Original Article

Comparison of dexmedetomidine in two different doses on emergence agitation in children under sevoflurane anaesthesia: A double-blind randomised controlled trial

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ABSTRACT

Background and Aims: Emergence agitation (EA) in children is one of the most common postoperative problems encountered in the recovery room. Sevoflurane has been strongly associated with EA owing to its lower solubility and rapid recovery. Dexmedetomidine has been found to reduce the incidence of EA. This study was designed to evaluate the effectiveness of dexmedetomidine in two doses in reducing EA in children. **Methods**: This was a prospective double-blinded randomised study done on eighty children aged 5–14 years undergoing adenotonsillectomy/tonsillectomy under sevoflurane anaesthesia. Patients in Group A (n = 40) received 0.3 μg/kg/h and patients in group B (n = 40) received 0.5 μg/kg/h infusion after a bolus dose of 0.5 μg/kg of dexmedetomidine. The primary objective was to compare two different doses of dexmedetomidine on EA in the postoperative period. The secondary objectives were to assess the pain and perioperative haemodynamics in the recovery room. The anaesthesiologist blinded to the study charted the paediatric anaesthesia emergence delirium score (PAED), perioperative haemodynamic parameters, objective pain score and rescue medications if given. The data were analysed using Student's unpaired t-test, Chi-square test, repeated measures Analysis of Variance (ANOVA) and Mann-Whitney U test wherever appropriate. **Results**: The incidence of EA was comparable between both groups (P = 0.960). The haemodynamic parameters (P > 0.05) and the objective pain score (P = 0.810) also did not show a statistically significant difference. **Conclusion**: A lower dose of dexmedetomidine (0.3 μg/kg/h) is equally effective as a higher dose (0.5 μg/kg/h) after a bolus dose of 0.5 μg/kg in decreasing EA.

Key words: Adenotonsillectomy, dexmedetomidine, emergence agitation, sevoflurane, tonsillectomy

INTRODUCTION

Emergence agitation (EA) is an abnormal mental state that develops in the early postoperative period during the transition from unconsciousness to complete wakefulness which can last up to 2 days.[1] There is a disturbance in the child's awareness, perception, cognition, physical agitation and hypersensitivity to external stimulus. Though self-limiting, it creates a disturbance to the parents and recovery room attendants. It can lead to self-harm, inadvertent removal of intravenous (IV) cannulas and dressings, and injure the surgical repair and drains.[2]

Adenotonsillectomy is one of the independent risk factors for EA.[3] Sevoflurane is a pleasant-smelling

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inhalational agent most commonly used in paediatric anaesthesia because of its rapid induction without significant airway irritation. But it has been strongly associated with EA owing to its lower solubility and rapid recovery.[4] A number of pharmacological and non-pharmacological techniques are utilised to help the children to have a smoother recovery profile.[5]

Dexmedetomidine, a selective alpha 2 agonist, has been shown to reduce the incidence of postoperative agitation with sevoflurane anaesthesia.[6] It also reduces the requirement of anaesthetic agents. However, it has the property to cause dose-dependent hypotension and bradycardia.[7] A detailed review of literature has not given one particular dose of dexmedetomidine for the prevention of EA. Various doses have been studied for this purpose. Larger doses produced haemodynamic disturbances.[8-10] Hence, we aimed to compare 0.3 μg/kg/h versus 0.5 μg/kg/h infusion following a bolus dose of 0.5 μg/kg dexmedetomidine in reducing emergence delirium in children undergoing adenotonsillectomy/tonsillectomy. The secondary objectives were to compare the perioperative haemodynamics and postoperative pain between the two groups.

METHODS

After getting institutional ethical committee approval and an informed written consent from the parents, eighty children aged 5 to 14 years belonging to American Society of Anesthesiologists physical status I and II undergoing adenotonsillectomy/tonsillectomy under sevoflurane anaesthesia were included in the study. The study was registered with the Clinical Trials Registry of India. Children with hypersensitivity to the study medication, medications known to interact with dexmedetomidine, developmental delay and mental retardation, liver, renal or respiratory disorders were excluded from the study.

All the children had fasted for solids for 6 hours preoperatively. Premedication was omitted for the study requirements and an intravenous cannula was secured in the preoperative holding area with parental presence. The patients were transferred to the operating room and baseline parameters like heart rate (HR), peripheral oxygen saturation and blood pressure (BP) were noted.

In both groups, anaesthesia was induced with inj. glycopyrrolate 5 μg/kg, inj. fentanyl 1 μg/kg, inj. propofol1.5 mg/kg, sevoflurane 2% and inj. vecuronium 0.1 mg/Kg. Patients were intubated with appropriately sized endotracheal tubes and tube position was confirmed by bilateral air entry and end tidal carbon dioxide. The patients were mechanically ventilated and anaesthesia was maintained with oxygen, nitrous oxide (FiO_2 0.5) and sevoflurane at one minimum alveolar concentration (MAC) intraoperatively. Loading dose of 0.5 μg/kg of dexmedetomidine was given to all the children after intubation for 10 minutes using an infusion pump.

Patients were then randomly allocated into 2 groups by a computer-generated randomisation chart with 40 children in each group. An anaesthesiologist not involved in the study loaded the drugs as per the randomisation chart. Subsequently, the patients in group A received dexmedetomidine 0.3 μg/kg/h infusion and group B 0.5 μg/kg/h infusion till surgical haemostasis was achieved. The blinding of the anaesthesiologists for the rate of infusion administered was achieved by covering the syringe with the non-transparent plaster. Sevoflurane concentration was adjusted to maintain the haemodynamics (HR and BP) within 20% from baseline. Reduction in sevoflurane concentration was done and rescue medications (ephedrine 0.5 mg/kg and atropine 20 μg/kg) were administered in case the BP and HR dropped to <20% of baseline, respectively. Intraoperative haemodynamics such as HR and mean arterial BP were monitored at 0, 1, 3, 5, 10, 15, 30 minutes and every 15 minutes thereafter till surgical closure was achieved and the patient was extubated. Inj. dexamethasone 0.1 mg/kg was given after intubation as an antiemetic and to reduce the airway edema. Paracetamol suppository 30 mg/kg was given at the end of the procedure and the anaesthetics were discontinued. After thorough oral suctioning and demonstrating a partial muscle reversal, muscle paralysis was reversed with inj. neostigmine 50 μg/kg and inj. atropine 20 μg/kg and the patients were extubated in a fully awake state.

In the postoperative care unit, the children were observed by the anaesthesiologist blinded to the study for EA using paediatric anaesthesia emergence delirium scale (PAED scale)[11] [Table 1] and postoperative pain using objective pain scale[12] [Table 2].

Rescue medication Inj. fentanyl 1 μg/kg was given to those patients who complained of pain or had an objective pain score of more than 4. The patients were

Table 1: Paediatric anaesthesia emergence delirium (PAED) scale (PAED score >16 suggests emergence delirium)

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

Table 2: Objective pain score

Parameter	Finding	Point
Crying	Not crying	0
	Responds to age-appropriate nurturing (tender loving care)	1
	Does not respond to nurturing	2
Movements	No movements relaxed	0
	Restless (moving about in bed constantly)	1
	Thrashing (moving wildly)	2
	Rigid (stiff)	2
Agitation	Asleep or calm	0
	Can be comforted to lessen the agitation (mild)	1
	Cannot be comforted (hysterical)	2
Complaints of pain	Asleep	0
	States no pain	0
	Cannot localise	1
	Localises pain	2
Systolic Blood Pressure	Increase <20% of preoperative blood pressure	0
	Increase 20%-30% of preoperative blood pressure	1
	Increase >30% of preoperative blood pressure	2

1-3: none/insignificant pain. 4-6: moderate pain. 7-10: severe pain

transferred to the ward when the modified Aldrete score was more than 9.

The sample size was calculated with emergence delirium as the primary outcome. The sample size was calculated for a non-inferiority trial with the binary outcome at a power of 80% and 5% significance level with an expected 90% successful outcome using standard therapy (0.5 μg/kg/h dexmedetomidine) and a non-inferiority margin, not more than 10%, using alternative therapy (0.3 μg/kg/h). The calculated sample size was a total of 78 patients (39 in each group). To account for dropout of 2%, the sample size was increased to 80 (40 in each group). Data were statistically described in terms of mean ± standard deviation (± SD), percentage, median and frequency. Age, body mass index (BMI), duration of surgery and anaesthesia were compared using Student's unpaired *t*-test. Categorical variables were analysed using Chi-square test and Fisher's Exact test. Mann-Whitney U test was used to compare the PAED scores, objective pain score and time of onset of pain. Repeated measures Analysis of Variance (ANOVA) and pairwise comparison were used for haemodynamic parameters over various time intervals. P value < 0.05 was considered as statistically significant.

RESULTS

A total of 80 children were enroled in the study with 40 in each group [Figure 1]. The two groups were comparable in demographic details such as age, gender, BMI and ASA grade. The surgical procedures (adenotonsillectomy/tonsillectomy) were equally distributed between both the groups ($P = 0.133$). The mean duration of surgery in group A was 67.2 and in group B was 67.4 minutes, respectively ($P = 0.970$). The mean duration of anaesthesia was 76.1 in group A and 78.9 minutes in group B, respectively ($P = 0.575$). There was no statistically significant difference in time for extubation in group B compared to group A.

The mean PAED score was comparable in both groups A and B at varied time intervals [Figure 2]. Similarly, the mean objective pain score was similar in both groups A and B [Figure 3].

The mean HR and mean arterial pressure (MAP) showed no significant difference between both the groups (P- value > 0.05) [Figure 4].

DISCUSSION

EA in a paediatric age group is one of the most common postoperative problems encountered in the recovery room (Incidence 80%).[13,14] Hospitalisation, anaesthesia and surgery result in postoperative behavioural alterations which can cause substantial psychological impact. A number of non-pharmacological techniques like parental presence during induction (PPIA), playing animated videos on a smartphone, operating room tours, are advocated to prevent this.[15] Drugs like opioids, benzodiazepines, clonidine, ketamine, propofol, gabapentin, magnesium and hydroxyzine have been used to reduce the incidence of EA.[16-18]

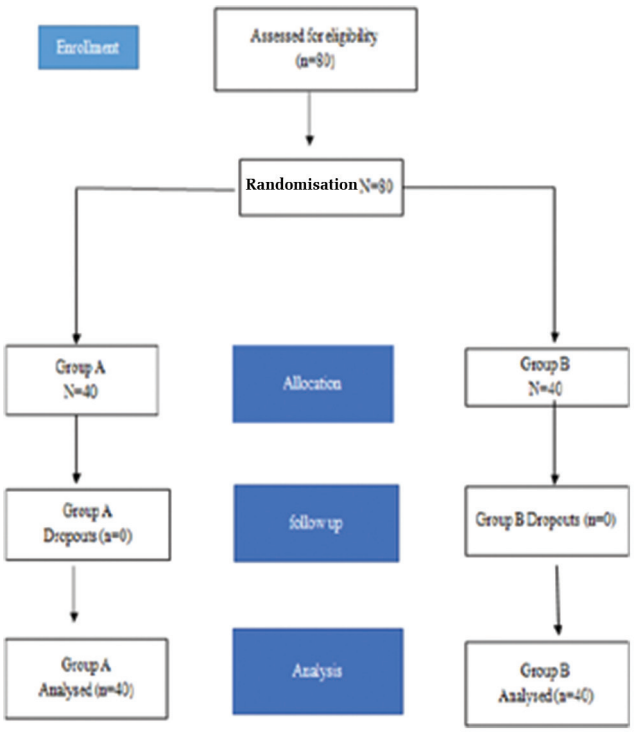

Figure 1: CONSORT flow diagram

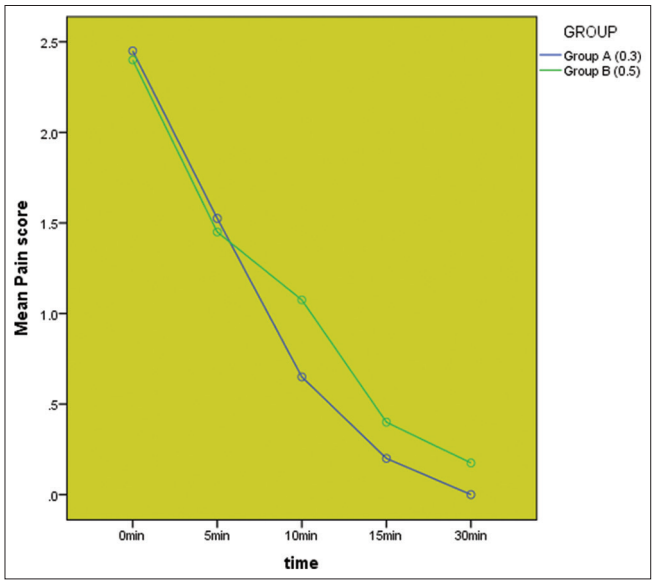

Figure 3: Distribution of objective pain scores among the groups

Even now there is no consensus regarding any specific intervention. Dexmedetomidine is used in different routes and doses to reduce the incidence of EA and improve the wake-up scores in children.[19,20]

The EA was recorded by using PAED scale at 0, 5, 10, 15, 30 minutes after extubation. A score of 1–15 suggested no agitation and ≥16 showed the presence of agitation. At 0 minute, i.e., extubation, 6 patients in

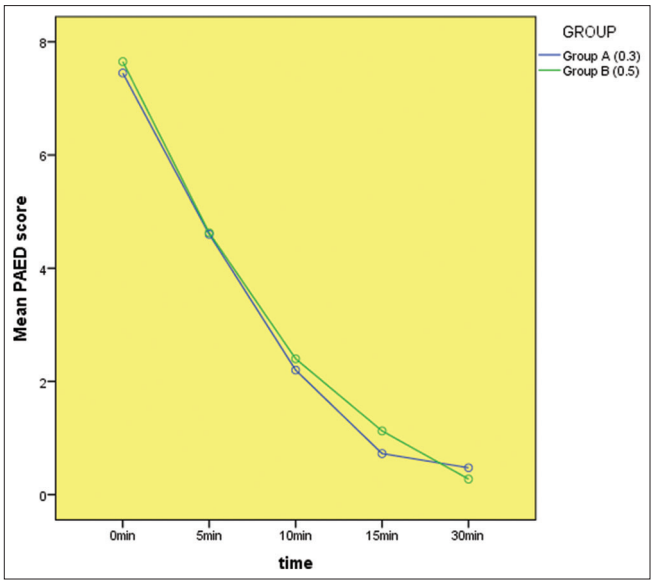

Figure 2: Distribution of PAED scores among the groups

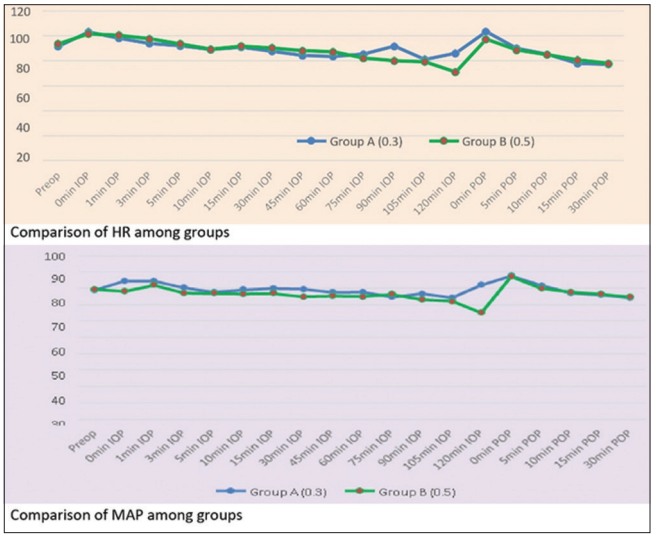

Figure 4: Comparison of haemodynamic parameters among the groups. HR-Heart rate; MAP-Mean arterial pressure

both group A and group B had a score ≥16 suggesting a 15% incidence of EA with the mean score of 7.5. Since extubation is considered a stressful stimulus, this was considered normal.[21,22] At 5 minutes after extubation, only 3 patients (7.5%) from group A had a PAED score ≥16. No patients in group B had score ≥16 at 5 minutes. At 10th minute, only 1 patient (2.5%) from group A had a score of ≥16 suggesting agitation and none in group B. All the 4 patients were treated with fentanyl 1 μg/kg. At 15 and 30 minutes following extubation, none of the patients' scores were higher and none showed agitation.

Guler *et al*.[23] found that administration of single dose of dexmedetomidine 0.5 μg/kg IV 5 minutes

before the end of surgery prevented the incidence and severity of EA as well as pain. Begum *et al*.[24] found both bolus (0.4 μg/kg/h) and infusion (0.4 μg/kg/h) of dexmedetomidine to be equally effective in preventing EA in children undergoing ambulatory surgeries. However, the bolus dose was more effective and it did not produce any haemodynamic instability.

In order to differentiate EA from pain, as pain is one of the confounding factors, we used an objective pain score to quantify pain. There was no statistically significant difference in the pain score in both the groups up to the 15-minute period. At 30 minutes, 4 patients in group B showed a mean pain score of 0.18 compared to 0.00 of group A and this difference was statistically significant. This discrepancy probably occurred because fentanyl 1 μg/kg was administered if the patient complained of pain even if the pain score was less than 4.

Twelve patients (30%) in group A complained of pain and received rescue medication with the mean time of onset of pain being 2.08 and 14 patients (35%) in group B had pain and received Inj. fentanyl with the mean time of onset of pain being 2.50 minutes. However, there was no statistically significant difference in the onset of pain between the 2 groups ($P = 0.817$).

In another study by Ghai *et al*.,[25] dexmedetomidine was compared in dosages of 0.15 μg/kg and 0.3 μg/kg to prevent EA in midazolam premedicated children undergoing cataract surgeries. They concluded that both 0.15 μg/kg and 0.3 μg/kg prevented EA in comparison with normal saline group without any significant variation in the haemodynamic parameters which could be possibly attributed to midazolam premedication, paracetamol and sub tenon's block.

Haemodynamic parameters over time were studied in each of the groups individually and it was found that both the HR and MAP remained within 20% of the baseline values.

Patel *et al*.[26] compared dexmedetomidine 2 μg/kg over 10 minutes followed by 0.7 μg/kg/h against inj. fentanyl 1 μg/kg bolus in 122 children aged 2–10 years undergoing adenotonsillectomy. Though the incidence of EA was lower in dexmedetomidine group than the fentanyl group, the mean HR and systolic blood pressure were significantly lower in the dexmedetomidine group ($P > 0.05$). This could be probably explained by the higher dose of dexmedetomidine (0.7 μg/kg/h) in their study.

In another study by Kim *et al*.,[27] 1 μg/kg bolus followed by 0.1 μg/kg/h dexmedetomidine infusion was compared with volume matched normal saline in children undergoing ambulatory surgeries. Incidence of emergence was lower in the dexmedetomidine group (5% vs 55%). However, MAP and HR were reduced by 22%–28% in the dexmedetomidine group. Atropine was given to 6 children who developed bradycardia with or without hypotension. They concluded that dexmedetomidine reduced the intraoperative requirement of sevoflurane and incidence of EA without delaying discharge from the recovery room.

Garg *et al*.[28] studied the efficacy of dexmedetomidine 1 μg/kg bolus followed by 0.4 μg/kg/h infusion with placebo in 72 patients undergoing nasal surgeries under desflurane anaesthesia. Though dexmedetomidine reduced the incidence of EA (5.6% in dexmedetomidine group vs 52.8% in placebo), it was associated with delayed extubation, residual sedation and prolonged post-anaesthesia care unit (PACU) stay.

In order to prevent the occurrence of bradycardia, hypotension and delayed extubation, we reduced the loading and the maintenance dose of dexmedetomidine in our study. Despite the relatively lower dose, we were able to reduce the incidence of EA and maintain haemodynamic stability without causing any untoward effects.

Our study had some limitations. Postoperative monitoring for haemodynamics as well as pain scores was done only for 30 minutes and 54/80 patients did not receive postoperative analgesia in the recovery room and we did not chart when the first dose of rescue analgesia was given in the ward. Subgroup analysis regarding the incidence of EA according to age was not done due to the relatively smaller sample size..

CONCLUSION

From our study, we conclude that intraoperative dexmedetomidine infusion of 0.3 μg/kg/h and 0.5 μg/kg/h following an initial bolus dose of 0.5μ g/kg is equally effective. Hence, we recommend a smaller dose of dexmedetomidine as sufficient to provide adequate relief from emergence agitation without having to resort to a higher dose.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients' parents have given their consent for their children images and other clinical information to be reported in the journal. The parents understand that their children's names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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