Evaluation of Intranasal Dexmedetomidine as a Procedural Sedative for Ophthalmic Examination of Children With Glaucoma

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Precis: This study evaluated 2 doses of intranasal dexmedetomidine (IND) (3.0 and 3.5 µg/kg) as a procedural sedative for postoperative examination of children with glaucoma. A dose of 3.5 µg/kg was more efficacious and obviated the need for repeated general anesthesia.

Purpose: This study was carried out to determine the safety and effective dose of IND as a procedural sedative for postoperative follow-up examinations after glaucoma surgery in children in place of repeated examination under anesthesia.

Materials and Methods: In this prospective randomized double-blinded interventional study, consecutive children aged 6 months to 6 years were randomized to receive 3.0 and 3.5 µg/kg IND using a mucosal atomizer device in the preoperative area of the operating room, under continuous monitoring of vital signs. Intranasal midazolam 0.25 mg/kg was used as a rescue agent in case of inadequate sedation, and general anesthesia was administered in case of persistent failure. All infants underwent a complete anterior and posterior segment evaluation including intraocular pressure and corneal diameter measurements.

Results: A total of 30 and 31 children aged 23.9 ± 15.0 and 19.2 ± 10.1 months, respectively, received 3.0 and 3.5 µg/kg IND. Adequate sedation was possible in 18 of 30 (60%) children receiving 3.0 µg/kg IND at 3.5 µg/kg and 24 of 31 (77.4%) receiving 3.5 µg/kg IND alone (P = 0.17). In combination with midazolam, successful sedations were 86.6% versus 100%, respectively (P = 0.052). One patient in the 3.5 µg/kg group had ventricular arrhythmia, reversed with dextrose-saline infusion and injection glycopyrrolate.

Conclusions: IND appears to be a safe and effective procedural sedative for postoperative follow-up examinations of pediatric glaucoma patients at doses of 3 and 3.5 µg/kg. The dose of 3.5 µg/kg was successful in more children.

Key Words: glaucoma, anesthesia, sedation, examination, dexmedetomidine, chloral hydrate

C}hildhood glaucoma is a heterogenous group of diseases, which share the common pathway of elevated intraocular pressure (IOP)-related progressive damage to the optic nerve. It is responsible for a significant percentage of blindness in children, from 1.2% in UK to 3% to 7% in India.1-3 Because the treatment of childhood glaucoma is primarily surgical, these children require long-term monitoring of their IOP, corneal diameter, optic disc status, etc., even after successful surgery, and may require repeated surgery. They need to be examined reliably under some form of sedation or general anesthesia (GA). Recent reports have cautioned against repeated anesthesia exposures in small children. Frequent exposure to anesthetic agents has been shown to adversely affect cognition, memory, and behavior among exposed infants.4-8 GA also requires additional resources and is an additional financial burden for the parents of these children. It would be desirable to have a safe and effective sedating agent that would allow examination of children without the use of GA.

An ideal sedating agent should be efficacious, safe, painless, easy to administer, reversible, and provide consistent sedation with rapid onset and offset of action, and with minimal or no side effects. Several drugs have been used for years in clinical practice for the sedation of children.9,10 Chloral hydrate is one of the oldest, safe, and the best-studied sedative-hypnotic and had the advantage of ease of administration and a high success rate. However, it is now less preferred owing to its pungent odor, with a bitter taste, and frequent, unpleasant side effects of nausea, vomiting, and diarrhea.

Dexmedetomidine is a highly selective α2 adrenoceptor agonist that has emerged as a newer sedative with analgesic and sympatholytic properties.11 Despite the lack of pediatric labeling, its use in the pediatric population has been described for almost a decade in the literature. Its favorable physiological effects, combined with a limited adverse-effect profile, have facilitated its introduction into the perioperative setting.12 It is widely used as a safe and well-tolerated sedative agent for computed tomography/magnetic resonance imaging (MRI) in children, with reported doses ranging from 2 to 4 µg/kg.13-16 In ophthalmic practice, there are isolated reports of intravenous (IV) Dexmedetomidine as a sedative agent for the examination of children with congenital cataract, and cataract surgery in adults under topical anesthesia.17,18 However, the IV route is invasive and may not be acceptable for children. Intranasal dexmedetomidine (IND) has better acceptability in children as it avoids IV cannulation and does not cause nasal irritation or burning.18 There is very little literature on the efficacy, the optimum dose required, and the appropriate protocol to be followed for IND sedation for
ophthalmic evaluations of small children. A study by Cao et al \(10\) on examination of congenital cataract patients with IND \(2 \mu g/kg\) versus oral chloral hydrate reported a better success rate (85.9% vs. 64.3%, \(P=0.003\)) with IND. Chen et al \(20\) reported a higher success rate with IND \(3 \mu g/kg\) than \(2 \mu g/kg\) for pediatric ocular examinations. The evaluation of children with glaucoma requires more corneal touch procedures, including measurement of IOP, complete evaluation of anterior and posterior segments, and corneal diameter measurement.

There is no study on the use of IND for the evaluation of pediatric glaucoma patients. We carried out this study to evaluate the safety and efficacy of IND (3 vs. 3.5 \(\mu g/kg\)) for the examination of pediatric glaucoma patients who require frequent follow-up examinations until they are co-operative for examination on slit-lamp biomicroscopy.

**MATERIALS AND METHODS**

This randomized, prospective, double-blinded interventional study was carried out at the Advanced Eye Centre (AEC), Postgraduate Institute of Medical Education and Research, Chandigarh, India, with patients recruitment from January, 2019 to April, 2019. The study obtained Institute Ethics Clearance (vide INT/IEC/2018/2106) and was registered under the Clinical Trials Registry of India (vide no. CTRI/2019/01/017274). Informed consent was obtained from the parents of all children for participation in the study and to use photographs for academic purpose only. The study adhered to the tenets of the Declaration of Helsinki.

Children who underwent glaucoma surgery were scheduled for postoperative follow-up examinations under sedation with IND. Complete history, including relevant medical and ocular history, was obtained from the parents of the patients, and an anesthesiologist performed a detailed preanesthetic clinical examination.

**Inclusion Criteria**
- Age of 6 months and above to 6 years and below requiring surgery for pediatric glaucoma who were not co-operative for examination under slit-lamp or Goldmann applanation tonometry.
- American Society of Anaesthesiologists (ASA) physical status I/II.

**Exclusion Criteria**
- Children with cardiorespiratory distress, bradycardia, upper respiratory tract infection, liver disease, seizures, or an acute medical condition.

As there are no studies on the use of IND for the examination of children with glaucoma, a pilot study was carried out to determine an effective dose as glaucoma workup is different compared with cataract workup with more corneal touch procedures. The pilot study was carried out with doses of \(2, 2.5, 3,\) and \(3.5 \mu g/kg\) doses. Doses of \(2\) and \(2.5 \mu g/kg\) were the least effective. We evaluated the success rate and safety of IND doses of \(3.0\) and \(3.5 \mu g/kg\). Following simple randomization procedures (computerized random numbers), eligible patients were randomly assigned to 1 of 2 treatment groups: group 1 received \(3.0 \mu g/kg\) and group 2 received \(3.5 \mu g/kg\) IND. The ophthalmologists who examined the children and the parents were blinded to the dose of the drug.

**Primary Outcome Measure**

The primary outcome measure was the percentage of children having successful examination without requiring a rescue sedative agent up to 40 minutes after the administration of IND.

**Secondary Outcome Measures**

1. Mean time of onset of adequate sedation score.
2. Need for rescue drug.
3. Surgeon satisfaction score for completion of procedure.
4. Discharge time.
5. Adverse effects (bradycardia, nausea, vomiting, arrhythmia).
6. Parents’ satisfaction.

**IND Protocol**

The child was kept nil per oral as per standard guidelines of 8 hours for solids, 4 hours for breast milk, and 2 hours for clear fluid. Injection dexmedetomidine hydrochloride \((100 \mu g/mL;\) Neon Laboratories, Mumbai, India) was administered intranasally using a Magal Mucosal Atomizer Device (MAD) (Magal Healthcare Pvt Ltd, Bengaluru, India) (Fig. 1). The dose was calculated as either \(3.0\) or \(3.5 \mu g/kg\), depending on the group assigned by randomization. The requisite volume was filled in a \(1.0\) mL syringe. Half the dose was administered in each nostril.

Figure 2 depicts the workflow. Briefly, vital parameters including heart rate and oxygen saturation (SpO\(_2\)) were recorded before administering the drug, during the procedure, and continuously monitored and recorded at regular intervals of 10 minutes until the patient was fit for discharge. IND \((3\) or \(3.5 \mu g/kg\)) was administered using the MAD in a quiet, semi-dark environment of the recovery area of the operating room while being cradled by the mother/caregiver. The examiner was blinded to the dose of the drug used. The time of drug administration was noted. The Ramsay sedation score \(21\) was assessed at 10, 20, and 30 minutes after the dose administration (Table 1).

When adequate Ramsay sedative score was \(\geq 5\), the response to the glabellar stimulus was noted, followed by the response to topical Proparacaine. The time of onset of adequate sedation was recorded, and the desired ophthalmic examination was performed in the following sequence: IOP using a Perkins Applanation Tonometer and indirect

[FIGURE 1. Administration of intranasal dexmedetomidine using a mucosal atomization device with instillation of half the dose in each nostril. Figure 1 can be viewed in color online at www.glaucomajournal.com.]
ophthalmoscopy to examine the anterior and posterior segments of the eye and corneal diameter measurement using callipers. Children who were not co-operative for awake retinoscopy also underwent retinoscopy. The axial length measurement was performed using a USG B-scan (HiScan touch unit; Optikon, Roma, Italy).

If the Ramsay score was <5/6 at 40 minutes, a rescue drug (midazolam) was administered at a dose of 0.25 mg/kg intranasally at 40 minutes, and the Ramsay sedation score was reassessed at 5, 10, and 20 minutes till 30 minutes after the administration of the rescue drug. If the Ramsay score remained <5, the procedure was considered a failure, and the examination was completed under GA.

All children were continuously monitored, and any intra-procedural complications such as: bradycardia, arrhythmia, desaturation, or reduction in respiratory rate were recorded. Once the examination was complete, the sedation score, heart rate, SpO2, and the Revised Alderte Score22 (Table 2) were calculated. Every child was monitored until 2 hours after the procedure for episodes of vomiting, diarrhea, or irritability. The patient was discharged once the Revised Alderte Score of 9 to 10 was reached. The time of recovery was noted.

The ophthalmologist satisfaction score was rated by a Likert23 scale between 1 and 5 as very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, and very dissatisfied. The parents’ satisfaction scoring was graded as good/fair/poor.

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### TABLE 1. Ramsay Sedation Scale

| State of Wakefulness | Ramsay Score | Patient Behavior |
|----------------------|--------------|-----------------|
| Awake                | 1            | Anxious, agitated, restless |
|                      | 2            | Cooperative, oriented, tranquil |
|                      | 3            | Responsive to commands only |
| Asleep               | 4            | Brisk response to light glabellar tap or loud auditory stimulus |
|                      | 5            | Sluggish response to light glabellar tap or loud auditory stimulus |
|                      | 6            | No response to light glabellar tap or loud auditory stimulus |

![FIGURE 2. Workflow of examination under dexmedetomidine. IOP indicates intraocular pressure; SpO2, oxygen saturation. Figure 2 can be viewed in color online at www.glaucomajournal.com.](image-url)
Statistical Analysis

In the absence of published data for ophthalmic evaluation of children with glaucoma, the sample size was calculated on the basis of the results of a pilot study carried out before the present study. With expected differences between groups from 44.4% to 88.8% and using the Chi-square test of proportions and a study power of 85%, a minimum sample size of 30 patients in each group was calculated.

Demographic data were studied using descriptive statistics. The normality of the data was checked using the Kolmogorov-Smirnov test. For qualitative data, the \( \chi^2 \) test/Fisher exact test was used. For quantitative data, Student t test and Wilcoxon-signed rank test were used for normally and non-normally distributed quantitative data, respectively. A P-value of <0.05 was considered significant.

RESULTS

In our pilot study carried out before the present study, 25 patients, divided into 3 groups, received IND at a dose of 2.5, 3, and 3.5 µg/kg. Of 7 patients in group 1 who received 2.5 µg/kg, 2 had successful sedation (28.57%), 5 patients (71.42%) required additional intranasal midazolam, and 2 patients required GA because of inadequate sedation. There were 9 patients each in groups 2 and 3 who received 3.0 and 3.5 µg/kg, respectively. In group 2, successful sedation was achieved in 4/9 (44.44%), 5 patients (55.55%) required midazolam, and 1 patient required GA for completion of the procedure. In group 3, 8/9 (88.88%) patients achieved successful sedation without the need for rescue drugs (\( P = 0.13 \)). All patients maintained hemodynamic status and showed no side effects. The present study was carried out with doses of 3 and 3.5 µg/kg.

During the study period, 85 patients were assessed for eligibility. Twenty-four patients were excluded as 20 patients did not fulfill the inclusion criteria, 3 required surgery for the procedure being performed in their presence, without the need for intravenous injection or administration of GA.

There was no change in the SpO2 levels in both groups. Heart rate did decrease in both the groups, with >15% decrease from baseline seen in 9/30 (30%) in the 3 µg group and 12/31 (38.7%) in the 3.5 µg group (\( P = 0.47 \)), but this was not clinically significant and none of the patients required any intervention. Details of the parameters during the procedure in both groups are shown in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/IJG/A425).

In the 30 children who received the 3.0 µg dose, the procedure could be completed in 18 (60%) children with IND alone, and in 26 (86.6%) with injection midazolam (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/IJG/A425). With the 3.5 µg dose, IND alone was successful in 24 of 31 children (77.5%) and in all when combined with injection midazolam.

With dexmedetomidine alone, inadequate sedation score (Ramsay sedation score <5) was seen in 7 patients in group 1 compared with 1 patient in group 2 (\( P = 0.02 \)). However, despite an apparently adequate Ramsay score, examination was not possible in 12 and 7 patients, respectively. Midazolam was required as the rescue drug in 12 of 30 patients (40%) in group 1 and 7 of 31 patients (22.5%) of those in group 2 (\( P = 0.17 \)).

The procedure satisfaction score by the examiner was similar in both groups. Parents’ satisfaction scores were similar in both the groups (30/31 scored “good” with 3.5 µg/kg, and 25/26 (where the procedure could be completed under sedation) scored good with 3.0 µg/kg dose, \( P = 0.89 \)). Most parents felt a sense of security of the procedure being performed in their presence, without the need for intravenous injection or administration of GA.

Activity

| Score 2 | Score 1 | Score 0 |
|---------|---------|---------|
| Respiration | Able to take deep breath and cough | Dyspnea/shallow breathing | Apnea |
| O2 saturation | Maintains >92% on room air | Needs O2 inhalation to maintain O2 saturation >90% | Saturation <90% even with supplemental O2 |
| Consciousness | Fully awake | Arousable on calling | Not responding |
| Circulation | Blood pressure ± 20 mm Hg preoperative | Blood pressure ± 20-50 mm Hg preoperative | BP ± 50 mm Hg preoperative |
| Activity | Ability to move 4 extremities voluntarily or on command | Ability to move 2 extremities voluntarily or on command | Ability to move 0 extremities voluntarily or on command |

In the 3 children who received the 3.0 µg dose, the procedure could be completed in 18 (60%) children with IND alone, and in 26 (86.6%) with injection midazolam (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/IJG/A425). With the 3.5 µg dose, IND alone was successful in 24 of 31 children (77.5%) and in all when combined with injection midazolam.

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### TABLE 2. Revised Alderte Score

| Score 2 | Score 1 | Score 0 |
|---------|---------|---------|
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### TABLE 3. Baseline Characteristics in Both Groups

|                | Intranasal Dexmedetomidine (3 µg/kg) (n = 30) | Intranasal Dexmedetomidine (3.5 µg/kg) (n = 31) | P     |
|----------------|--------------------------------------------|-----------------------------------------------|-------|
| Males:females  | 19:11                                      | 21:10                                         | 0.7   |
| Age [mean ± SD (range)] (mo) | 23.86 ± 15.1 (6-66) | 19.19 ± 10.13 (9-60) | 0.16  |
| Sedation score [mean ± SD (range)] | 1.96 ± 0.72 (1-3) | 1.87 ± 0.56 (1-3) | 0.58  |
| Heart rate [mean ± SD (range)] | 110.63 ± 20.91 (67-150) | 119.5 ± 21.91 (64-154) | 0.11  |
| SpO2 [mean ± SD (range)] | 99.3 ± 0.99 (97-100) | 98.96 ± 1.73 (92-100) | 0.35  |

SpO2 indicates oxygen saturation.
There were no serious adverse effects, except an episode of arrhythmias in 1 patient of each group. One child in group 1 developed irregular sinus rhythm briefly (for 15 s), which spontaneously resolved. One child in group 2 had an episode of ventricular arrhythmia, which was diagnosed to be due to prolonged hypoglycemia and hypotension as the veins were collapsed and the lips were dry. It was reversed by IV dextrose-saline infusion and injection glycopyrrolate.

The discharge time was similar in both groups. With dexmedetomidine alone, it was 111.76 ± 25.77 (79 to 155) and 119.76 ± 26.6 (81 to 194) minutes in the 3 and 3.5 μg/kg groups, respectively, P = 0.33. In patients who required the rescue drug, the discharge time was 30 to 40 minutes later [146.12 ± 23.4 (120 to 193) and 164.66 ± 22.76 (120 to 184) min in 3 and 3.5 μg/kg groups, respectively, P = 0.14]. None of the patients had nausea, vomiting, or any other adverse complaints.

**DISCUSSION**

With advances in neonatal care and ophthalmic surgery, an increasing number of infants are undergoing major ocular surgery for retinopathy of prematurity, congenital cataract, and congenital glaucoma. These infants are in the amniogenic age, and frequent examinations are required until they can co-operate for slit-lamp examination in the office. Although dexmedetomidine infusion is widely used for premedication in children, IND as a sedative agent for pediatric ophthalmic examination has been less extensively studied. It appears to be a useful agent for adequate ophthalmic examination without subjecting these infants to repeated GA. We found no reports in the literature for the use of IND for examining infants with congenital glaucoma. This study evaluated the feasibility and success rate of IND for the examination of children suffering from glaucoma. Chen et al. reported a higher sedation success rate with 3 μg/kg IND than 2 μg/kg IND for pediatric ocular examination in children with congenital cataract, without any significant side effects. In a comparison between oral chloral hydrate and IND, Cao et al. reported more successful sedation along with better quality of ocular examinations with IND than chloral hydrate for younger children with congenital cataract.

In our study, we chose the higher doses of 3 and 3.5 μg/kg because we found meager success rates with 2.5 μg/kg doses in our pilot study. Although 3.0 μg/kg had been reported to be efficacious for infants with congenital cataracts, we found that both 3 and 3.5 μg/kg doses are effective for the follow-up examinations of congenital glaucoma, with no significant effects on the heart rate or SpO2. However, the 3.5 μg/kg group had marginally better success rates, with less need for midazolam and inhalational anesthesia. This may be related to more tactile procedures required during the glaucoma examination, including IOP measurement using an application tonometer after instillation of topical anesthetic drops and staining with a fluorescein strip and measurement of the corneal diameter using a caliper, besides the complete evaluation of anterior and posterior segments of the eye.

IND is effective with adequate bioavailability for sedation. Olgun and Ali reported successful sedation in 94% of the cases, with 4 μg/kg IND for MRI in children without any side effects. A recent meta-analysis showed that dexmedetomidine provides better success rates of procedural sedation and fewer episodes of desaturation than chloral hydrate, pentobarbital, and midazolam.

Dexmedetomidine is a safer agent even in cardiac patients, but its effect on sinoatrial and atrioventricular nodes can have effects on cardiac contractility. There are isolated reports of long QT syndrome unmasked by dexmedetomidine in a child in an intensive care setting. The present study found 1 case of arrhythmia in each group. One patient had sinus arrhythmia with spontaneous resolution in the 3.0 μg group, and one had ventricular arrhythmia in the 3.5 μg group, which was most likely due to prolonged hypoglycemia and hypotension. It may be prudent to avoid prolonged fasting and monitor the electrocardiography (ECG) carefully in all these babies. Because the various studies carried out for MRI/computed tomography studies have not mentioned ECG monitoring, there is a possibility of underreporting of the side effects.

There have been concerns about the effect of dexmedetomidine on IOP. Most studies report a blunting of the increase in IOP induced by intubation, or a reverse Trendelenberg position during laparoscopic surgery in patients receiving IV dexmedetomidine. Lili et al. reported no effect on intraoperative hemodynamics and IOP in children undergoing vitreoretinal surgery with adjuvant injection dexmedetomidine 0.5 μg/kg. However, Nagy et al. reported a reduction in IOP until 15 minutes after the addition of 0.25 μg dexmedetomidine to the peri-bulbar block for phacoemulsification. Ghodki et al. reported a decrease in IOP in the nonoperated eye, after IV dexmedetomidine was used as premedication during cataract surgery. Cao et al. compared the IOP when using oral chloral hydrate and IND for the examination of congenital cataract patients and reported no difference in the 2 modalities. It is difficult to infer whether the intranasal route would have a similar effect on the IOP as the IV route, although the possibility must be kept in mind.

The effect of IND on the IOP must be taken in the context of the known reduction in IOP seen with commonly used inhalational agents such as sevoflurane during EUA, as is widely practiced. We still have to find an ideal anesthetic/sedative agent that would not affect the IOP measurement. There is no denying that infants undergoing glaucoma surgery require periodic measurements of the IOP to be sure of the efficacy of the procedure and disease control. Inhalational anesthetics used for EUA are known to affect the IOP as well. In a study evaluating the effects of sevoflurane and ketamine on IOP in children during EUA, sevoflurane anesthesia significantly reduced the IOP after induction, and the IOP measured after ketamine sedation was more likely to represent the awake IOP than that after sevoflurane anesthesia.

Against this backdrop, the advantages of sedation with IND appear to outweigh the reduced IOP that may be recorded. In infants, other surrogate factors such as corneal clarity, the increasing corneal diameter, axial length, and progressive myopia out of proportion to the average growth rate of the eyeball also hold great importance.

The strength of our study is that it is a prospective double-blinded study carried out with different doses of IND in an operation theater recovery room setting with continuous ECG monitoring throughout the procedure. The major limitation of our study is the relatively small sample size and the effect of IND on IOP measurement in infants with congenital glaucoma. Another limitation is that we did not compare our results with those of a subset of patients undergoing EUA using other gold-standard anesthetic agents. However, in the event of other anesthetic agents...
having been widely studied, we believed that it was important to share our results using only sedation and no inhalational anesthetic agent. Before and over different periods, the IOP measurement is not feasible with Perkinplanation tonometry unless the child achieves an adequate sedation score. In this study, we did not measure IOP several times during the procedure, but in the clinical setting, we also wished to complete the examination before the child awoke. Future studies could include an assessment of the effect of IND on IOP possibly using the iCare tonometer for IOP measurement before and at different intervals after IND as the IOP can be measured with iCare even in smaller children.

Procedural sedation for pediatric examination for uncooperative children remains a challenge. IND provides a comfortable, safe, and effective sedation modality for the ophthalmic examination of small children without exposing them to the risks of repeated GA.

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