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RESEARCH ARTICLE

Dexmedetomidine versus nalbuphine in prevention of emergence agitation following adenotonsillectomy in pediatrics

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ABSTRACT

Background: Adenotonsillectomy is considered one of the most common surgical procedures in preschool age children. Postoperative emergence agitation (EA) is a major problem that faces anesthesiologist and can be managed by different drugs as opioids, sedatives and propofol. The present prospective, randomized double blinded study was designed to evaluate the effect of intraoperative 0.5 µg/kg dexmedetomidine infusion versus 0.1 mg/kg nalbuphine IV for prevention of postoperative emergence agitation.

Methods: After ethical committee's approval and written informed consent, 160 patients were enrolled in the study, 80 in each group. Patients enrolled in the study were randomized into dexmedetomidine 0.5 µg/kg infusion (DEX group) or nalbuphine 0.1 mg/kg IV (NAL group). Both groups were under standard anesthetic regimen with sevoflurane anesthesia. Postoperative measurements included pediatric anesthesia emergence delirium (PAED) score, Ramsay sedation score, hemodynamic changes at arrival to post anesthesia care unit (PACU) 5, 10 minutes then every 10 minutes till discharge from PACU.

Results: After ethical committee approval and written informed consent, 160 patients were enrolled in the study, 80 in each group. PAED score was significantly higher in NAL group than DEX group (13(12–16) vs. 12(11–13), respectively (p value <0.001). Number of patients needed rescue sedation was statistically higher in NAL than DEX group (12 vs. 3), respectively (p value 0.027). Ramsay sedation score was statistically higher in DEX group than NAL group at 10 and 20 minutes at PACU (p value <0.001). Both groups had similar length of stay in PACU.

Conclusion: Dexmedetomidine is better than nalbuphine in prevention of postoperative EA in preschool children, with more postoperative sedation and similar stay in PACU.

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1. Introduction

One of the major problems that encountered anesthesiologist in cases of adenotonsillectomy (AD) is post-operative emergence agitation (EA), especially when sevoflurane anesthesia is used [1]. Presence of agitation after (AD) may increase the risk of post-operative complications as cough, stridor and bleeding [2]. EA is a condition characterized by dissociative state of crying, incoherence, excitation and delirium. Although EA is a self limiting condition, it may cause self-injury or annoying to the care giver persons [3].There were many studies done before to treat postoperative EA after (AD) using drugs like morphine, alfentanil and nalbuphine (NAL), but there is no reported comparison between dexmedetomidine (DEX) and NAL [4,5].

DEX is a selective α2 agonist that acts centrally to reduce the sympathetic outflow in order to cause sedation with slight analgesia [6]. DEX does not affect respiration so no respiratory depression occurs in patients under DEX sedation in the postoperative period [7]. Bradycardia and hypotension are the most common and serious adverse effect of DEX [8].

NAL is a synthetic opioid agonist antagonist acts on kappa and mu opioid receptor producing analgesia and sedation [9]. One of the advantages of NAL over pure narcotic agonists is inducing minimal respiratory depression, so it is safely used in operation in airway like AD [10].

2. Aim of study

The aim of the present study is to compare the effect of IV infusion 0.5 µg/kg DEX and IV 0.1 mg/kg NAL in preschool children for prevention of EA after AD under sevoflurane anesthesia. Primary outcome is postoperative agitation prevention, while secondary outcome is sedation in early postoperative period in PACU, and monitoring of possible postoperative side effects.

3. Methods

This prospective randomized double blinded study was conducted on 160 patients undergoing elective AD in the period between March 2019 and July 2019 after

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consent from their legal guardians. Ethical committee approval with reference number is FWA000017585. Declaration of Helsinki and its ethical and legal applications was implicated in this study. Clinical trial.gov number is NCT04058899; Inclusion criteria were children of ASA physical status grade I or II aged 2–5 years undergoing AD. Exclusion criteria were history of hypersensitivity to the studied drug, refusal of the legal guardian to participate in the study, severely agitated child at induction of anesthesia and occurrence of postoperative bleeding at PACU.

After consent was obtained, children were randomized according to computer randomization to one of two groups, DEX group that received 0.5 µg/kg DEX diluted in 50 ml of normal saline 0.9% to be given by IV infusion over 10 minutes after induction of anesthesia then 5 ml of 0.9% normal saline IV, NAL group received IV infusion of 50 ml of 0.9% normal saline by IV infusion over 10 minutes then 0.1 mg/kg NAL diluted in 5 ml of 0.9% normal saline IV after induction of anesthesia.

After a preoperative fasting period of a 6–8 hours, all patients were monitored before induction of anesthesia as regards basal pulse, basal MAP and SpO2 on room air, then received a standardized anesthetic regimen with induction of anesthesia by sevoflurane 8% in 100% of oxygen via facemask without premedication, severely agitated child at induction of anesthesia was excluded from the study. Endotracheal intubation was facilitated with 0.5 mg/kg atracurium. Anesthesia was maintained with sevoflurane 2–3% adjusted to maintain heart rate and arterial blood pressure within 20% of preinduction levels. Paracetamol 15 mg/kg suppository was given to all patients after endotracheal intubation. No opioid was given; no propofol was used during the procedure.

Intraoperative dexamethasone 0.15 mg/kg and ondansetron 0.15 mg/kg were administered per routine intraoperative management of AD patients at our hospital for prevention of postoperative nausea and vomiting. Intraoperative fluid management includes infusion of lactated Ringer solution infusion at 7 ml/kg/hour operation for replacement of deficit and maintenance. At the end of operation discontinuation of sevoflurane, reversal of neuromuscular blockade was done by neostigmine 0.07 mg/kg and atropine 0.01 mg/kg. When patient was awake, eye opening, purposeful movement and good tidal volume extubation was done then patient was shifted to post anesthesia care unit (PACU). In the PACU, O_2 was continued to patients through face mask till maintenance of SpO_2 equal or more than 95%.

Data collection in the recovery was documented by a nurse who was blinded to the individual group of the patient. Pediatric Anesthesia Emergence Delirium (PAED) scale [11] (Table 1), Ramsay sedation score [12] (Table 2), hemodynamic parameters including, pulse rate, mean arterial blood pressure and SpO2 were recorded at arrival of patient to PACU (T0) 5 minutes after (T1), 10 minutes after (T2) and then each 10 minutes till discharge from PACU. The highest PAED score was recorded during stay in PACU. If patient had a PAED score more than or equal to 16, a rescue sedation of NAL 0.05 mg/kg was given. Patients were considered to be ready for discharge from the PACU when they attained a modified Aldrete score of 9 or more and were free from pain, nausea and vomiting. The duration of surgery, need for antiemetic and total duration of PACU stay were also recorded. Adverse effects in the form of bradycardia (means decrease of HR equal to or more than 20% of basal), hypotension (means decrease of MAP equal to or more than 20% of basal), hypersensitivity reaction were also documented in the stay at PACU. Adverse effects in the form of bradycardia, treated with 0.01 mg/kg atropine IV, or Hypotension treated with 0.01 mg/kg atropine IV, or hypersensitivity reaction treated with 1 mg/kg hydrocortisone, were also documented in the stay at PACU. End point of the study was that if there was postoperative bleeding during stay of patient in PACU then the patient was excluded from the study.

Table 1. The pediatric anesthesia emergence delirium scale [11].

Point	Description	Not at all	Just a little	Quite a bit	Very much	Extremely
1	The child makes eye contact with the caregiver	4	3	2	1	0
2	The child actions are purposeful	4	3	2	1	0
3	The child is aware of his/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. Ramsay sedation score [12].

Score	Response
1	Anxious or restless or both
2	Cooperative, orientated and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

Children with a PAED score of 16 or greater were defined as having emergence agitation (EA): the higher the total score, the more severe the EA.

Sample size calculation was based on previous study Martin et al. [1], to be 160 patients (80 in each group), using power and sample size calculation program version 3. Frequency of agitation in NAL group was 19.6% and in alfentanil group was 39.66%; α error = 0.05, power of study = 80%. The statistical analysis was performed using a standard SPSS software package version 17 (Chicago, IL). Normally distributed numerical data were presented as mean ± SD and differences between groups were compared using the independent Student's *t*-test. Data not normally distributed were

compared using Mann-Whitney test and were presented as median (IQR), and categorical variables were analyzed using the χ^2 test or fisher exact test and were presented as number. All *P* values were two-sided. $P < 0.05$ is considered statistically significant.

4. Results

All the 160 patients were randomized and included in the study; all surgical procedures were performed by the same surgical team. There were no statistically significant differences as regards the two groups' age, sex, weight and duration of surgery (Table 3). There was statistically significant lower heart rate at 0, 5 and 10 minutes at PACU in DEX group than NAL group (*p* value < 0.05) (Table 4). MAP was statistically significant lower in DEX group than NAL group at 0, 5 and 10 minutes during PACU stay (*p* value < 0.05) (Table 5). Ramsay sedation score was statistically significantly higher in DEX than NAL group at 10 and 20 min at PACU (4(3–4) vs. 3(3–4)) and (4(3–4) vs. 3(2–4); *p* value (<0.001 and <0.001), respectively (Table 6; Figure 1). There was significantly higher PAED score in NAL group than DEX group (13(12–16) vs. 12(11–13)); *p* value (<0.001) (Table 7), so number of patients needed 0.05 mg/kg NAL as rescue sedation in NAL group were statistically higher than DEX (12 vs. 3), *p* value (0.027). Incidence of nausea and vomiting was similar in both groups, while incidence of postoperative hypotension and bradycardia was significantly higher in DEX than NAL group (Table 7).

Table 3. Demographic data.

Age (in years)	4.5 ± 0.81	4.7 ± 1	0.407
Weight (kg)	17.18 ± 2.5	16 ± 2.53	0.8
Sex (M/F)	45/35	43/37	0.753
Duration of surgery (min)	32.96 ± 6.59	34.39 ± 7.44	0.157

Data are presented as mean ±SD or ratio.
p-value > 0.05 is considered statistically non significant.

Table 4. Postoperative heart rate (beat/minute).

	Group (Dex) (*n* = 80)	Group (Nal) (*n* = 80)	*p*-value
Baseline	110.68 ± 5.39	112.75 ± 6.36	0.935
PACU 0 min	97.23 ± 7.35	100.17 ± 9.2	0.03
5 min	104.34 ± 5.96	114 ± 8.78	<0.001
10 min	100.16 ± 6.45	107.68 ± 5.94	0.01
20 min	100.9 ± 7.39	104.17 ± 8.9	0.278
30 min	99.8 ± 6.456	105 ± 6.16	0.4
40 min	96.82 ± 6.8	101.8 ± 6.9	0.068

Data are presented as mean ±SD.
*p-value <0.05 is considered statistically significant.
PACU: post anesthesia care unit.

Table 5. Postoperative mean arterial pressure (mmHg).

	Group (Dex) (*n* = 80)	Group (Nal) (*n* = 80)	*p*-value
Baseline MAP	68.97 ± 4.35	67.5 ± 4.49	0.1
PACU 0 min	63.39 ± 4.99	67.58 ± 5.7	0.034
5 min	61.06 ± 5.67	66.44 ± 6.31	<0.001
10 min	61.55 ± 6.77	65.76 ± 6.8	0.002
20 min	62.8 ± 6.46	63.7 ± 6.72	0.45
30 min	62.1 ± 6.13	63.14 ± 6.2	0.27
40 min	59.8 ± 6.3	60.16 ± 6.16	0.447

Data are presented as mean ±SD.
*p-value <0.05 is considered statistically significant.
MAP: mean arterial blood pressure.

Table 6. Postoperative Ramsay sedation score.

	Group (Dex) (*n* = 80)	Group (Nal) (*n* = 80)	*p*-value
PACU 0 min	3(3–4)	3(2–4)	0.75
5 min	3(3–4)	3(3–4)	0.479
10 min	4(3–4)	3(3–4)	<0.001
20 min	4(3–4)	3(2–4)	<0.001
30 min	3(2–3)	3(2–4)	0.79
40 min	3(2–3)	3(2–4)	0.62

Data are presented as median (IQR).
p-value > 0.05 is considered statistically non significant.
*p-value < 0.05 is considered statistically significant.

5. Discussion

This study was designed to demonstrate the effect of DEX versus NAL in prevention of postoperative agitation following AD in preschool children under sevoflurane anesthesia, the main finding of this study is that intravenous DEX 0.5 µg/kg infusion is better in prevention of postoperative agitation and causes more sedation than intravenous NAL 0.1 mg/kg after AD in pediatric age group. On the other hand, DEX has more incidences of postoperative bradycardia and hypotension than NAL.

It is well known that EA occurred more frequently in patients anaesthetized with sevoflurane even without surgical intervention like for magnetic resonance imaging (MRI) scan when compared to those who received other inhalational anesthetics. DEX is a potent α2 agonist with a high affinity for these receptors that is 8 times greater than that of clonidine. DEX has an analgesic effect that is attributed to its acting on dorsal horn of the spinal cord and also by inhibition of substance P [13]. There were studies on adults shown that intraoperative use of DEX decreases postoperative opioid consumption [14,15]. However, this reduction in opioid requirement has been shown in another pediatric study in which IV DEX was used for reduction of postoperative opioid administration after hypospadius repair surgery [16]. The etiology of EA in pediatrics after operation is not fully understood but there are so many risk factors as postoperative pain, otolaryngeal surgery, preschool age children and rapid recovery from anesthesia [17].

In the present study, all patients received 15 mg/kg of paracetamol suppository after induction of anesthesia to exclude the element of pain as a factor in postoperative EA in pediatric. PAED score was significantly lower in DEX group than NAL group during stay in PACU. Our findings are in agreement with Patel et al. [18], who found that DEX is used for prevention of postoperative agitation but they used DEX only in group of children undergoing AD for obstructive sleep apnea but with higher dose of DEX 2 µg/kg. In

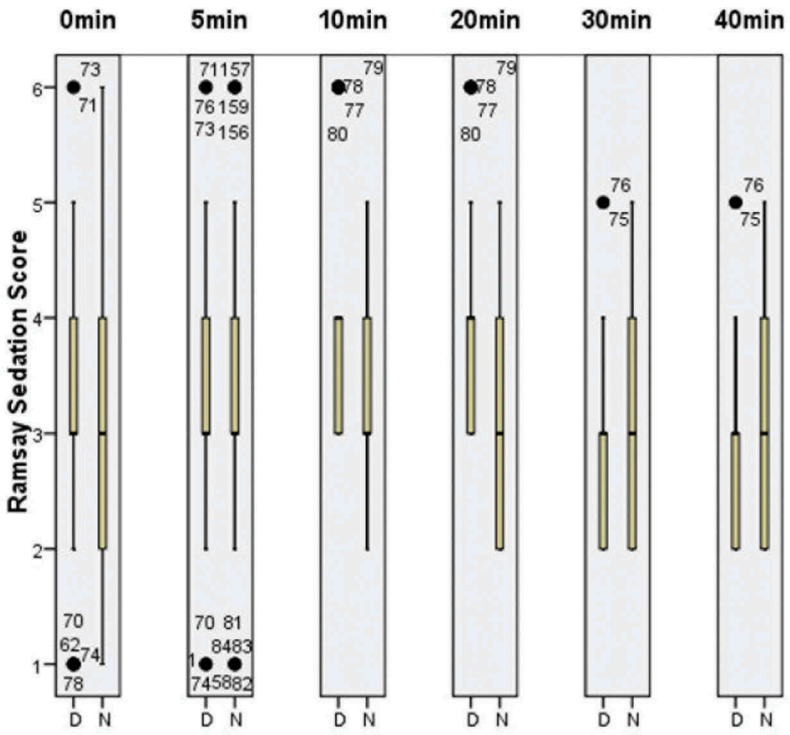

Figure 1. Ramsay sedation score at different times in PACU.

The middle black solid line represents the median, the upper and lower margins of each box are IQR and the whiskers are maximum and minimum values. Dots and asterisks represent number of patient with outlier data (D: Dex group, N: Nal group).

Table 7. Postoperative characteristics.

	Group (Dex) (n = 80)	Group (Nal) (n = 80)	p-value
PAED	12(11–13)	13(12–16)	<0.001
Nausea	4	6	0.746
Vomiting	4	5	1
Bradycardia	11	2	0.012
Hypotension	11	3	0.047
Time in PACU (min)	40.38 ± 7.43	37.16 ± 9.38	0.17
No. of patients needed rescue sedation	3	12	0.027

Data are presented as mean± SD, or number of patients.
P-value > 0.05 is considered statistically non-significant.
*P-value < 0.05 is considered statistically significant.

another study done by Monaz and Ashraf [19], they found that 0.3 µg/kg of Dex 5 minutes before the end of anesthesia for AD in pediatrics decreases incidence and severity of postoperative agitation but the study did not measure postoperative sedation score. Monaz and Ashraf found that 3 patients out of 40 needed rescue sedation, whereas in our study only 3 out of 80 patients in DEX group needed rescue NAL sedation.

One of important issues in the present study that we did not use premedication as midazolam for children to show the sole effect of the studied drug either DEX or NAL on EA after sevoflurane anesthesia [20]. Two meta-analyses showed the role of DEX in the prevention or reduction of incidence and severity of EA in children after sevoflurane anesthesia with different dose regimens, timing, techniques and route of administration done by Sun and Guanesh [21,22].

Another study done by Mostafa and Hany, 2017 demonstrated that a dose of 1 µg/kg intranasal DEX administered after the induction of anesthesia reduces post-sevoflurane incidence and severity of EA in children undergone tonsillectomy and/or adenoidectomy, but our study differs in that we did not use the intranasal route of DEX or intraoperative IV fentanyl for all patients as done in that study [23].

There was no respiratory depression in both groups as determined by no incidence of desaturation in PACU in both groups, this is agreed by other studies that NAL for comparison with alfentanil in pediatric AD was based on its good analgesic potential, which is described to be similar with morphine, and poses lower risk of opioid side effects, such as nausea, vomiting or respiratory depression [24]. Martin et al. (2017) found that intraoperative NAL 0.1 mg/kg causes postoperative hypotension in 36% of pediatric patient undergoing AD operation as undesired postoperative effect without clear explanation. In the present study, only 3% of NAL group had hypotension, it is well

known that opioid causes hypotension but in large doses not in optimal dose [1].

Postoperative Ramsay sedation score findings were statistically higher in DEX than NAL group at 10 and 20 minutes at PACU, these results are in agree with Nazai and Mazhar [25], who found that two doses of NAL either 0. 25 or 0.1 mg/kg caused mild sedation following AD in pediatrics. However, our findings as regards postoperative sedation are different than Olutoyin et al. [26], who found no statistically differences in postoperative Ramsay sedation score at different times at PACU but they used larger doses of DEX (0.75 or 1 µg/kg) than only 0.5 µg/kg we had used in comparison to 50 or 100 µg/kg morphine for prevention of EA following AD.

Postoperative incidence of nausea and vomiting were similar in DEX and NAL groups. Our result as regards DEX was similar to Monaz and Ashraf, who found that DEX and propofol in prevention of EA after AD were similar in prevention of postoperative nausea and vomiting (PONV) [19]. Guler et al. [6] found different result than the present study as regards nausea and vomiting following AD that there were no difference of postoperative attacks of vomiting between DEX and placebo.

One of the adverse effects of DEX in the current study was association of statistically significant higher incidence of postoperative bradycardia and hypotension than NAL group. These adverse effects were easily treated with IV 0.01 mg/kg atropine as most of attacks of hypotension were associated with bradycardia. Severe bradycardia may occur with use of DEX [26], which was not reported in any case in the present study.

In the present study, there was no statistically significant difference in time of stay in PACU in both groups. Most of the patients were discharged between 35 and 45 minutes from PACU. Olutoyin et al. [27] found that time of stay in PACU after DEX 2 doses in comparison to 2 doses of morphine in postoperative AD was similar in both DEX and morphine groups like our findings as regards time of stay in PACU in both groups.

Conclusion of the present study implies that DEX 0.5 µg/kg infusion is better than 0.1 mg/kg NAL IV after induction of anesthesia in preschool children undergoing AD in prevention of postoperative agitation under sevoflurane anesthesia. DEX is associated with more sedation and more incidences of bradycardia than NAL. Similar stay in postoperative care unit was observed in both groups.

Disclosure statement

No potential conflict of interest was reported by the authors.

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