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CLINICAL INVESTIGATION

# Dexmedetomidine improves surgical field in cochlear implant surgery: a randomized, double-blind, placebo-controlled trial

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## ABSTRACT

Objectives: Sympatholytic properties of dexmedetomidine have many advantages to use in general anesthesia especially in pediatric age group undergoing cochlear implant surgeries. This study is designed to compare the effects of bolus dose of dexmedetomidine followed by infusion with placebo in cochlear implant surgeries for quality of hypotensive anesthesia with hemodynamic stability and incidence of complications in pediatric age group particularly emergence delirium with sevoflurane.

Methodology: 60 pediatric patient of ASA grade I or II with congenital or acquired deafness of age ranging from 2 to 8 years scheduled for cochlear implant surgery were included in this study.

Group D were administered dexmedetomidine 0.5 µg/kg in 100 ml 0.9% NaCl over 10 min followed by infusion of dexmedetomidine at 0.5 µg/kghr$^{-1}$ and Group P was given placebo only i.e. 0.9% NaCl 100 ml over 10 min followed by infusion at 2 ml.hr$^{-1}$. Heart rate (HR) and mean arterial pressure (MAP) at different time interval, intraoperative fentanyl and propofol consumption, surgeons' satisfaction score and complications, particularly incidences of emergence delirium were recorded.

Statistical analysis: Mean with standard deviation of various parameters of both groups was compared using student's t test were analyzed.

Result: statistical significant lowering of MAP, HR, opioid consumption and rate of complications were lower in dexmedetomidine group compared to placebo group.

Conclusion: Intraoperative administration of dexmedetomidine provides better surgical field and subsequently higher surgeon's satisfaction score leading to reduced surgery time with better recovery profile.

Keywords: Dexmedetomidine; Cochlear implant; Pediatric patients; Dexmedetomidine

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## INTRODUCTION

Dexmedetomidine is an active isomer of medetomidine and an agonist at $\alpha_2$ –adrenoceptors that causes sedation without respiratory depression leading to its increasing use in critical care for sedation and in minor surgical procedures as a sole anesthetic agent.[1] It has many uses as adjuvant in anesthesia in adults though there are few studies to substantiate its role in pediatric age group. One review concludes that dexmedetomidine provides perioperative analgesia thus decreasing opioid

requirement, reduced pain scores and postoperative nausea and vomiting (PONV).[2,3] Dexmedetomidine is also used to decrease stress response to laryngoscopy, lowers intra ocular pressure and as an agent for controlled hypotension in FESS surgeries.[4,5] In a large number of studies dexmedetomidine has been used successfully to prevent emergence delirium and postoperative shivering in children.[6,7] A 2013 meta-analysis of various trials done proved that pharmacokinetics and dose effects of dexmedetomidine are similar in pediatric age group as seen in adults.[8]

Recently large numbers of cochlear implantations are done in pediatric age group due to better outcomes, as well as availability of newer anesthetic adjuvants and hemodynamic monitoring. The anesthesia management in cochlear implantation requires a balanced approach so as to provide a stable intraoperative hemodynamics and fewer postoperative complications like sedation, emergence delirium and postoperative pain.[9] Good results in this surgery are obtained by providing bloodless surgical field with controlled hypotension.[10]

This study was designed to compare the effects of adding a bolus dose of dexmedetomidine followed by infusion, with placebo for hypotensive anesthesia in pediatric age group undergoing cochlear implant surgery. Perioperatively, we compared the amount of fentanyl consumption and the incidence of emergence delirium and other complications.

## METHODOLOGY

60 pediatric patient of physical status ASA classes I or II (with hemoglobin 8- 10 gm%) with congenital deafness, ages 2 to 8 years, scheduled for cochlear implant surgery over a period of 1 year were included in this prospective, randomized, double blind study after taking due approval from the ethical committee of our institution.

Informed and explained consent about the method of anesthesia was taken from the parents, preoperative assessment was done and children were screened for any exclusion criteria. Children with cardiac anomalies, sinus bradycardia and atrioventricular block, QTc interval > 440 ms, severe milestone delay, seizure disorders, neuromuscular disorder, hepatic impairment and on drugs for any chronic ailment, were excluded from the study.

After keeping NPO for 6 hours patients were given 0.5 mg/kg oral midazolam preoperatively before taking to the induction room where patients were attached to electrocardiogram, non-invasive blood pressure and pulse oximetry with a multichannel monitor (Datex-Ohmeda, Cardiocap/5, GE healthcare, Helsinki, Finland). Separate intravenous lines were secured for giving maintenance fluid and test drug after induction with 4-8 % v/w of sevoflurane in 100% oxygen, fentanyl 3 µg/kg and intubation was facilitated with rocuronium 0.6 mg/kg. Anesthesia was maintained with oxygen and nitrous oxide mixture with sevoflurane concentration adjusted to keep mean arterial pressure (MAP) and heart rate (HR) within the range of 20% of baseline. Further doses of rocuronium were not given till fascial nerve was identified by surgeon after which rocuronium 0.1 mg/kg was given for muscle relaxation. Hypothermia was avoided by heated air blanket and warm RL at 10 ml/kg/hr as maintenance fluid. Just before completion of surgery paracetamol rectal suppository 20 mg/kg and IV ondansetron 0.1 mg/kg were given. Muscle relaxation was reversed with neostigmine/ glycopyrrolate and sevoflurane was stopped at completion of surgery with patient extubated in a deeper plane of anesthesia. In the post anesthesia care

Table 1: Objective pain score [11] for postoperative assessment of pain

| Parameter | | Score |
|---|---|---|
| Systolic blood pressure | < 20% of baseline | 0 |
| | 20-30 % of baseline | 1 |
| | 30% of baseline | 2 |
| Crying | Not crying | 0 |
| | Crying but responds to age-appropriate nurturing | 1 |
| | Does not respond to nurturing | 2 |
| Movements | No movement relaxed | 0 |
| | Restless ( moving constantly) | 1 |
| | Thrashing (moving wildly) | 2 |
| Agitation | Asleep or calm | 0 |
| | Can be comforted to lessen the agitation (mild) | 1 |
| | Cannot be comforted (hysterical) | 2 |
| Complain of pain | Asleep or states no pain | 0 |
| | Cannot localize | 1 |
| | Localizes pain | 2 |

Table 2: Pediatric Anesthesia Emergence Delirium (PAED scale) [12]

| Clinical status | Not at all | Just a little | Quite a bit | Very much | Extremely |
|---|---|---|---|---|---|
| The child makes eye contact with the care giver | 4 | 3 | 2 | 1 | 0 |
| The child's actions are purposeful | 4 | 3 | 2 | 1 | 0 |
| The child is aware of his/her surroundings | 4 | 3 | 2 | 1 | 0 |
| The child is restless | 0 | 1 | 2 | 3 | 4 |
| The child is inconsolable | 0 | 1 | 2 | 3 | 4 |

unit (PACU) children were monitored for any pain using objective pain scores (OPS) (Table 1), sedation or agitation using Pediatric Anesthesia Emergence Delirium (PAED) scoring system (Table 2).

Dexmedetomidine infusion was prepared by a nursing assistant (not involved in the study) in a concentration of 4 µg/ml in a 50 ml syringe and another nursing assistant who was not aware of the content of the syringe started the infusion with a syringe pump (SP102, Larsen and toubro Ltd). 60 children were randomly assigned equally into two groups- Group D and Group P using a computer generated randomization sequence for the study. Demographic profile of patient with regard to age, sex, weight and ASA grade were recorded. After intubation, Group D participants were administered dexmedetomidine (Dextomid, Neon Laboratories) 0.5 µg/kg diluted in 100 ml 0.9% NaCI over 10 min followed by infusion of dexmedetomidine at 0.5 µg/kg/hr. Group P was given normal saline as placebo 100 ml over 10 min followed by infusion at 2 ml hr. The surgeon assessing the quality of surgical field and the anesthetist recording the hemodynamic variables and other measurement of the participants were blinded to the study.

Glycopyrrolate at 10 µg/kg was given if heart rate fell below 60/min and IV mephenteramine 0.5 mg was given if MAP went below 50 mmHg or < 30% of baseline. Fentanyl 0.5 µg/kg and propofol 2 mg/kg both were given if HR and MAP rose above 30% of baseline. Infusion of test drug was stopped 15-20 min prior to the conclusion of surgery. IV fentanyl 0.25 µg/kg was given OPS > 4 and IV ondansetron 0.1 mg/kg were used for any episode of nausea and vomiting in PACU.

Baseline HR and MAP, immediately after intubation (before starting bolus of study drug), 5 min after starting of bolus dose and thereafter at different time interval till patients were discharged from PACU. Intraoperatively fentanyl consumption, total duration of surgery and surgeons satisfaction score based on surgical site bleeding every 15 min after start of surgery was recorded. In the PACU modified Aldrete score, OPS and PAED score immediately on arrival, 30, 60, 90 and 120 min after extubation were recorded. Any episodes of shivering, total amount of rescue analgesia, PONV, hypotension, bradycardia or any other complication were recorded.

Statistical analysis: All the data was expressed as arithmetic mean ± SD, ranges, numbers and percentages as appropriate at various time intervals. Statistical analysis was performed for 2 groups utilizing Statistical Program for Social Science Data version 23 (letter no SGRR/MC/PO/LiB/2015/-11164; License code e27995dcb17243a98de5). Comparisons between the hemodynamic variables, duration of surgery and fentanyl consumption were made between the two groups using student's *t*-test. Comparison of Aldrete score, OPS and PAED score were made with Mann-Whitney U test; Chi-square test was used to compare Surgeons Satisfaction Score based on bleeding at the surgical site. Fisher's exact test was used to compare any episode of complication like bradycardia, hypotension, shivering and PONV. To compare variables at different time intervals from baseline within the group, repeated measures ANOVA was used. Significant difference is considered when value of $p < 0.05$. The main measured variable was intraoperative Surgeons Satisfaction Score which should be 2 to 3 with SD close to 1.1, the sample size was determined to be 30 patients per group at an $\alpha$ error margin of 0.05, $\beta$ value of 0.95, and 10% dropout rate to be able to reject the null hypothesis.

## RESULTS

All the enrolled 6o patients completed the study. The demographic profile of two groups was similar in age, sex, weight, baseline HR and MAP ($p > 0.05$) (Table 3). With regards to HR statistical difference existed between group D and group P at all time intervals ($p < 0.05$) till the time of extubation (Figure 1) and in PACU. Significant fall in HR is seen in group D at 15,

20, 25, 30, 60, 75, 90 min after induction from baseline and 10, 30, 60 min after extubation. MAP was significantly lower in group D than in group P at 15, 20, 25, 30, 45, 60, 75, 90 and 105 min after induction from baseline and at 30 min after extubation (Figure 2). Consumption of fentanyl and propofol was significantly high in group P compared to group D (Table 3) while Surgeons Satisfaction Score and surgical field remained significantly better in Group D compared to Group P at 15, 30, 60, 75 min after start of surgery while OPS remained significantly low in Group D at 30 and 60 min after extubation while incidence of postoperative delirium was significantly more in Group P (Table 4). Incidence of postoperative complications were very low in dexmedetomidine group (Table 5).

Significant difference ($p < 0.05$) is observed after starting of test drug at MAP15, MAP20, MAP25, MAP30, MAP45, MAP60, MAP75, MAP90, MAP105 AND Postoperatively (PO) at PO30 using Student's t test. MAP BI = mean arterial pressure before induction, MAP AI = mean arterial pressure after induction.

## DISCUSSION

In many studies dexmedetomidine is given for sedative, amnestic, and analgesic properties in a bolus dose of < 0.5 µg/kg in pediatric patient to avoid bradycardia giving further infusion dose with titrated

Table 3: Comparison of demographic profile and baseline variables expressed as mean ± standard deviation.

| Variable | Group D (n=30) | Group P (n=30) | p value |
|---|---|---|---|
| Age (in years) | 3.18 ± 0.72 | 3.22 ± 0.86 | 0.55 |
| Sex (M:F) | 16:14 | 15:15 | 0.76 |
| Weight (in kg) | 12.96 ± 1.88 | 13.39 ± 1.68 | 0.95 |
| Peri-operative fentanyl consumption | 40.81 ± 7.34 | 58.12 ± 7.27 | 0.02 |
| Intraoperative propofol consumption | 24.68 ± 6.34 | 42.24 ± 6.22 | 0.01 |
| Baseline heart rate( / min) | 121.5 ± 3.38 | 120.94 ± 3.99 | 0.65 |
| Baseline Mean arterial pressure( in mm Hg) | 75.88 ± 2.87 | 76.44 ± 1.75 | 0.35 |
| Duration of surgery | 112 ± 0.27 | 130 ± 4.95 | 0.00 |

Group D, Dexmedetomidine group; Group P, placebo group. Data is expressed as Mean ± SD. P values calculated using Mann Whitany U test and $p < 0.05$ is shown in bold.

Table 4: Comparison of surgical score (SS), objective pain score (OPS), emergence agitation score (EAS) and Aldrete Score (AS) at various times interval.

| Parameter | Group D (n=30) | Group P (n=30) | p value |
|---|---|---|---|
| SS at 15 min | 1.25 ± 0.45 | 1.94 ± 0.25 | 0.00 |
| SS at 30 min | 1.62 ± 0.50 | 2.06 ± 0.57 | 0.02 |
| SS at 45 min | 1.72 ± 0.34 | 2.87 ± 0.34 | 0.30 |
| SS at 60 min | 2.10 ± 0.42 | 3.26 ± 0.44 | 0.01 |
| SS at 75 min | 1.31 ± 0.61 | 2.87 ± 0.50 | 0.03 |
| SS at 90 min | 1.84 ± 0.57 | 1.87 ± 0.52 | 0.50 |
| SS at 105 min | 1.26 ± 0.51 | 1.25 ± 0.45 | 0.63 |
| OPS on arrival | 4.2 ± 0.7 | 7.9 ± 0.3 | 0.01 |
| OPS at 30 min | 2.0 ± 0.3 | 5.4 ± 0.8 | 0.03 |
| OPS at 60 min | 2.4 ± 0.6 | 4.9 ± 0.6 | 0.01 |
| OPS at 90 min | 6.2 ± 0.9 | 6.7 ± 0.9 | 0.78 |
| OPS at 120 min | 2.4 ± 0.6 | 2.1 ± 0.6 | 0.54 |
| PAED on arrival | 7.1 ± 0.3 | 13.4 ± 0.7 | 0.00 |
| PAED at 30 min | 10.6 ± 0.4 | 16.6 ± 0.8 | 0.01 |
| PAED at 60 min | 8 ± 0.2 | 14.8 ± 0.4 | 0.00 |
| PAED at 90 min | 13.9 ± 0.4 | 14.6 ± 0.2 | 0.56 |
| PAED at 120 min | 5.0 ± 0.5 | 8.3 ± 0.6 | 0.66 |

response with a maximum dose of 2 µg/kg/hr. At these doses in children Dexmedetomidine acts as an effective sedative and analgesic agent without any significant hemodynamic effects.[13,14]

Bloodless surgical field in surgery is dependent mainly on two factors surgical technique and patient profile with regards to coagulation and hemodynamic parameters namely HR and MAP. Dexmedetomidine has been used successfully as an agent for providing controlled hypotension and bloodless surgical field in endoscopic sinus surgeries, middle ear and spine surgeries.[15] Bloodless surgical field is achieved by dexmedetomidine due to lowering in MAP that has been compared to various other agents used for controlled hypotension.[16] However, peripheral vasoconstriction due to postsynaptic $\alpha_{2b}$ receptors leads to transient hypertension which is usually observed after starting higher loading doses i.e. > 1 µg/kg.[17] In our study no episode of hypertension (MAP > 30% of baseline) is seen in either of the group. However, in 5 patients of Group D significant bradycardia i.e. (HR < 30% of baseline or < 60 bpm) develops after 15-20 min of giving the bolus test drug which when treated with glycopyrrolate 10 µg/kg IV, immediately led to raising of MAP and HR. Such episodes of bradycardia may be due to decrease in sympathetic outflow or due to reflex slowing of HR secondary to transient increase in MAP after the bolus dose of dexmedetomidine. Mason et al. [18] reported 3 cases where anticholinergics used for dexmedetomidine induced bradycardia led to exaggerate hypertensive response. According to them and Buck ML[19], bradycardia induced by dexmedetomidine should not be treated with

Table 5: Incidence of complications [n]

| Complication | Group D | Group P |
|---|---|---|
| Shivering | 2 | 6 |
| PONV | 1 | 8 |
| Hypotension | 1 | 1 |
| Bradycardia | 5 | 2 |
| Emergence agitation (PAED Score >16) | 1 | 12 |
| Dry mouth | 5 | 2 |

Values are expressed as number of patients. Bradycardia (HR < 60) episodes occur intraoperatively

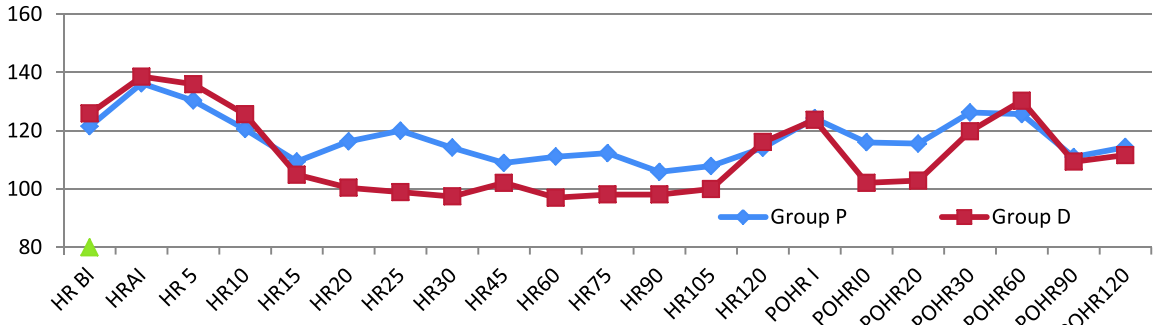


Figure 1: Comparison of heart rate (HR) at various time intervals

Significant difference (P value <0.05) is observed at HR15, HR20, HR25, HR30, HR60, HR75, POSTOPERATIVELY AT PO10, PO30. Significant difference is observed if P value is <0.05 (Student's t test). HR BI = heart rate before induction, HR AI = heart rate after induction, POHR 10 = 10 mins after extubation

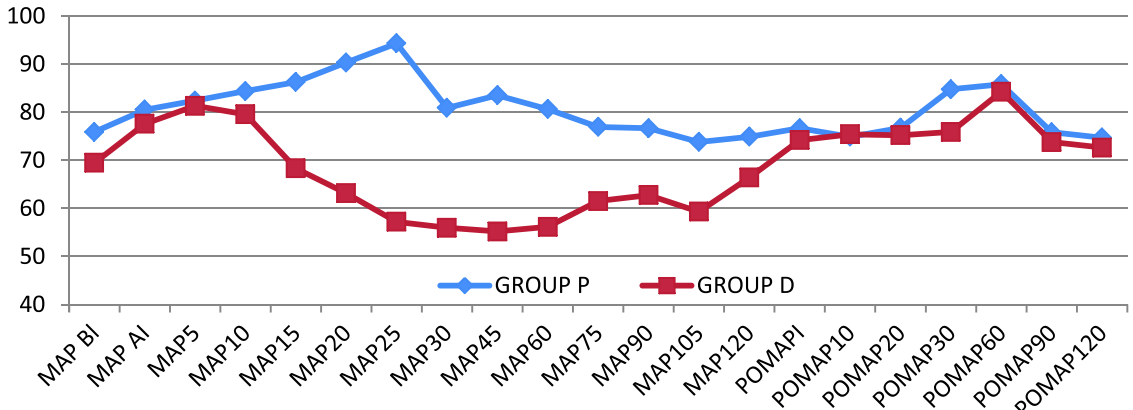


Figure 2: Shown here comparison of mean arterial pressure (MAP) at various time intervals

anticholinergics, unless bradycardia induced by dexmedetomidine is coincident with hypotension, which is unresponsive to fluids.

Significant fall in MAP from baseline is seen in all time intervals in Group D as compared to Group P which may be the reason for the optimal surgical condition with significant low bleeding scores seen in Group D as compared to Group P. Fentanyl and propofol consumption used for maintenance is significantly high in Group P which has been substantiated in a similar study by El Saied et al. who concluded that recovery time was significantly shorter with dexmedetomidine group with reduced requirement of fentanyl in PACU.[20]

Shams T[21] conducted a study to compare dexmedetomidine and esmolol in functional endoscopic sinus surgery to provide bloodless surgical field. They found that both dexmedetomidine and esmolol provides equal surgeons satisfaction score but dexmedetomidine have additional benefit in terms of postoperative analgesia with opioid sparing effect. In our study in pediatric age group dexmedetomidine also provided added benefits of reducing emergence agitation, postoperative shivering and nausea vomiting. In PACU, patients achieved modified Aldrete score of > =9 in Group D compared to placebo Group early and consequently have shorter stay in PACU. The mechanism of action of dexmedetomidine for analgesia was studied in detail by various authors who found that interaction of dexmedetomidine with $\alpha_{2A}$ and $\alpha_{2C}$ receptor in the spinal cord led to modulation of pain in the descending noradrenergic pathways and affect release of endogenous opioids.[22]

Emergence delirium is a distressing problem seen in pediatric patient after receiving sevoflurane anesthesia that delays recovery from PACU. Various theories have been postulated for emergence delirium with pain as one of the main causative factor and therefore IV fentanyl is the preferred drug to decrease agitation.[23] Alternative nonpharmacological and pharmacological methods including dexmedetomidine have been used successfully to prevent emergence delirium in various studies.[24] In our study also 12 patients in placebo group showed incidences of agitation after arrival in PACU with average onset time of agitation being between 10 to 15 min. Use of fentanyl, considerably reduces severity and score of agitation but invariably adds to nausea and vomiting.

Other common adverse events of dexmedetomidine are bradycardia and dry mouth. Bradycardia is due to increase sinus node recovery times and AV nodal effective refractory periods[25] especially when co administering drugs causing bradycardia or doing maneuvers causing vagal stimulation like intubation. Easly[26] reported the efficacy of dexmedetomidine in reducing postoperative shivering in children by reducing the threshold for shivering. In our study also shivering was less in children receiving dexmedetomidine. No other incidence of hypoxia or any respiratory complication was observed with dexmedetomidine in PACU which was consistent with its safety profile in the study by Koroglu A.[27]

## LIMITATIONS

The limitation of our study was that the monitoring of quality of the surgical field visualization was done with a subjective scoring system and we depended upon the assessment by the operating surgeon for this. Further, we did not use laser Doppler flowmetry to evaluate blood supply to the implant site, that would have added to the authenticity of the observation in a measurable method.

## CONCLUSION

The main ?ndings of our study are: intraoperative dexmedetomidine provides controlled hypotension, better surgical field and higher surgeon's satisfaction score leading to reduced surgery time. Dexmedetomidine significantly reduces consumption of propofol and fentanyl to achieve hemodynamic stability. Compared to placebo, dexmedetomidine provides better recovery profile and lower incidence of postoperative complications like emergence agitation, postoperative pain and nausea/vomiting.

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Authors' Contribution: NG-Conduction of study work; SD-Conceptualized idea of the study; VPS-Conduction of clinical cases; VR-Manuscript edition; PK-Statistical analysis

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