Retrospective Comparison of Intranasal Dexmedetomidine and Oral Chloral Hydrate for Sedated Auditory Brainstem Response Exams

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OBJECTIVE: Satisfactory conditions for auditory brainstem responses (ABR) screening tests for pediatric hearing loss are usually achieved with oral chloral hydrate (CH) sedation. When the US manufacture of this drug was discontinued for business reasons, we developed an alternative sedation regimen using intranasal dexmedetomidine (IN DEX) 4 μg/kg. This institutional review board–approved retrospective study compared the efficacy and adverse effect profiles of these 2 sedative regimens.

METHODS: Medical records of children receiving oral CH or IN DEX for ABR were surveyed for demographic data and times from sedative administration to start and completion of the ABR procedure and recovery times. We also noted if the examination was completed with or without interruptions, failed for inadequate sedation, and if predefined cardiorespiratory adverse events occurred.

RESULTS: In the IN DEX cohort, the examination could be completed more frequently with a single dose of medication (P = .002). Satisfactory sedation in these patients permitted an earlier start of both the ABR examination and recovery to the awake status (P < .001 and < .045, respectively). Hypoxia requiring oxygen therapy was more frequent in the CH group.

CONCLUSIONS: This retrospective study found that IN DEX provides effective sedation for ABR examinations, with the benefits of an ability to begin the test sooner and complete the examination with a single dose, in addition to a decreased incidence of hypoxemia. A randomized controlled trial should test the hypothesis that the IN DEX technique is superior to the well-established standard oral CH regimen.
Chloral hydrate has a long history of use in pediatrics as an effective sedative/hypnotic for facilitating a wide range of diagnostic procedures not associated with pain.\(^1\) In the large database of the Pediatric Sedation Research Consortium, chloral hydrate was the drug used in ~25% of 11,822 cases in which sedation was provided by pediatricians.\(^2\) Although chloral hydrate has long been regarded as “safe,” it does have the potential for profound respiratory depression and re sedation.\(^3\) In a review of 118 critical adverse sedation events in children, death or severe neurologic injury occurred in 13 of 20 children who received chloral hydrate, including some cases in which standard doses were administered.\(^4\)

Auditory brainstem responses (ABR) are used as a noninvasive screening examination for hearing loss in children. This method is the diagnostic procedure of choice for children who are unable to cooperate with the standard audio booth hearing examination. This procedure must be performed during sleep, which requires sedation in most children aged >6 months.\(^5\) For many years, it was common practice to use oral chloral hydrate for ABR procedures.\(^6\)

At our freestanding tertiary pediatric care institution, we perform >1000 sedated ABR examinations annually, with the vast majority receiving nurse-administered sedation according to protocol. This protocol involves an initial oral dose of chloral hydrate 50 mg/kg. If the child is not adequately sedated in 30 minutes, a second dose of 25 mg/kg is administered, with a maximum total dose that does not exceed 2 g. During the procedure, children are monitored by a dedicated nurse in keeping with the American Academy of Pediatrics’ updated guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures.\(^7\)

The manufacture of oral chloral hydrate in the United States was discontinued for business reasons in 2013. This scenario has led to the search for an alternative sedative drug for procedures that historically were accomplished by using chloral hydrate. Dexmedetomidine is a potent and highly selective \(\alpha_2\)-receptor agonist with sedative, anxiolytic, and analgesic effects in children.\(^8,9\) Intravenous dexmedetomidine has become well established for procedural sedation in children, particularly for noninvasive imaging.\(^10-12\)

The pharmacokinetics of dexmedetomidine given by the oral, buccal, and intramuscular routes have been studied, with an average bioavailability of 82% absorption across all mucosal membranes in healthy adult volunteers.\(^13\) The bioavailability varies, with a median of 65% when administered across the nasal mucosa.\(^14\) Intranasal dexmedetomidine (IN DEX) has been shown to be effective as a premedication before anesthesia.\(^15-17\)

Mekitarian et al\(^18\) recently published an observational study of IN DEX as the sole sedative to provide satisfactory conditions for successful completion of computed tomography (CT) scans in 60 children. Li et al\(^19\) showed that IN DEX at a dose of 3 \(\mu\)g/kg provided satisfactory sedation for transthoracic echocardiograms.

When the availability of oral chloral hydrate became limited, a new protocol for nurse-administered, physician-supervised sedation for ABR examinations was established at our institution, using IN DEX in a dose based on pharmacokinetic data as described earlier: A single dose of IN DEX 4 \(\mu\)g/kg (maximum, 100 \(\mu\)g) was delivered via a LMA MAD Nasal needle-free intranasal drug delivery system (Teleflex Medical, Research Triangle Park, NC).\(^20\) Patients who failed sedation were referred to a pediatric sedation provider or anesthesiologist for a rescheduled visit or for intravenous sedation on the same day. Patients received care consistent with hospital policy for moderate sedation, which included immediate availability of a designated physician from the start of sedation through the recovery period until the patient met hospital discharge criteria.

The present study was designed as a retrospective comparison of 2 patient cohorts receiving either IN DEX or oral chloral hydrate for sedation for ABR.

**METHODS**

The Baylor College of Medicine institutional review board approved this study. We identified patients who had received nurse-administered sedation for ABR in the audiology clinic in 2 epochs: (1) from October 30, 2009, to April 30, 2010, when chloral hydrate was used; and (2) from January 1, 2013, to December 3, 2013, when IN DEX was used. The policies for nurse-administered sedation at our institution did not change during the 2 epochs. This approach included evaluation by the nurse, discussion with a designated physician regarding potential problems, drug administration under the supervision of this physician, and monitoring in keeping with the guidelines from the American Academy of Pediatrics.\(^1\) In keeping with institutional policies, this physician was immediately available from the start of sedation through the recovery period. Patients were excluded from nurse-administered sedation and from the study if they were aged <6 months or >8 years, weighed <5 kg or >25 kg, or had a history of a previous failed sedation, a BMI >30, or a diagnosis of attention-deficit/hyperactive disorder. Charts were reviewed in reverse sequential order until data from a convenience sample of 200 children in the chloral hydrate cohort were entered in the database. These patients (epoch 1) were originally enrolled to obtain data for power analysis calculation for a planned prospective randomized study. A sample of 100 was available for comparison in the IN DEX cohort (epoch 2). This smaller sample size was on account of the hospital reacquiring a supply of chloral hydrate and requesting a comparative analysis of the 2 groups before continuing the use of IN DEX for this indication.

Data collected in both groups included age, gender, weight, procedure, doses and time of administration of sedative drugs, time of the start and end of the ABR examination, examination status (completed, completed with interruptions, rescheduled, or canceled), adverse events (bradycardia, hypotension, hypoxia, or other), interventions required, time to awake, and time to discharge. Major complications were defined as aspiration, death, cardiac arrest, unplanned hospital admission or level-of-care increase, or emergency anesthesia consultation.\(^21\)
Cardiorespiratory adverse events were defined in keeping with consensus-based recommendations for standardized terminology in reporting adverse events. This approach included the criterion that minor events be defined as only those that require intervention or a change in disposition.

Data were summarized by using descriptive statistics of number of patients; percentage with 95% confidence intervals (CIs) for categorical data; and mean, median, and SDs for continuous data. Group data were examined for normality by using the Shapiro-Wilk test. Student’s t tests were used for comparisons of continuous data that were normally distributed and by nonparametric Mann-Whitney U tests for data not normally distributed. For categorical data, we used chi-squared tests or Fisher’s exact test. The primary outcome was the ability to complete the ABR examination with a single sedative dose. P values <.05 were considered statistically significant.

RESULTS

Demographic characteristics are presented in Table 1 for both groups. There were no significant group differences in gender or age. The primary outcome of the ability to complete the examination with a single dose of medication and the secondary outcomes of time from administration of the first sedative dose to start of the ABR examination, time for the child to be awake, time to discharge, and the ability to complete the examination are presented in Table 2. The ability to complete the examination with a single dose of medication was superior in the IN DEX cohort (P = .002).

In this cohort (IN DEX), patients achieved a level of sedation that allowed the examination to be started sooner (P < .001), and the time from administration of sedation to the child being awake was shorter (P = .045). However, there was no significant difference in the time to discharge compared with the chloral hydrate cohort.

There were no major events in either cohort. However, there were 12 (6%) minor events requiring intervention in the chloral hydrate cohort and none in the IN DEX cohort (Fisher’s exact test, P = .01). All the events in the chloral hydrate cohort were transient oxygen desaturations responsive to oxygen administration. There were no hemodynamic changes that met our definitions for bradycardia or hypotension in either cohort.

DISCUSSION

This study has shown that sedation with IN DEX at a dose of 4 μg/kg was effective for ABR examinations. However, the ability to begin the examination sooner and complete the examination with a single dose suggests IN DEX may be a superior alternative to oral chloral hydrate. An additional benefit is the lower incidence of procedural hypoxemia requiring supplemental oxygen in the IN DEX group. Although the outcomes of this study may be related to the medication itself, there are several other potential explanations.

The first is the route of administration. Oral chloral hydrate is generally administered with an oral syringe and requires a semi-cooperative child. Despite the best attempts, some children may not receive the entire dose because they “spit it out” or some of the medication is lost during attempts to get the child to swallow the medication. Conversely, intranasal administration with a mucosal atomizing device is a much more reliable way to administer medications. Thus, more reliable drug delivery could account for some of the differences in this study, especially the improved success with a single dose in the IN DEX cohort.

A second explanation involves the absorption of medications delivered intranasally. The clinical effects of medications delivered nasally are believed to be a consequence of drugs traversing the nasal mucosa and entering the bloodstream where they avoid first-pass metabolism in the liver. This mechanism is an obvious advantage of IN DEX. However, it has also been demonstrated that there is a nose–brain pathway in which drugs can enter the central nervous system directly across the nasal mucosa or via a transport mechanism across the olfactory nerves.

All of these mechanisms would favor IN DEX over orally administered medications and may account for the shortened onset time for satisfactory sedation to permit the start of the ABR examination.

There are few published data on the use and safety profile of high-dose IN DEX. We selected the dosing protocol for this study based on published reports regarding the bioavailability of dexmedetomidine delivered across mucosal membranes and on dose-related reports of the safety of high-dose intravenous dexmedetomidine. Given a reported bioavailability between 35% and 93%, we would expect a single IN DEX dose of 4 μg/kg to be equivalent to intravenous dosing between 1.4 and 3.73 μg/kg, with a peak effect seen at 38 minutes. This outcome would be well within the reported safe range when using intravenous dexmedetomidine as a sole agent for MRI examinations in children.

Lower doses of 2.5 and 3 μg/kg of IN DEX have been used to provide satisfactory conditions for CT scans and transthoracic echocardiograms, respectively.

An unexpected difference between the 2 cohorts was noted in the need for supplemental oxygen. In the chloral hydrate cohort, supplemental oxygen was administered to 12 (6%) of 200 patients (95% confidence interval [CI], 7.5–16.5). This finding is consistent with the reported incidence of supplemental oxygen administration from the much larger Pediatric Sedation Research Consortium. However, none of the 100 patients (95% CI, 0–3.7) in the IN DEX group required supplemental oxygen. This finding was not significantly different from the incidence of 1.6% (95% CI, 0–3.6) noted in the study by
Mekitarian et al. in which a lower dose of IN DEX was given for CT imaging. The results from the present study may be due to factors intrinsic to the medications, reflect a difference in care between the original cohorts of chloral hydrate–treated patients versus the subsequent IN DEX–treated patients, or just be a consequence of other differences that can affect airway patency during sedation in the 2 samples. Obesity and obstructive sleep apnea are factors known to be associated with increased hypoxemia. Because data on the heights of all subjects were not available, we could not calculate their BMI. However, obesity is a relative contraindication for nurse-administered sedation in our institution, and this policy was not changed between the 2 epochs. It is of interest that children in the IN DEX group had significantly higher weights although the ages were similar. The incidence of hypoxemia was lower than in the chloral hydrate group, however.

Bradycardia, hypertension, and hypotension have been reported with intravenous dexmedetomidine sedation. Even though these effects are common, they generally resolve and do not require intervention. The original studies that examined high-dose intravenous dexmedetomidine for MRI scans noted approximately 16% of children with a heart rate 20% below the age-specific normal values, and a few children had heart rates <60 beats/min. In subsequent studies of IN DEX for CT imaging, Mekitarian et al. noted a 15% incidence of decrease in heart rate 20% below baseline. However, baseline heart rate and blood pressures in children undergoing procedures are probably higher than sleeping values as a result of anxiety. In addition, these minor alterations in heart rate and blood pressure associated with dexmedetomidine sedation are not of clinical significance, as they do not warrant interventions. We defined bradycardia as a heart rate <60 beats/min, which is in keeping with the definitions of the American Heart Association guidelines for interventions in the Pediatric Advanced Life Support Provider manual. Consistent with the consensus-based recommendation for standardized terminology and reporting adverse events during procedural sedation and analgesia, we only considered bradycardia an adverse event if it required intervention. Our definition of hypotension was also based on the same criteria as in the Pediatric Advanced Life Support manual and the aforementioned consensus-based recommendations.

No patient in either cohort met our criteria for bradycardia or hypotension as an adverse event. This finding differs from reports of patients receiving high-dose intravenous dexmedetomidine that used decreases from baseline values as the criteria for cardiovascular changes. However, it is consistent with the report by Mekitarian et al. that noted 1 of 63 administrations of IN DEX was associated with a 20% reduction in mean arterial blood pressure. The causes for the difference between the reported incidence of hypotension between intravenous and intranasal administration is unclear but may reflect differences in the definition of hypotension. Another likely explanation is the relatively slower absorption of intranasal medications with subsequently diminished physiologic alterations.

A major limitation of the present study was its retrospective design, which only reflects data that were documented and collected from the nursing sedation record. Thus, it is possible that the overall number of events was underreported. It is also important to note that severe cardiorespiratory adverse events that require interventions are rare in the setting of an organized sedation program. Thus, it is difficult to make any definitive conclusions regarding the overall safety of either medication based on this study alone because it was not adequately powered to detect differences in the low incidence of adverse effects. Much larger studies may be required to determine these adverse effect profiles.

A second limitation was the temporal gap between the 2 groups of patients. Small differences in efficiency or patient selection may have made considerable differences in the outcomes described in our study. However, this study does suggest IN DEX is an effective medication for sedation in ABR examinations. A randomized controlled study will be required before any definitive conclusions can be drawn regarding the superiority of this technique over the previous standard chloral hydrate regimen.

A third limitation of the study was the method of data collection. We only collected data on patients who were enrolled in the study and did not collect data on the reasons patients were excluded from receiving nurse-administered sedation. Because the same exclusion criteria were applied to both patient cohorts, the 2 patient cohorts should be similar at baseline.

It is important to note that there are many different models for sedation delivery in children. Although there are clear guidelines

**TABLE 2 Primary and Secondary Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Oral Chloral Hydrate (n = 200)</th>
<th>IN DEX (n = 100)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to complete ABR examination with 1 sedative dose</td>
<td>157 (78.5)</td>
<td>91 (91)</td>
<td>.002</td>
</tr>
<tr>
<td>Ability to complete ABR examination during this hospital visit</td>
<td>181 (90.5)</td>
<td>91 (91)</td>
<td>.95</td>
</tr>
<tr>
<td>Time from first sedative dose to ABR procedure start, min</td>
<td>31 ± 19</td>
<td>24 ± 11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time from first sedative dose to awake, min</td>
<td>112 ± 51</td>
<td>105 ± 27</td>
<td>.045</td>
</tr>
<tr>
<td>Time from first sedative dose to discharge, min</td>
<td>135 ± 71</td>
<td>127 ± 24</td>
<td>.15</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>12 (6)</td>
<td>0</td>
<td>.01</td>
</tr>
</tbody>
</table>

Data are presented as number (%) or mean ± SD.
REFERENCES


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