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# ASSESSING THE EFFECTS OF INTRAVENOUS NALBUPHINE AT DIFFERENT TIMES FOR POSTOPERATIVE SEDATION AND ANALGESIA IN CHILD SUBJECTS FOLLOWING ADENOTONSILLECTOMY

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## ABSTRACT

**Background:** Effective pain control has been reported in children after intravenous nalbuphine before anesthesia induction, before surgery, and postoperatively. However, existing literature data is scarce in the literature concerning this issue.

**Aim:** The present study aimed to comparatively assess the efficacy of intravenous nalbuphine at different times for postoperative sedation and analgesia in child subjects following adenotonsillectomy.

**Methods:** The study assessed child subjects scheduled for adenotonsillectomy for obstructive sleep apnea and were divided into three groups where Group I (n=80) subjects were given intravenous 0.2 mg/kg nalbuphine before anesthesia induction, Group II (n=82) intravenous 0.2 mg/kg nalbuphine before end of surgery, and Group III (n=78) subjects were given no nalbuphine. The outcomes were assessed at T0, T1, T2, T3, T4, and T5 signifying before anesthesia induction, extubation, 0, 15, 30, and 45 minutes in PACU (post-anesthesia care unit).

**Results:** Group II subjects had significantly lower FLACC (Face, Legs, Activity, Cry, Consolability) pain scores at T2-T5 assessments compared to Group III ($p<0.05$). Significantly higher Ramsay sedation scores were seen in Group Iin compared to Group III at T2-T4 ($p<0.05$). Subjects needing remedial anesthesia were significantly lower in Group I and II compared to Group III with p=0.006 and <0.001 respectively.

**Conclusions:** The present study concludes that intravenous nalbuphine administration 10 minutes before completion of adenotonsillectomy in children can increase sedation levels and decrease pain intensity in the recovery period while reducing medical analgesia in PACU.

**Keywords**: analgesia, anesthesia, adenotonsillectomy, nalbuphine, sedation

## INTRODUCTION

OSAS (obstructive sleep apnea syndrome) is a respiratory sleep disorder seen in child subjects and is more common in males compared to females. The reported prevalence of OSAS is in the range of 2% to 4%. OSAS is characterized by episodes of complete or partial upper airway obstruction during sleep leading to abnormal sleep patterns and atypical ventilation. OSAS is linked to increased incidence of metabolic and cardiovascular disease and is reported to be linked with growth retardation, mood abnormalities, behavioral abnormalities, and neurocognitive impairment in children when adequate treatment or diagnosis is not been provided.[1] The conventional adenotonsillectomy is done under general anesthesia as a first-line treatment to manage subjects with obstructive sleep apnea syndrome. However, adenotonsillectomy can lead to various risks from minimal complications to life-threatening conditions that are usually related to postoperative events and factors.[2]

The most common reason for contact of patients with their operating surgeon in the postoperative era of adenotonsillectomy is the pain which might lead to bleeding, respiratory concerns, nausea, insufficient oral intake, and dehydration which can further lead to repeated visits to the emergency department, parental anxiety, or re-hospitalization.[3] With the recent advancements in the use of different anesthetic drugs, a significant reduction has been reported in the pain effects postoperatively. Various studies in the literature have reported that pain management following adenotonsillectomy in child subjects includes the administration of dexamethasone and xylocaine.[4]

Recently, nalbuphine has been reported to have equal efficacy as morphine which has also gained interest as an analgesic agent and as an agent for sedation. Nalbuphine is a μ receptor antagonist and κ receptor agonist which can be used as a long-standing opioid used systemically in child subjects having mild to moderate pain. Previous literature data has reported that nalbuphine has a sufficient analgesia effect in pain therapy with reduced agitation and the emergence of delirium in child subjects using general anesthesia for ophthalmic surgical procedures.[5]

Also, literature studies have reported that the administration of intravenous nalbuphine postoperatively in child subjects to control pain used before anesthesia induction showed positive effects. Similar efficacious results have been reported during anesthesia induction, before the end of the surgical procedure, and after arrival in the recovery room. However, these studies of the literature only assessed the use of nalbuphine at a single point in time and lacked the component of the longitudinal comparison for the use of nalbuphine in controlling pain in child subjects following adenotonsillectomy.[6]

Hence, the present study aimed to comparatively assess the efficacy of intravenous administration of nalbuphine at different points of time for sedation and analgesia in subjects

following adenotonsillectomy in child subjects during the recovery period from general anesthesia and to assess more appropriate time for nalbuphine treatment.

## MATERIALS AND METHODS

The present prospective randomized controlled clinical study was aimed to comparatively assess the efficacy of intravenous administration of nalbuphine at different points of time for sedation and analgesia in subjects following adenotonsillectomy in child subjects during the recovery period from general anesthesia and to assess more appropriate time for nalbuphine treatment. The study subjects were from the Department of Pediatric Surgery of the Institute. Verbal and written informed consent was taken from parents/guardians of all the participating subjects.

The study assessed child subjects with obstructive sleep apnea syndrome in the age range of 4 to 10 years who had to undergo adenotonsillectomy under general anesthesia at the Institute within the defined study period. The inclusion criteria for the study were subjects with normal physical examination, normal weight, and in the ASA (American Society of Anesthesiologists) physical status I and II. The exclusion criteria for the study were subjects that presented any contraindication to any drug used, had a temperature of >38$^{o}$C, presented with signs and symptoms of upper respiratory tract infection 24 hours before adenotonsillectomy, had vascular, hematological, neurological, or immunological disorders, having drug allergy to any drug used in the study, and subjects where parents were not willing to give informed consent. The final sample size comprised 60 subjects that met the inclusion criteria.

In all the included subjects, the data were gathered from the hospital records including the BMI (body mass index) in kg/m2, weight in kilograms, height in centimeters, age in months, and gender of the participants. The subjects were randomly divided into three groups where Group I comprised children who were given intravenous nalbuphine in the dose of 0.2 mg/kg diluted with 5ml normal saline before induction of anesthesia, Group II included child subjects theta were administered intravenous nalbuphine in the dose of 0.2 mg/kg diluted with 5ml normal saline 10 minutes before the adenotonsillectomy completed, and Group III included child subjects that were not administered nalbuphine. Before anesthesia, all the subjects were kept fasted for 8 hours for food and 2 hours for water.

Following monitoring, all subjects were given preoxygenation and intravenous anesthetic drug injections using standard anesthetics such as 0.1mg/kg dose of dexamethasone, 0.01mg/kg dose of atropine, 0.6mg/kg dose of rocuronium, 4µg/kg dose of fentanyl, 2–3mg/ kg dose of propofol, and 0.1mg/kg dose of midazolam. 3-5 minutes after these drugs, tracheal intubation was done to give mechanical ventilation. Maintenance of anesthesia was done with remifentanil at 0.3-0.5 µg/kg/min and propofol infusion at 50-100µg/kg/min. The subjects were not given local anesthesia intraoperatively, rocuronium, or any other anesthetic/sedative drug. The subjects were then directly sent to PACU (post-anesthesia care unit) following recovery with spontaneous breathing (oxygen saturation of inhaled air: >92%, respiratory rate: 18 breaths/min, and tidal volume: 6mL/kg).

The outcomes were assessed at various time points including T0, T1, T2, T3, T4, and T5 signifying time as before anesthesia induction, extubation, 0 minutes in the PACU, 15 minutes in the PACU, 30 minutes in the PACU, and 45 minutes in the PACU respectively. The outcomes assessed included the serum levels of cortisol, IL-6 (interleukin 6), TNF-α (Tumor necrosis factor- α), postoperative side effects such as itching, rash, edema, and respiratory depression, MAP (mean arterial pressure), heart rate, recovery time, remifentanil/propofol dose from surgery end to extubation, surgery time, sedation level, and pain intensity. Postoperative sedation and pain scores from T0-T5 were assessed by an examiner expert in the field using FLACC (Face, Legs, Activity, Cry, Consolability) pain score and the Ramsay Sedation Score.[7] The FLACC scale scoring was done in the range of 0-10 where 0 signified no pain and 10 depicted maximum pain. The Ramsay sedation score was used on the following scale score 1 to 6 as follows: 1: anxious, agitated, or restless; 2: cooperative, oriented, and tranquil; 3: responsive to commands; 4: asleep, but with a brisk response to a light glabellar tap or a loud auditory stimulus; 5: asleep, sluggish response to a glabellar tap or auditory stimulus; 6: asleep, no response.

Intravenous blood was collected from all the participants using strict aseptic and sterile protocol at T0 and T4. The collected blood was subjected to centrifugation at 3000 rpm/min for 5 minutes. This was followed by freezing samples at −80°C for detection of cortisol, IL-6, and TNF-α with commercially available ELISA (Enzyme-linked immune sorbent assay) kits following the instructions by the manufacturer.

The data gathered were analyzed statistically using the SPSS software version 21.0 (IBM Corp., Armonk, NY, USA) and the one-way ANOVA (analysis of variance). The data were expressed as mean and standard deviation for normally distributed and non-normally distributed continuous variables and frequency and percentage for categorical variables. Statistical significance was kept at a p-value of <0.05.

## RESULTS

The present prospective randomized controlled clinical study was aimed to comparatively assess the efficacy of intravenous administration of nalbuphine at different points of time for sedation and analgesia in subjects following adenotonsillectomy in child subjects during the recovery period from general anesthesia and to assess more appropriate time for nalbuphine treatment. The study assessed 60 subjects that were divided into three groups where Group I comprised children who were given intravenous nalbuphine in the dose of 0.2 mg/kg diluted with 5ml normal saline before induction of anesthesia, Group II included child subjects theta were administered intravenous nalbuphine in the dose of 0.2 mg/kg diluted with 5ml normal saline 10 minutes before the adenotonsillectomy completed, and Group III included child subjects that were not administered nalbuphine.

The mean age of the study subjects was 69.31±17.13, 73.91±17.46, and 67.29±15.95 months respectively showing a statistically non-significant difference with p=0.201. There were 12 males and 8 females in Group I, 14 males and 7 females in Group II, and 14 males and 5 females in Group III respectively. The mean weight of the study subjects was 20.18±5.05, 21.94±6.47, and

19.38±5.03 kg respectively in Groups I, II, and III respectively depicting statistically non-significant differences with p=0.112. The mean height of the child subjects was 116.06±10.03, 118.83±11.26, and 113.95±9.61 cm respectively in Group I, II, and III respectively depicting statistically non-significant differences with p=0.109. The mean BMI of the study subjects was 14.83±2.12, 15.25±2.40, and 14.76±2.32 kg/m2 respectively depicting statistically non-significant differences with p=0.579 as shown in Table 1.

The study results showed that for the comparison of sedation level and pain intensity in the three groups of study subjects where Ramsay sedation scores and FLACC scores for pain intensity were assessed postoperatively. It was seen that subjects from Group II had significantly lower FLACC scores at T2-T% compared to the subjects from Group III with p<0.05. Also, subjects from Group I depicted significantly lower FLACC scores at T3 compared to subjects from Group III with p<0.05. Concerning the sedation level, the subjects from Group II showed significantly higher Ramsay Sedation scores at T2-T4 compared to Group III with all p<0.05. The subjects from Group I showed significantly higher Ramsay sedation scores at T3 compared to Group III with p<0.05. In the study, no case of excessive sedation was seen.

On assessing the perioperative characteristics in three groups of study subjects, it was seen that a proportion of remedial analgesia was given in 20% (n=4), 9.52% (n=2), and 47.36% (n=9) subjects from Groups I, II, and III respectively showing statistically significant difference with p<0.001. Mean recovery time was comparable in three groups with 15.31±13.25, 17.47±11.93, and 12.24±5.63 minutes respectively in Groups I, II, and III with p=0.11. Time from surgery end to extubation was 9.61±4.98, 8.76±3.32, and 10.21±4.12 minutes respectively in Groups I, II, and III respectively which was statistically non-significant with p=0.302. The dose of remifentanil was 0.45±0.20, 0.41±0.16, and 0.39±0.14 mg respectively in Groups I, II, and III showing a statistically non-significant difference with p=0.369. The dose of propofol was 91.36±48.06, 92.91±49.82, and 80.75±42.83 mg respectively showing statistical non-significance with p=0.458. The mean surgery time was 34.01±13.98, 34.69±12.79, and 34.72±12.87 minutes respectively showing statistically non-significant differences with p=0.961 as summarized in Table 2.

## DISCUSSION

The present study was designed as a prospective randomized controlled clinical study that comparatively assessed the efficacy of intravenous administration of nalbuphine at different points of time for sedation and analgesia in subjects following adenotonsillectomy in child subjects during the recovery period from general anesthesia and to assess more appropriate time for nalbuphine treatment. The study assessed 60 subjects that were divided into three groups where Group I comprised children who were given intravenous nalbuphine in the dose of 0.2 mg/kg diluted with 5ml normal saline before induction of anesthesia, Group II included child subjects theta were administered intravenous nalbuphine in the dose of 0.2 mg/kg diluted with 5ml normal saline 10 minutes before the adenotonsillectomy completed, and Group III included child subjects that were not administered nalbuphine. The study design was similar to Pfiffner M

et al[8] in 2022 and Aldamluji M et al[9] in 2021 where the study design used by the authors was similar to the present study.

For demographic characteristics, the mean age of the study subjects was 69.31±17.13, 73.91±17.46, and 67.29±15.95 months respectively showing statistically non-significant differences with p=0.201. There were 12 males and 8 females in Group I, 14 males and 7 females in Group II, and 14 males and 5 females in Group III respectively. The mean weight of the study subjects was 20.18±5.05, 21.94±6.47, and 19.38±5.03 kg respectively in Groups I, II, and III respectively depicting statistically non-significant differences with p=0.112. The mean height of the child subjects was 116.06±10.03, 118.83±11.26, and 113.95±9.61 cm respectively in Group I, II, and III respectively depicting statistically non-significant differences with p=0.109. The mean BMI of the study subjects was 14.83±2.12, 15.25±2.40, and 14.76±2.32 kg/m2 respectively depicting statistically non-significant differences with p=0.579. these data were comparable to the studies of Zhang Y et al[10] in 2017 and Gong Y et al[11] in 2018 where authors assessed subjects with demographic data comparable to the present study.

It was seen that for the comparison of sedation level and pain intensity in the three groups of study subjects where Ramsay sedation scores and FLACC scores for pain intensity were assessed postoperatively. It was seen that subjects from Group II had significantly lower FLACC scores at T2-T% compared to the subjects from Group III with $p<0.05$. Also, subjects from Group I depicted significantly lower FLACC scores at T3 compared to subjects from Group III with $p<0.05$. Concerning the sedation level, the subjects from Group II showed significantly higher Ramsay Sedation scores at T2-T4 compared to Group III with all $p<0.05$. The subjects from Group I showed significantly higher Ramsay sedation scores at T3 compared to Group III with $p<0.05$. In the study, no case of excessive sedation was seen. These results were consistent with the findings of He J et al[12] in 2023 and Chen F et al[13] in 2020 where similar levels of pain and sedation to the present study were reported by the authors in the present study.

The study results showed that on assessing the perioperative characteristics in three groups of study subjects, it was seen that a proportion of remedial analgesia was given in 20% (n=4), 9.52% (n=2), and 47.36% (n=9) subjects from Groups I, II, and III respectively showing statistically significant difference with $p<0.001$. Mean recovery time was comparable in three groups with 15.31±13.25, 17.47±11.93, and 12.24±5.63 minutes respectively in Groups I, II, and III with p=0.11. Time from surgery end to extubation was 9.61±4.98, 8.76±3.32, and 10.21±4.12 minutes respectively in Groups I, II, and III respectively which was statistically non-significant with p=0.302. The dose of remifentanil was 0.45±0.20, 0.41±0.16, and 0.39±0.14 mg respectively in Groups I, II, and III showing a statistically non-significant difference with p=0.369. The dose of propofol was 91.36±48.06, 92.91±49.82, and 80.75±42.83 mg respectively showing statistical non-significance with p=0.458. The mean surgery time was 34.01±13.98, 34.69±12.79, and 34.72±12.87 minutes respectively showing a statistically non-significant difference with p=0.961. These findings were in agreement with the results of Liaqat N et al[14] in 2017 and Eladi IA et al[15] in 2019 where perioperative characteristics reported by the authors in their study were in line with the present study.

## CONCLUSIONS

Within its limitations, the present study concludes that intravenous nalbuphine administration 10 minutes before completion of adenotonsillectomy in children can increase sedation levels and decrease pain intensity in the recovery period while reducing medical analgesia in PACU. However, the study had a small sample size, and further longitudinal studies are needed for a better conclusion.

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## TABLES

| Characteristics | Group I (n=20) | Group I (n=21) | Group I (n=19) | p-value |
|---|---|---|---|---|
| **Mean age (months)** | 69.31±17.13 | 73.91±17.46 | 67.29±15.95 | 0.201 |
| **Gender** | | | | |
| Males | 12 | 14 | 14 | |
| Females | 8 | 7 | 5 | |
| **Mean weight (kg)** | 20.18±5.05 | 21.94±6.47 | 19.38±5.03 | 0.112 |
| **Mean height (cm)** | 116.06±10.03 | 118.83±11.26 | 113.95±9.61 | 0.l09 |
| **BMI (kg.m2)** | 14.83±2.12 | 15.25±2.40 | 14.76±2.32 | 0.579 |

**Table 1: Demographic data of the study subjects**

| Characteristics | Group I (n=20) | Group I (n=21) | Group I (n=19) | p-value |
|---|---|---|---|---|
| **Remedial analgesia proportion n (%)** | 4 (20) | 2 (9.52) | 9 (47.36) | **<0.001** |
| **Mean recovery time (min)** | 15.31±13.25 | 17.47±11.93 | 12.24±5.63 | 0.11 |
| **Time from surgery end to extubation (min)** | 9.61±4.98 | 8.76±3.32 | 10.21±4.12 | 0.302 |
| **Remifentanil dose (mg)** | 0.45±0.20 | 0.41±0.16 | 0.39±0.14 | 0.369 |
| **Propofol dose (mg)** | 91.36±48.06 | 92.91±49.82 | 80.75±42.83 | 0.458 |
| **Surgery time (min)** | 34.01±13.98 | 34.69±12.79 | 34.72±12.87 | 0.961 |

**Table 2: Perioperative characteristics in the child subjects undergoing adenotonsillectomy**