] 4.71 [1.34–16.6], $P = 0.02$).

There were no major events in either cohort. There were two minor events, both in the IN DEX group. One patient had persistent oxygen saturation between 90% and 93%, which resolved with blow by oxygen. A second patient had an oxygen desaturation to 86%, which resolved with repositioning. No patient in either group met our criteria for bradycardia or hypotension as an adverse event.

Discussion

This study has shown that IN DEX is a more efficient sedative than the well-established technique of sedation with oral chloral hydrate as it took less time to achieve the desired state of hypnosis that allowed the audiologist to place the ABR electrodes and start ABR testing. This level of sedation was achieved more often with a single dose of medication in the IN DEX group. A possible explanation of these findings may be related to the intranasal route of administration with a mucosal atomizing device, which provides a more reliable delivery of the drug dose even in uncooperative children. In contrast, oral chloral hydrate generally requires a child to swallow the entire drug dose, and often some of the medication may be lost in less cooperative children during attempts to get the child to swallow the medication.

A second explanation could be differing pathways of absorption for medications delivered to the nasal cavity. Medications are absorbed across the nasal mucosa more rapidly and avoid first-pass metabolism with higher brain effector site concentrations achieved compared to the oral route. There are also reports of a nose–brain pathway allowing medications delivered in the nasal cavity to traverse the olfactory mucosa and directly enter the CSF (21). Both mechanisms may account for more rapid delivery to the CNS and subsequent improved efficiency.

While the time to the start the desired effect was shorter, we were unable to demonstrate a difference in the primary outcome of time to complete testing. The study was designed to detect a difference that would permit reliable completion of an additional case to justify the increased costs of dexmedetomidine. The study may have been underpowered to detect smaller differences in testing times and a recent retrospective study did demonstrate such a difference (14). Another possible explanation is that the audiologist may continue to test the patient as long as the child is sedated and stops when the effects of sedation wear off and the child begins to move. We have a clinical impression that ABR testing performed under general anesthesia tends to be much longer than with nurse-administered sedation as the audiologist tries to get the maximum possible data to avoid bringing the child back for repeat testing under anesthesia because the quality of the ABR testing was inadequate. We speculate that ABR testing may take

Table 2 Sedation outcomes: Data presented as numbers (percentages), odds ratio with 95% CI

	Intranasal dexmedetomidine	Chloral hydrate	Odds ratio (95% CI)	*P* value[a]
Total number enrolled	44	41		
Number of subjects with satisfactory sedation from a single dose to complete ABR test with or without interruptions	39 (89%)	27 (66%)	4.04 (1.34–12.6)	0.018
Number of subjects who required two doses before ABR test could be completed with or without interruptions	3 (6.8%)	7 (17.1%)	2.81 (0.68–11.7)	0.19
Number of subjects where ABR tests could not be completed (failed sedation)	2 (4.5%)	7 (17.1%)	4.32 (0.85–22.2)	0.08
Postdischarge follow-up data available	37 (84%)	33 (88%)		
Number of patients who were reported to return to baseline activity on the same day of the procedure (Percentage of patients who could be contacted after discharge)	33 (89%)	21 (64%)	4.71 (1.34–16.6)	0.02
Side effects				
Respiratory events (minor)	2	0		
Respiratory events (major)	0	0		
Cardiovascular events	0	0		

[a]Fisher's exact test.

more time in patients with effective sedation. However, we did not assess qualitative differences in the ABR testing results.

We did show that parents reported better rates of same day return to baseline activity in the IN DEX group. One explanation is the pharmacokinetic profile of dexmedetomidine, which has a much shorter half-life compared to chloral hydrate. However, this may also represent an intrinsic property of the individual drugs as they act on very different receptor systems to produce a state of hypnosis. The clinical importance of a faster return to baseline is that it permits the child's caretakers to resume normal routines without the concerns of continued close observation to prevent injuries from falls in a child with residual partial sedation. However, a limitation of this study is that we did not perform more rigorous objective tests of the quality of delayed recovery (e.g., QoR -15, Treiger dot test, digit symbol substitution test), or tests of balance (dynamic balance test) to determine the time of return of these functions (22,23). We relied on the parent's opinion of when the child had returned to normal activity. This is in keeping with an earlier report on prolonged recovery after sedation (24).

There are few large-scale published data on the use and safety profile of high-dose dexmedetomidine by the intranasal route. It is important to note that severe cardiorespiratory adverse events that require interventions are very rare in the setting of an organized sedation program (25). Thus, it is difficult to make any definitive conclusions regarding the overall safety of either medication based on this study alone as it was not adequately powered to detect differences in the low incidence of side effects. There were no major adverse events in either group but we did have two minor respiratory adverse events in the IN DEX group. This is consistent with other reports of IN DEX (12,13).

No patient in either group met our criteria for bradycardia or hypotension. This differs from reports of patients receiving high-dose IV dexmedetomidine and high-dose IN DEX, where decreases from baseline values were used as the criteria for cardiovascular changes (11,13). The cause of the difference between the reported incidence of bradycardia and hypotension between these reports and our study is unclear but likely reflects differences in the definition of adverse events. In keeping with the International Sedation Task Force of the World Society for Intravenous Anesthesia reporting tool, we only considered events that required clinical intervention as an adverse event and did not use absolute values of heart rate or blood pressure as criteria for adverse events (20). As none of our patients in the study had cardiovascular events requiring intervention, we did not detect any differences between the groups in the incidence of bradycardia or hypotension.

An important consideration of this study, and all studies about pediatric sedation, involves the sedation environment. The audiology clinic at our institution has a specialized set of rooms for procedural sedation. These rooms are designed to look nonthreatening to patients and families. They have low-lighting, standard cribs for children, and recliners or rocking chairs for the primary caregivers. The impact of this environment on sedation success is unclear but likely played a role in the overall outcomes described in our study. However, as both groups were managed in the same environment and the choice of drugs was randomized, differences in results may reflect the effect of the sedative drugs. The major strengths of this study are related to randomization of

allocation and a double-dummy design for blinding of participants and their caretakers.

In summary, this prospective, randomized, double-blinded study demonstrates that intranasal dexmedetomidine is an acceptable method of sedation for ABR testing in children. Additionally, it shows that IN DEX has the advantages of a faster time to start the procedure, greater success with a single dose of medication, and improved incidence of reported same day return to baseline activity. Future studies are needed to evaluate the safety profile of IN DEX and compare the effectiveness to other commonly utilized sedation medications such as pentobarbital.

Ethics approval

This study was approved by the Baylor College of Medicine Institutional Review Board and received Investigational new drug approval from the Food & Drug Administration.

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Conflict of interest

The authors have no financial relationships or other conflicts of interest relevant to this article to disclose.

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ORIGINAL ARTICLE

Comparison of rescue techniques for failed chloral hydrate sedation for magnetic resonance imaging scans—additional chloral hydrate vs intranasal dexmedetomidine

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What is already known

- Dexmedetomidine, a highly selective α-2 agonist, has better pharmacokinetic properties than chloral hydrate; however, the efficacy of intranasal dexmedetomidine with that of a second oral dose of chloral hydrate for rescue sedation during magnetic resonance imaging (MRI) studies in infants is unknown.

What this article adds

- Intranasal dexmedetomidine at a dosage of 1 or 2 mcg·kg^{-1} was used successfully for rescue sedation in place of an additional dose of chloral hydrate, in 1- to 6-month-old infants in whom initial chloral hydrate failed during the MRI study.
- Intranasal dexmedetomidine appears to cause rescue sedation in a dose-dependent manner.

Keywords
dexmedetomidine; intranasal administration; deep sedation; chloral hydrate

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Summary

Background: Chloral hydrate, a commonly used sedative in children during noninvasive diagnostic procedures, is associated with side effects like prolonged sedation, paradoxical excitement, delirium, and unpleasant taste. Dexmedetomidine, a highly selective α-2 agonist, has better pharmacokinetic properties than chloral hydrate. We conducted this prospective, double-blind, randomized controlled trial to evaluate efficacy of intranasal dexmedetomidine with that of a second oral dose of chloral hydrate for rescue sedation during magnetic resonance imaging (MRI) studies in infants.

Methods: One hundred and fifty infants (age group: 1–6 months), who were not adequately sedated after initial oral dose of 50 mg·kg^{-1} chloral hydrate, were randomly divided into three groups with the following protocol for each group. Group C: second oral dose chloral hydrate 25 mg·kg^{-1}; Group L and Group H: intranasal dexmedetomidine in a dosage of 1 and 2 mcg·kg^{-1}, respectively. Status of sedation, induction time, time to wake up, vital signs, oxygen saturation, and recovery characteristics were recorded.

Results: Successful rescue sedation in Groups C, L, and H were achieved in 40 (80%), 47 (94%), and 49 (98%) of infants, respectively, on an intention to treat analysis, and the proportion of infants successfully sedated in Group H was more than that of Group L ($P < 0.01$). There were no significant differences in sedation induction time; however, the time to wake up was significantly shorter in Group L as compared to that in Group C or H ($P < 0.01$). No significant adverse hemodynamic or hypoxemic effects were observed in the study.

Conclusion: Intranasal dexmedetomidine induced satisfactory rescue sedation in 1- to 6-month-old infants during MRI study, and appears to cause sedation in a dose-dependent manner.

Introduction

Good quality magnetic resonance imaging (MRI) needs sufficient immobility during the procedure. Owing to the sound produced by MRI equipment, narrow tube, and the relatively long scanning duration (10–30 min), adequate and safe sedation or anesthesia is a prerequisite to successful MRI study in children (1). Chloral hydrate is a nonopiate, nonbenzodiazepine sedative-hypnotic drug, which is widely used for inducing sedation in pediatric patients (2), especially in China.

Even though MRI scanning in infants using chloral hydrate sedation carries a relatively low risk of adverse effects (3), there are still some concerns about its potential for having a prolonged sedative effect, paradoxical excitement or delirium (4), airway obstruction, respiratory depression, and oxygen desaturation (5). A study reported an 89% success rate with use of chloral hydrate (mean initial dose, 72 $mg{\cdot}kg^{-1}$ body weight) in 119 children undergoing computed tomography (CT) or MRI. Furthermore, the success rate after augmentation (mean total dose, 78 $mg{\cdot}kg^{-1}$ body weight) was 98% (6). Another study showed that an initial dose of 40 $mg{\cdot}kg^{-1}$ was successful in 94.3% of infants undergoing MRI or CT. Furthermore, an augmentation dose of 25 $mg{\cdot}kg^{-1}$ increased this success rate to 97.1% (7). At our institution, sedation with chloral hydrate (50 $mg{\cdot}kg^{-1}$) is routinely used for children undergoing 1.5 Tesla MRI study because of its relative safety and low cost. For an initial failure rate of nearly 20% (7–9), the rescue sedation is effected with a second lower dose of chloral hydrate.

Dexmedetomidine is a highly selective alpha 2 receptor agonist that has sedative as well as analgesic properties (10). Sedation with dexmedetomidine is associated with minimal respiratory depression (11–13), and there is an expanding body of evidence demonstrating its safety and efficacy for use in pediatric noninvasive diagnostic procedures (9,10,14–17). A retrospective analysis (14) demonstrated the successful use of intravenous dexmedetomidine as a rescue sedative for children who failed to be sedated using chloral hydrate and/or midazolam for MRI.

However, most sedation studies for MRI have reported on the efficacy of a single pharmacologic regimen in a wide range of pediatric age groups (18), including our previous study (9). Few studies have reported the efficacy of deep sedation plus anesthesia regimes in infants of 12 months of age (3,8,19). Infants are more likely to require deep sedation or anesthesia in order to ensure their immobility during the MRI scan. Such use is associated with a higher risk of the cardiorespiratory adverse effects of these drugs (20). In this study, we tested the hypothesis that intranasal dexmedetomidine is more effective than a second dose of oral chloral hydrate for rescue sedation in infants aged between 1–6 months of age, who were inadequately sedated following the initial dose of chloral hydrate.

Methods

Subjects and study protocol

The study protocol was approved by the local Institutional Review Board (GCP/IEC2014010); written informed consent was obtained from the patients' parents or legal guardians. Infants corresponding to ASA (American Society of Anesthesiologists) physical status I or II, aged between 1 and 6 months, who failed chloral hydrate sedation during clinical routine diagnostic MRI scanning, (i.e., at 30 min postadministration, there was no evidence of sedation, as assessed using the modified Observer Assessment of Alertness and Sedation Scale [MOAA/S; Table 1]) (21), were enrolled in this prospective, randomized, double-blind, controlled trial. Sedation status was evaluated in the supine position by a blinded observer, every 5 min before and after MRI study on 6-point sedation scale of MOAA/S. Successful sedation was defined as a MOAA/S score between 0 and 3, and failure as MOAA/S score >3. Exclusion criteria included, known allergy to dexmedetomidine or chloral hydrate, recent or current treatment with alpha 2 adrenergic receptor agonist or antagonist, organ dysfunction, pneumonia, acute upper respiratory airway inflammation, history of preterm birth, cardiac arrhythmia, and known congenital heart disease.

Eight parents did not consent to participation of their ward in the study; a total of 150 infants in the age group of 1–6 months were enrolled. Oral chloral hydrate was administered as a single agent at an initial dose of 50 $mg{\cdot}kg^{-1}$, after at least 1 h fasting for liquid, as per the protocol followed in our unit. This is a relatively moderate dose compared to what has been reported elsewhere (3). The children were randomly allocated to one of the three groups using a computer-generated random number table. Group C received 25 $mg{\cdot}kg^{-1}$ chloral hydrate diluted with oral syrup up to a maximum dose of 5 ml and 0.2 ml intranasal placebo (normal saline). Groups L and H received intranasal dexmedetomidine in a dose of 1 and 2 $mcg{\cdot}kg^{-1}$, respectively, and 5 ml oral syrup which mimicked chloral hydrate in terms of appearance and consistency.

Undiluted preservative-free dexmedetomidine (Aibeining; Jiang Su HengRui Medicine Co. Ltd, Jiangsu Province, China) was prepared at a concentra-

Table 1 Modified observer's assessment of alertness/sedation scale

0 Does not respond to a noxious stimulus
1 Does not respond to mild prodding or shaking
2 Responds only after mild prodding or shaking
3 Responds only after name is called loudly and repeatedly
4 Lethargic response to name spoken in normal tune
5 Appears asleep, but responds readily to name spoken in normal tone
6 Appears alert and awake, responds readily to name spoken in normal tone

tion of 100 mcg·ml^{-1} and dripped into both nostrils by a 1-ml syringe (precision graduated) with the infant lying in the supine position. This position was maintained for 5 min in order to maximize drug absorption.

All study drugs were prepared by an independent investigator not involved in the observation of the children. Furthermore, observers and attending anesthesiologists were blinded to the study drug administration. Noninvasive monitoring of systolic blood pressure (SBP), heart rate (HR), and pulse oximetry (SpO_2) was done from the time of presedation assessment up to discharge; readings were recorded at baseline (T_0), before (T_1) and at 15 (T_2), 30 (T_3), 60 (T_4), 75 (T_5), and 90 (T_6) min.

Previous reports (8), as well as our unpublished findings, have shown that children with a MOAA/S score of 3 following rescue sedation tend to achieve satisfactory immobilization after comfort maneuvers (repositioning, swaddle) due to slight body motion during acquisition. Therefore, successful sedation was defined as a MOAA/S of between 0 and 3, and failure as MOAA/S of above 3. Sedation induction time was defined as the time from rescue drug administration to the onset of satisfactory sedation. Failure of sedation was defined as inadequate sedation observed within 30 min of rescue sedation. Children were classified as awake if the MOAA/S was between 4 and 6; wake-up time was defined as the time from successful sedation until the time that the child awoke. Children were discharged on attaining an Aldrete score (9) of $\geq$9.

Hypotension or bradycardia was defined as a reduction in systolic blood pressure or heart rate, respectively, of more than 20% from the baseline level. Significant oxyhemoglobin desaturation was defined as SpO2 < 90%.

Data analysis

Demographic characteristics were analyzed by one-way analysis of variance (ANOVA) or chi-squared test, as appropriate. The variability of successful sedation among the three groups was analyzed by chi-square test, and the Bonferroni correction was used for *posthoc* pair-wise comparison with the adjusted P value of 0.0167. Sedation induction time and time to wake up were compared among groups using one-way ANOVA, and *posthoc* pair-wise comparison by the least significant difference test. Hemodynamic variables including SBP and HR were analyzed by mixed model analysis of variance, with repeat measurements to determine group and time effects. The Dunnett's t-test was used for *posthoc* pair-wise comparison of the changes in SBP and HR from baseline (as control) to that at different time points in each group. The adjusted P value of 0.00238 was then applied for conducting *posthoc* pair-wise comparisons. Statistical analyses were performed using SPSS for Windows version 19.0 (SPSS Inc., Chicago, IL, USA). A P value of <0.05 was considered statistically significant.

Results

In our study, all routine MRI examinations were completed in <35 min, which is significantly shorter than the duration of rescue sedation. Therefore, we took the success of sedation as the endpoint. The failure rate of chloral hydrate for the initial sedation was 18.9% (158/839). Seven (4.7%) patients withdrew from the study due to severe vomiting after an additional dose of chloral hydrate. Three (2%) children were transferred directly back to the ward. Of 134 patients included in the study, there were 40, 48, and 46 children in Groups C, L, and H, respectively, who met the inclusion criteria and were eligible for analysis (Figure 1). Demographic data and baseline status are summarized in Table 2. All three groups were comparable with respect to age, weight, and gender. Diagnostic brain MRI accounted for a vast majority of the scans, other imaging sites included a small number of joints or sacral tumors scans with enhancement or not. There was no significant difference between the groups with respect to the site of MRI scans.

Primary outcome

None of the children were uncomfortable with intranasal drug administration. There were no significant inter-group differences in the duration of MRI examination as well as that of sedation status among the three groups at 30 min (T3). Satisfactory rescue sedation was found to be achieved in 40 (80%), 47 (94%), and 49 (98%) infants in Groups C, L, and H, respectively, on an intention to treat analysis, and the proportion of patients successfully sedated in Group H was more than that of Group L ($P < 0.01$). All MRI scans were completed within 35 min. There were no significant inter-group differences with respect to the

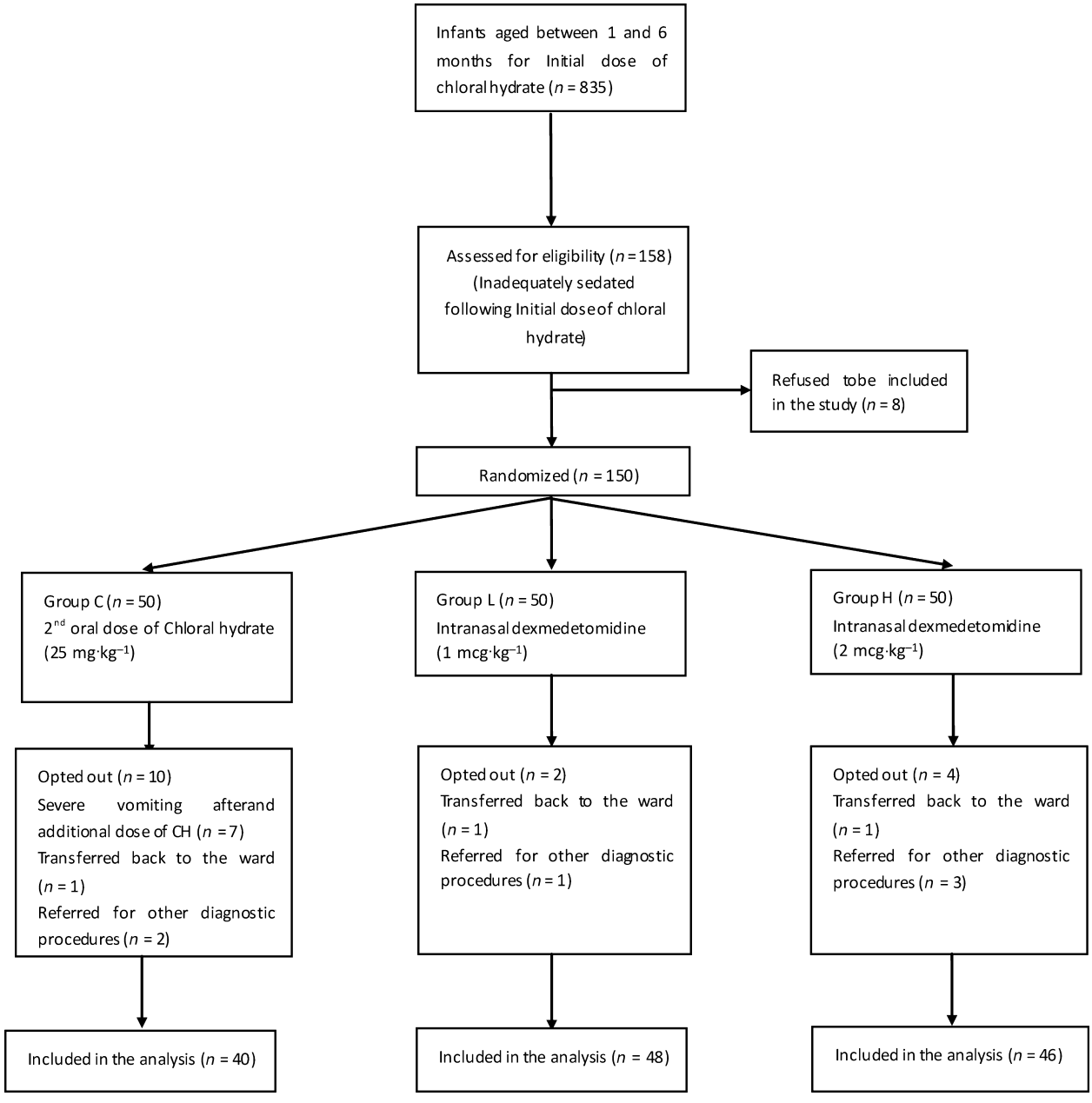

Figure 1 CONSORT flow diagram.

Table 2 Baseline characteristics by study group, expressed as mean ± SD (range) or frequency (%)

	Group C (n = 40)	Group L (n = 48)	Group H (n = 46)
Age (months)	3.8 ± 1.5	3.3 ± 1.6	3.3 ± 1.5
Weight (kg)	6.1 ± 1.6 (3.5–10)	5.6 ± 1.6 (2.6–9)	5.5 ± 1.2 (3.6–8)
Male (%)	19 (47.5%)	30 (62.5)	22 (47.8)

sedation induction time among the three groups. However, the time to wake up in Group L was significantly shorter than that in the other groups ($P < 0.001$, Table 3).

Respiratory and hemodynamic effects

No clinically significant effect of the drugs on SpO_2 levels was observed in any of the study groups. Fur-

Table 3 Sedation induction time and wake-up time for infants who were successfully sedated according to the rescue sedation protocol

	Group C (n = 37)	Group L (n = 45)	Group H (n = 45)
Sedation induction time; min	14.6 ± 4.3	15.1 ± 3.2	14.1 ± 3.1
Wake-up time; min	85.9 ± 14.6 (81.0–90.8)	61.8 ± 11.2* (58.5–65.2)	91.5 ± 15.6 (76.0–82.7)

Values are expressed as mean ± SD [95% CI] or as frequencies.
*Significantly shorter than that in Group C or Group H ($P < 0.01$).

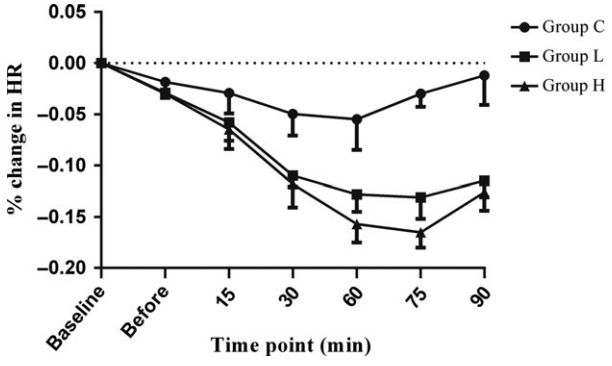

Figure 2 Percentage change in heart rate (HR) from baseline in infants after rescue sedation with chloral hydrate (●) and intranasal dexmedetomidine 1 mcg·kg^{-1} (■) or 2 mcg·kg^{-1} (▲). Error bars indicate standard deviation.

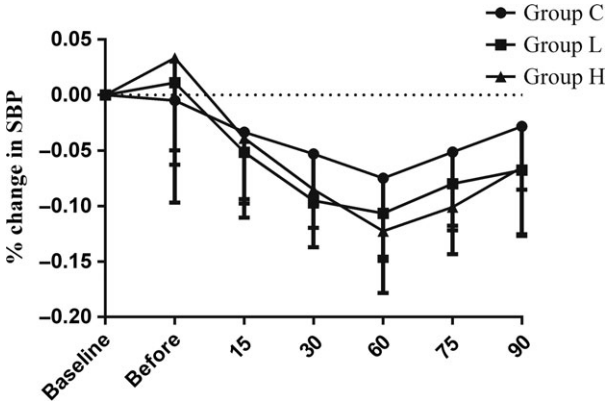

Figure 3 Percentage change in systolic blood pressure (SBP) from baseline in infants after rescue sedation with chloral hydrate (●) and intranasal dexmedetomidine 1 mcg·kg^{-1} (■) or 2 mcg·kg^{-1} (▲). Error bars indicate standard deviation.

thermore, none of the children had oxyhemoglobin desaturation <94% during the observation period. The changes in SBP and HR during the procedure are shown in Figures 2 and 3. There was a significant group and time effect on SBP or HR ($P < 0.01$, respectively). HR and SBP decreased significantly with time in Group L ($P < 0.01$) and Group H ($P < 0.01$), as compared to that in the Group C. *Posthoc* analyses showed a significant reduction in SBP and HR from baseline at 30, 60, 75, and 90 min after drug administration in group L and H ($P < 0.0001$, respectively). The maximum reduction in SBP was 15.8%, 21.1%, and 25.3%, and the maximum reduction in HR was 10%, 15.9%, and 24.3% in Groups C, L, and H, respectively. There were no instances of clinically significant hemodynamic disturbance that required intervention.

Discussion

An ideal agent for MRI sedation should have a rapid onset of action, duration of action >30 min, and no delayed recovery. In the present study, intranasal dexmedetomidine at a dosage of 1 or 2 mcg·kg^{-1} was used successfully for rescue sedation in place of an additional dose of chloral hydrate, in patients in whom initial chloral hydrate failed during the MRI study. With respect to wake-up time, infants in Group L attained more significant and satisfactory sedation than those in the other groups. The time to wake up in Group L was 61.8 min (95% confidence intervals CI, 58.5–65.2), which was shortest among the three groups. All children tolerated the intranasal administration well with no crying. Intranasal dexmedetomidine demonstrated a dose-dependent effect in causing hypotension or bradycardia; however, no serious adverse events were observed.

Chloral hydrate is a relatively mild sedative that is known to induce sleep with no major untoward respiratory or hemodynamic effects in most infants, when administered orally in doses of 50–75 mg·kg^{-1} (22,23). In our study, the maximum oral dose of chloral hydrate used was 75 mg·kg^{-1}, and the success rate of initial sedation was moderately higher (92.5%) than that reported in earlier studies, where success rate of chloral hydrate rescue sedation ranged from 50% to 100% (6,7,24). However, in certain patients, chloral hydrate use has been associated with prolonged recovery time and with requirement for oxygen supplementation (25). In our study, the average time to wake up in Group C was 85.9 min (range, 60–115 min), which is comparable to that in Group H, but longer than that in Group L.

This is likely attributable to the relatively long half-life of its active metabolite, trichloroethanol, which tends to be higher in infants (3,20). In addition, chloral hydrate has an unpleasant taste and its use is associated with a high incidence of nausea and vomiting. In our experience, children often refused to receive a second dose of chloral hydrate, probably due to its bitter caustic taste, whereas all children showed good tolerance to intranasal administration of dexmedetomidine.

Previous studies have shown that intranasal dexmedetomidine is an effective way to sedate children (9,26). It is relatively easy to administer and has a higher bioavailability (27). To attain a target plasma concentration, younger children evidently need larger initial doses of dexmedetomidine, as in young children the volume of distribution of the drug is higher than that in older children and adults (11,28). The doses of intranasal dexmedetomidine used in this study were 1 and 2 $mcg \cdot kg^{-1}$, which is higher than the rescue dose of intravenous dexmedetomidine (14). However, the dose is much lower than that of intravenous dexmedetomidine when used as the sole agent for sedation covering MRI scanning (15). Successful rescue sedation may be attributable to the additive, as well as to the residual effect of chloral hydrate.

Effects of dexmedetomidine

Our recent investigation (9) showed that intranasal dexmedetomidine could be used successfully as a rescue sedation in failed chloral hydrate sedation for non-painful diagnostic procedures; and the successful rescue sedation rate in that study ranged from 83.6% to 96.2%, which is lower than that observed in the present study. The possible reason could be the lower age group of children (1–6 months) included in this study. Also, as the metabolic clearance of dexmedetomidine increases proportionally with weight and age, infants required a lower dosage of dexmedetomidine as compared to that required in children >1 year old (29,30). Therefore, a higher success rate was achieved in younger infants under the same dosage condition. Secondly, the young children are likely to become more sedated than the older during the procedure (7,31).

Nichols *et al.* (14) reported a mean time to recovery to baseline status of 112.5 min, and the mean time to discharge of 173.8 min, when intravenous dexmedetomidine was used as a rescue sedative in failed chloral hydrate and/or midazolam sedation for MRI study. Another study (21) reported significant sedation occurring 45–60 min after both doses of intranasal dexmedetomidine, with a peak sedative effect achieved after approximately 90–105 min. In the present investigation, the average time to wake up in Group L was 61.8 min (range, 44–90 min) which is much shorter than that observed in the other groups.

Hemodynamic effects of alpha 2 agonists produce a modest reduction in SBP and HR. In a study comparing sedative and analgesic effects of intranasal dexmedetomidine, both 1 and 1.5 $mcg \cdot kg^{-1}$ doses resulted in a reduction in SBP of up to 23% and 21%, respectively (21). Available evidence (10,32) shows that the maximum mean reduction in systolic blood pressure of children range from 13.2% to 16.4%, and the maximum reduction in heart rate is about 14.9% after intranasal administration (1.0 $mcg \cdot kg^{-1}$). In our study conducted on infants aged between 1–6 months, intranasal dexmedetomidine at doses of 1 or 2 $mcg \cdot kg^{-1}$ caused a maximum dose-dependent decrease in HR ranging from 15.9% to 24.3%, and SBP ranging from 21.1% to 25.3%. No infant had clinically significant hemodynamic or respiratory disturbance that required intervention.

Study limitations

The peak effect time of 1 and 2 $mcg \cdot kg^{-1}$ intranasal dexmedetomidine was about 60–105 min after intranasal dexmedetomidine (21). We did not assess the peak effects of the two doses. We also did not assess the inter-rater reliability of multiple observers. Only heart rate was monitored because a dedicated monitor for MRI was not available at our center. This study involves only infants aged between 1 and 6 months. Future studies should further evaluate the sedative effect and optimal dosage of this drug in other age groups.

Conclusion

In this study, use of intranasal dexmedetomidine appeared to be a relatively quick and feasible alternative to chloral hydrate as a rescue sedative in infants aged between 1 and 6 months who failed in initial oral chloral hydrate sedation for MRI scanning. The wake-up time associated with 1 $mcg \cdot kg^{-1}$ intranasal dexmedetomidine was comparable to that observed with chloral hydrate. The hemodynamic and respiratory effects associated with use of both doses of intranasal dexmedetomidine were modest, and there were no disturbances that required intervention.

Registry

Url: https://clinicaltrials.gov/ Identifier: NCT02239445.

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Conflict of interest

No conflicts of interest declared.

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