Is intranasal dexmedetomidine superior to oral chloral hydrate for procedural sedation in children: A systematic review

ABSTRACT

Background: This systematic review was undertaken to compare the benefits of intranasal dexmedetomidine (IND) versus oral chloral hydrate (OCH) in the pediatric age group undergoing procedural sedation analgesia (PSA). Randomized clinical trials (RCT) of the various studies done over the years were taken up and analyzed. Since IND has the additional advantages of a faster onset of action, greater success with a single bolus dose, and enhanced recovery, this systematic review was conducted to prove the superiority of IND over OCH in pediatric PSA. Objective: To compare the efficacy of IND versus OCH for PSA in pediatric patients. Search Strategy: We searched the electronic databases from August 2012 to September 2019 without language restrictions. Design and Selection Criteria: A review of 10 RCTs on the use of IND and OCH for PSA in the pediatric age group for a variety of diagnostic procedures was done and the superiority of IND as per the sedation time and adverse effects were analyzed. Results: Out of the RCTs considered, six trials were a direct comparison between OCH and IND which showed that IND had a faster onset of action, improved recovery characteristics with better return to baseline physical activity on the same day of the procedure. When compared to OCH, IND showed no evidence of second-dose requirement and no record of postoperative nausea and vomiting (PONV). Conclusion: This systematic review revealed that IND is superior to OCH for PSA in the pediatric age group and proved to be safe and effective with better recovery characteristics.

Key words: Procedural sedation; Intranasal dexmedetomidine; Oral chloral hydrate

Introduction

The main goals of pediatric PSA vary according to the specific procedure, but generally encompass relief of anxiety, pain control, and control of excessive movement. This assists the physician in carrying out the procedure smoothly without any chances for errors. The American Academy of Pediatrics (AAP) defines the goals of PSA in the pediatric patient as follows: to guard the patient’s safety and welfare; to minimize physical discomfort and pain; to control anxiety, minimize psychological trauma, and maximize the potential for amnesia; to control behavior and/or movement to allow for the safe completion of the procedure; and to return the patient to a state in which there is safe discharge from medical supervision, as determined by the recognized criteria.

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Dexmedetomidine is a highly selective alpha-2 adrenergic agonist with sedative, anxiolytic, and analgesic properties. Sedation with dexmedetomidine is reported to be associated with minimal respiratory depression and acceptable cardiovascular effects, such as hypertension, hypotension, and bradycardia.\(^\text{[5,12]}\) Since in the pediatric age group, it is difficult to achieve intravenous access, hence, the intranasal route is opted as it is easily accepted by the subject and can be easily administered as well.

Many methods of sedation through various routes have been tried and have shown some limitations. In this study, the superiority of IND is emphasized to be an easier option with a better outcome compared to OCH.

**Methods**

We used a systematic review to identify the RCTs that compared the efficacy and safety of IND with OCH in pediatric PSA. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. Ethical approval was not necessary because this was a review of the previously published RCTs.

**Literature search**

Reviewers searched the PubMed, Google Scholar, and Cochrane library databases over a period of the past 5 years from August 2012 to September 2019. No limitation was imposed. The reference lists of identified articles were searched for relevant studies and manually scanned to include additional eligible studies.

The inclusion criteria included (a) studies done on children aged 5 months to 6 years undergoing a diagnostic procedure requiring sedation, (b) randomized control trials, (c) studies which included the use of IND and OCH as an adjuvant in PSA for pediatrics, (d) studies with full text available. Studies performed involving other sedative techniques were excluded from this systematic review.

**Data extraction and outcomes**

The data extraction was independently performed by the reviewers and the following items of information were extracted: the name of the first author, year of publication, type of examination, sample size, intervention in the IND and OCH groups, the onset of action, the success rate of sedation, recovery time, and adverse effects. The primary outcome was the success rate of sedation; the secondary outcomes were the onset time and adverse effects.

**Results**

Ten RCTs were considered out of which four studies assessed the efficacy of OCH in comparison to the other sedatives [Table 1], whereas the other six studies showed a direct comparison of IND to OCH in pediatric PSA [Table 2].

Among the six studies comparing IND to OCH, IND showed better acceptance among children compared to OCH in terms of the route of administration.\(^\text{[11]}\) With OCH, there was an increased chance of failure and the need for a second dose, whereas in the IND group with 2 mcg/kg b.w. dose, there was no need for a supplemental dose and sedation was achieved with a single dose. Intranasal was found to have a faster onset of time and improved recovery characteristics with the return of physical activity on the same day as per the study conducted in 2016 by Reynold J et al.\(^\text{[8]}\) where IND was compared with OCH for sedation for auditory brain response (ABR) testing in children aged 20–30 months. It could also be used as rescue sedation in case of failure of OCH as per the study carried out by Gan X et al.\(^\text{[9]}\) where 60 subjects aged 5–36 months undergoing noninvasive ophthalmic examination were administered IND as a successive dose following OCH failure. PONV was more evident in the subjects who received OCH versus IND as per a trial conducted by Yuen et al.\(^\text{[11]}\) in 2017, where successful sedation was obtained with IND for conducting a computerized tomography (CT) scan in children aged 7.5–70 months.

**Discussion**

According to the present systematic review, IND was found to be more effective and easily accepted as a procedural sedative in children. It seems to have a faster onset, effective single-dose action, and better tolerance with reduced incidence of PONV when compared to OCH.

OCH was the most widely used method of sedation in the pediatric population. Hence, the trials performed in 2012 by Kil HK et al.\(^\text{[3]}\) with OCH as the sedative for a day-case pediatric procedure concluded that there was decreasing preoperative anxiety with OCH which improved induction compliance and reduced postoperative pain intensity without delaying recovery.\(^\text{[3]}\)

In 2012, commercially available chloral hydrate products were discontinued and taken off the market. However, some ambulatory and hospital pharmacies are compounding an oral suspension of chloral hydrate for pediatric sedation in both inpatient and outpatient settings. Compounded drugs are presently not approved by the US Food and Drug
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Administration (FDA), which means the FDA does not verify the safety or effectiveness of the compounded drugs. Other reasons for its discontinuation were that chloral hydrate resulted in prolonged sedation or re-sedation with effects lasting longer than 24 h in children of all ages, no specific agent available for reversal, large doses, or overdoses had been reported to cause ventricular dysrhythmias and severe hypotension in the pediatric group. Hence, chloral hydrate was disapproved as a pediatric sedative by the FDA and European Medicines Agency (EMA).

Other trials conducted for OCH showed that it had a higher sedation success rate, shorter time to achieve sedation, shorter length of stay, longer sedation duration with faster recovery and better satisfaction. In 2016, IND was introduced as a sedative in comparison to OCH. Gan X et al. conducted a trial in 2016 where IND was used as rescue sedation for OCH failure. This was among the first to report that IND can be administered for rescue sedation in children undergoing noninvasive ophthalmic examination after OCH failure, without accompanying clinically significant complications, and that the 2 mcg/kg b.w. dose was more effective than the 1 mcg/kg b.w. dose, as measured using the rate of successfully completed ophthalmic examinations.

Reynolds J et al. in 2016 conducted a double-blind, double-dummy study on children undergoing ABR testing where the children received IND 3 mcg/kg b.w. plus oral placebo or OCH 50 mg/kg b.w. plus intranasal saline placebo. It was concluded that IND was an acceptable method of sedation for ABR testing in children. Additionally, it shows that IND 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.

Miller J et al. conducted a randomized, prospective study of 150 children under the age of 3 years with known or suspected congenital heart disease scheduled for transthoracic echocardiography with sedation as follows: Group OCH received 70 mg/kg b.w., group IND2 received 2 mcg/kg b.w. and group IND3 received 3 mcg/kg b.w. It was concluded that a second sedative dose (rescue) for failed single-dose sedation was required in 4% of the patients after OCH, none of the patients after IND 2, and 4% of the patients after IND3 required any rescue dose of IND.

A trial by Yuen et al. showed that successful sedation of children before CT studies was similar after OCH at 50 mg/kg b.w. or IND at a dose of 3 mcg/kg b.w. and IND was associated with better behavior and fewer gastrointestinal side effects.

The limitation of the present study was the inclusion of only 6 RCTs, which might be a relatively small sample size to assess the difference in efficacy and safety between IND and OCH. However, further larger trials are required to assess the clinical efficacy of IND.

In conclusion, IND is superior to OCH for PSA in the pediatric age group and proves to be safe and effective with fewer side effects and with better recovery characteristics.

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Conflicts of interest
There are no conflicts of interest.

Table 1: Comparison of the efficacy of OCH vs. other sedatives

| Characteristics                                         | Author                     | Study | Number of Participants | Year |
|---------------------------------------------------------|----------------------------|-------|------------------------|------|
| ↓ Anxiety and postoperative pain with OCH              | Kil HK et al.              | RCT   | 100, aged 12-60 months | 2012 |
| Single-dose efficacy of OCH vs. midazolam              | Hijazi et al.              | RCT   | 286, aged 12-144 months| 2014 |
| Early onset, faster recovery of OCH vs. midazolam      | Stephen et al.             | RCT   | 82, aged 12-72 months  | 2015 |
| OCH and phenobarbital equal efficacy                   | Ganigara et al.            | RCT   | 3851, median age 8 months| 2019 |

Table 2: Study characteristics between IND and OCH

| Characteristics                                         | Author                     | Study | Number of Participants | Year |
|---------------------------------------------------------|----------------------------|-------|------------------------|------|
| Faster onset and recovery with IND                       | Reynolds J et al.          | RCT   | 44, aged 20-30 months  | 2016 |
| Success of single dose of IND (2 mcg/kg b.w.)           | Gan X et al.               | RCT   | 60, aged 5-36 months  | 2016 |
| IND used as a rescue sedation                           | Miller J et al.            | RCT   | 150, aged 3-34 months | 2015 |
| PONV in OCH group                                       | Yuen V et al.              | RCT   | 107, aged 7.5-70 months| 2017 |
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