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The effect of low dose nalbuphine or ketamine in the prevention of emergence agitation after sevoflurane anesthesia in children undergoing tonsillectomy with or without adenoidectomy

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ABSTRACT

Background: Children's agitation increases following sevoflurane anaesthesia. With indefinite results, nalbuphine and midazolam have been used as preventative treatments.

Patients and Methods: This study involved 90 children with American Society of Anesthesiologists score I-II and aged 4–10 who had sevoflurane-based adenotonsillectomy. Each child was randomly assigned to one of three groups; group N, group K, and group S. Nalbuphine was given to Group N at 0.1 mg/kg, ketamine was given to Group K at 0.25 mg/kg, and saline was given to Group S at equivalent volume. Sevoflurane was discontinued after the procedure, and the study drugs were given. The emergence agitation (EA) scale was used in the post-anesthesia care unit (PACU) to measure agitation upon admission (T0), after 5 min (T5), 10 min (T10), 15 min (T15), 20 min (T20), 25 min (T25), and 30 min (T30). Clinical trials. gov ID: NCT05176119.

Results: In the PACU, the incidence of EA was significantly lowered in N (6.6%) and K Group (16.6%) compared to S group (33%) with ($p = 0.044$), the duration in PACU was significantly prolonged in S in comparison to K and N groups (p-value = 0.011), more patients experienced postoperative pain in S group compared to N group and K group (p-value < 0.001).

Conclusion: Children who had sevoflurane-induced adenotonsillectomy can avoid emergence agitation with ketamine 0.25 mg/kg or nalbuphine 0.1 mg/kg.

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1. Background

Emergent agitation (EA), especially in children, is a common clinical phenomenon. After general anaesthesia, mental confusion, irritability, disorientation, and uncontrollable crying occur [1]. Injuries, broken surgical dressings, lost intravenous catheters, disconnected cables, and monitoring devices may also cause it. Emergence agitation may delay hospital discharge due to the need for additional nursing care and sedatives/analgesics. In fact, emergence agitation frustrates parents, nurses, and other caregivers [2].

Children who experience emergence agitation have a seven-fold increased risk of developing new-onset separation anxiety, apathy, eating, and sleeping issues [2]. The incidence is highest in the first 30 min of emergence, but it is brief. Additionally, prolonged agitation episodes lasting up to 2 days have been reported [1]. Sevoflurane is well-liked for its speedy induction and emergence from general anaesthesia and depth control, as well as its hemodynamic stability and low blood solubility. However, sevoflurane alone increases EA in children.

Nalbuphine hydrochloride is a synthetic opioid agonist antagonist. It is a strong analgesic that has also been added to balanced anaesthesia analgesics supplement [3].

Ketamine is a noncompetitive N-methyl-D-aspartate receptor antagonist. It has a dose-dependent relationship between the anaesthetic and analgesic effects [4].

To the best of our knowledge, nalbuphine and ketamine for treatment of sevoflurane EA in children have never been compared in a prior study. Here, in this study, children undergoing tonsillectomy with or without adenoidectomy were given either a single dose of nalbuphine or ketamine prior to the discontinuation of sevoflurane-based anaesthesia and the incidence and severity of EA were compared.

2. Methodology

After institutional ethical approval (FMASU MS 160/2021) and parent or legal guardian of the child's informed consent, 90 children aged 4–10 years were included in this double-blind, randomized study from March to June 2021, at Ain Shams University Hospital's.

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All the children were either of American Society of Anesthesiologists (ASA) class I or II and were scheduled for tonsillectomy with or without adenoidectomy. NCT05176119 is the Clinical Trials.gov ID assigned to this study.

Children who had physical developmental delays, preoperative agitation, or parent refusal were not included in the study. The research used double blinding (both the parent and the investigator).

Patients were divided into three groups with the same characteristics using a computer-generated randomization table: The N group received 0.1 mg/kg of nalbuphine intravenously, the K group received 0.25 mg/kg of ketamine intravenously, and the S group received an equivalent volume of normal saline The N group received 0.1 mg/kg of nalbuphine intravenously, and the K group received 0.25 mg/kg of ketamine intravenously. A research nurse who was not involved in the study prepared sealed, opaque, and numbered envelopes that contained the group assignments. Local operating room (OR) pharmacy doctor was then informed by group allocation who then prepared either study drugs in 10 ml syringes and handed them to anesthesiologist in charge. Both the parent and the attending anesthesiologist were blinded to study drugs. The same team performed all surgical procedures; anesthesia was delivered according to standard protocol for Adenotonsillectomy for pediatric patients to minimize operative and anesthetic variables.

2.1. Anesthetic technique

Prior to surgery, patients fasted for 2 h for clear liquids and 6 h for solids. Each patient was observed in the OR for heart rate (HR), electrocardiogram (ECG), SPO2, noninvasive blood pressure, and end tidal carbon dioxide (ETCO2) upon entry. For all children, general anaesthesia was induced using 100% oxygen, fresh gas flow of 6 l/min, and sevoflurane at increments of 1% per breath up to 8%. An intravenous cannula was inserted once the proper level of anaesthesia had been achieved, and 10 ml/kg of 0.45 half normal saline (5 ml dextrose 5% mixed with 5 ml normal saline) was then administered, followed by standard maintenance fluids. The patients received (12.5–25) mg diclofenac sodium suppository according to body weight after adequate depth of anaesthesia, endotracheal tube insertion, and sevoflurane concentration reduction to 3% in 100%. When ETCO2 was below 50 mmHg, spontaneous breathing was allowed; otherwise, patient was taken out of study and given mechanical ventilation.

Following the administration of the study medication, sevoflurane was discontinued and oxygen flow was increased to 8 l/min. Patients were transported to post-anesthesia care unit (PACU) in a quiet, warm environment without stimulation after extubation.

The time of extubation defined as T0 and time of arrival at the PACU defined as T1 were calculated. Assessment of agitation was done at time 0 and time 1 and every 5 min for 30 min for occurrence of agitation according to the 5-step EA Scale [5] as a primary outcome, Score of 5 for more than 3 min was considered as EA and midazolam was given at 0.1 mg/kg intravenously as a rescue management, then patients were reassessed after 5 min and given the same dose if the score persisted. The following parameters were assessed as secondary outcomes:

(1) Occurrence of post-operative pain using Modified Children's Hospital of Eastern Ontario Pain Scale (mCHEOPS) [6]. Cut off value of the score to give analgesia is 8 or more, it is considered that agitation usually is caused by pain and it is an association that require management of both. However, mild pain despite being assessed as pain, yet it was managed by reassurance Score >8 however was managed by paracetamol 15 mg/kg before assessment of agitation. Narcotics was not given because it would confound the results.
(2) Number and timing and total dose of midazolam given for emergence agitation.
(3) Occurrence of postoperative nausea and vomiting, laryngeal spasm, post-tonsillectomy bleeding.
(4) Duration in PACU and time to hospital discharge.

The sample size was calculated using Minitab (2016) (Version 16. Minitab Incorporation, State College). Assuming that the incidence of postoperative sevoflurane agitation is about 30%, a sample size of 28 patient in each group is required to demonstrate a difference of at least 25% in that incidence with a power of 0.8 and a one-tailed significant level of 0.05. Sample size was rounded up to 30 cases in each group to compensate for any dropouts.

3. Statistical methods

Results were presented as means ± SD or number (percent). ANOVA was used to compare parameters in the three groups. Chi-square test compared categorical data. The data were deemed significant if the p-value was 0.05 or less and highly significant if < 0.01. SPSS was used for statistical analysis.

4. Results

Ninety cases (34 girls and 56 boys) aged 4–10 were included, 30 cases (11 girls and 19 boys) in S-group, 30

Table 1. Demographic data.

Demographic data	K (n :30)	N (n :30)	S (n :30)	P-value
Age	5.6 ± 1.32	5.7 ± 1.3	5.6 ± 1.36	0.059292
Sex	16 males (53.3%) 14 females (46.7%)	21 males (70%) 9 females (30%)	19 males (63.3%) 11 females (36.7%)	0.617
Weight	18.9 ± 2.91	19.1 ± 3	18.5 ± 3.6	0.090
ASA	21 (70%) ASA I 9 (30%) ASA II	24 (80%) ASA I 6 (20%) ASA II	22 (73.3%) ASA I 8 (26.7%) ASA II	0.424
Anesthesia duration (min)	37.9 ± 2.7	38.1 ± 2.9	38.4 ± 2.8	0.026171
Surgery duration (min)	23.3 ± 3.3	23.9 ± 3.1	23.5 ± 3.8	1.000
Duration in PACU (min)	30 ± 5.8	31 ± 4.9	39 ± 7.6	0.011

Values are in numbers and percentage or mean ± SD, P-value >0.05: Nonsignificant; if < 0.05: Significant; if < 0.01: Highly significant.

(14 girls and 16 boys) in K-group, and 30 (9 girls and 21 boys) in N-group (Table 1).

Three groups had non-significant differences regarding age, weight, ASA physical status, and anesthesia duration.

The S-group had more agitated children than K- or N-groups. At all times, more group-K cases developed agitation than group-N cases, but the difference reached significant at 15 min (Figure 1) (*p* value 0.025).

The S-group had more crying and thrashing children (score of 5) than the other two groups (one-third of the cases). In N group, only one patient (3.3%) was crying at 5 min and another one (3.3%) at 15 min and the result is significantly better than that demonstrated in S group (all times) where five children (16.7%) were crying at 10 min, three children (10.0%) at 20 min, and two children (6.7%) at 30 min and in K group three children (10.0%) at 20 min and two children (6.7%) at 30 min.

More cases in S group were given midazolam as rescue medication for agitation (6 as first dose 4 as second dose) and K group (4 as first dose and 1 as second dose) vs N group (2 as first dose only) (both p-value <0.05). Most of these rescue medications were given from 10 to 20 min (Figure 2).

Pain as a secondary outcome of this study, it was assessed by mCHEOPS score and it was significantly decreased in nalbuphine in comparison to ketamine and saline groups (Group N, 2 (6.6%) Group K, 6 (20%), and Group S, 11 (36.6%), $P = 0.001$) (Table 2).

In the PACU, nausea and vomiting were reported in 2, 3, and 2 children of the S group, K group, and

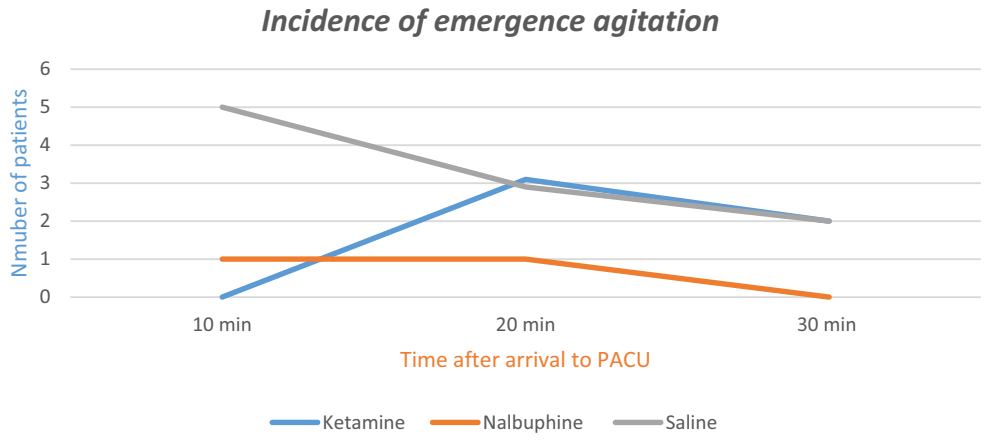

Figure 1. Incidence of EA between groups using emergence agitation scale.

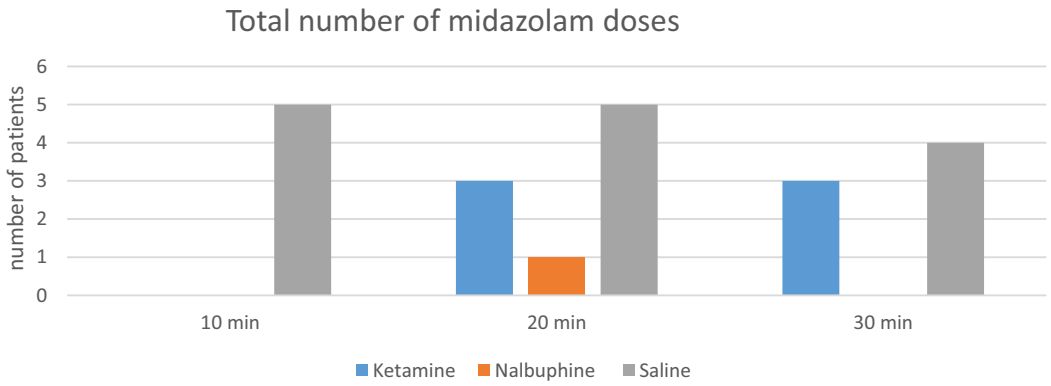

Figure 2. Number of patients who received midazolam in each group.

Table 2. Frequency and timing of postoperative pain using mCHEOPS.

Time	K (n :30)	N (n :30)	S (n :30)	P value
0–10 min	1 (3.3%)	0 (0%)	5 (16.6%)	0.012
10–20 min	2 (6.6%)	1 (3.3%)	3 (10%)	0.030
20–30 min	3 (10%)	1 (3.3%)	3 (10%)	0.211
0–30 min	6 (20%)	2 (6.6%)	11 (36.6%)	0.001

Values are in numbers and percentage, P-value >0.05: Nonsignificant if < 0.05: Significant; if < 0.01: Highly significant.

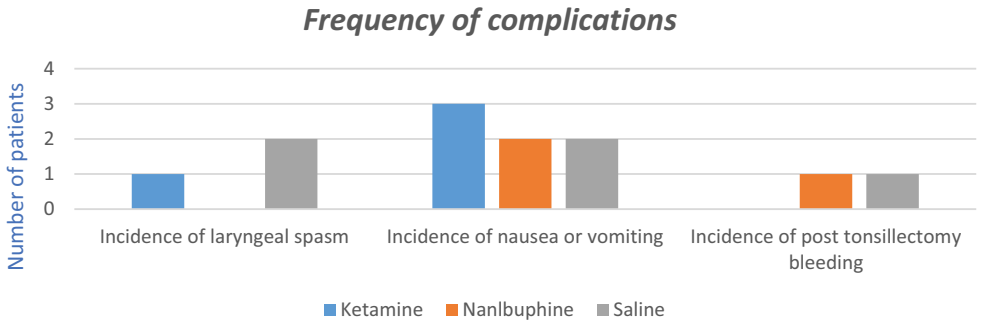

Figure 3. Number of patients that happen to have complication in each group namely incidence of laryngeal spasm, nausea and vomiting, and post tonsillectomy bleeding.

N group, respectively (difference not significant), 2 cases experienced laryngeal spasm in S group and 1 case in group of ketamine 1 min after extubation, 1 patient experienced post tonsillectomy bleeding in S group and 1 patient in nalbuphine group. No group had any other clinically relevant side effects (Figure 3).

All cases from K and N groups were leaved from hospital in >3 h (1.7 ± 0.50 and 1.5 ± 0.52, respectively, versus 2.2 ± 1.32 in S group) after leaving the PACU. Five S-group cases stayed 3–6 h due to agitation.

5. Discussion

In this research, the incidence and severity of EA in children undergoing tonsillectomy with or without adenoidectomy were compared after giving one dose of either nalbuphine or ketamine before sevoflurane-based anesthesia end. It was discovered that these effects were significantly different from the saline group with nalbuphine and ketamine ($p = 0.004$). Because of the clinical picture that postoperative pain shares with EA/emergence delirium, it has proven to be the most confusing factor when determining a child's behavior after emergence. Agitation may be brought on by inadequate pain relief, especially following quick surgical procedures where the peak analgesic effects may not be felt until the child is fully awake [7].

When used in small doses, ketamine and nalbuphine can both produce mild to moderate safe sedation. We investigated whether giving these sedatives before stopping sevoflurane anaesthesia would speed patient awakening and significantly reduce emergence agitation. Three patient groups had similar emergence conditions after sevoflurane cessation and the same anaesthesia duration.

In a line with our finding, Dalens et al. [8] concluded that intravenous nalbuphine at 0.1 mg/kg at the end of the procedure had the highest benefit/risk ratio when sevoflurane was the sole anaesthetic.

Previous studies demonstrate that nalbuphine 0.1 mg/kg given to pediatric cases after an MRI under sevoflurane anaesthesia decreased EA more than ketamine [8]. Similarly, nalbuphine 0.1 mg/kg given to children 5 min prior to conclusion of a cochlear implant procedure under sevoflurane anaesthesia was superior to propofol 1 mg/kg in reducing frequency and severity of EA [9]. Nalbuphine 0.1 mg/kg given after strabismus surgery in children under sevoflurane anaesthesia reduced EA, but propofol did not [10].

However, earlier research examined the effects of caudally administered nalbuphine on EA frequency and severity in children after sevoflurane anaesthesia. These studies found that nalbuphine either significantly increased or had no effect on emergence time [11]. Albuphine delayed emergence, but PACU stay did not increase, which aimed to remove the potential confounding influence of caudally administered nalbuphine on emergence time.

Ketamine has reportedly been shown to stop EA brought on by inhalation anaesthetic agents [12]. Children received 6 mg/kg of oral ketamine 30 min prior to having their tonsils removed under desflurane anesthesia, and Kararmaz et al. discovered that this decreased incidence of EA from 56% to 18% [12]. Dalens et al. [8] observed that children who received 0.25 mg/kg of ketamine intravenously at end of MRI procedures while under sevoflurane anaesthesia had a lower incidence of EA (12% vs 36% in control) [8]. Dalens et al. [8] showed that nalbuphine group's changes in vital parameters such as HR, MAP, and SPO2 were not statistically significant. Furthermore, Ozcan

et al. [13] found no significant changes in vital parameters between the ketamine and midazolam groups.

Andrew et al. [14] showed that a single low dose (<0.5 mg/kg) to moderate dose (≥0.5 mg/kg) of ketamine as an adjunct analgesic before the end of surgery lowers the postoperative pain score.

Schmitz and colleagues' findings were at odds with our results because they demonstrated that ketamine increased EA in children who'd undergone total intravenous anaesthesia (propofol) or inhalation anaesthetic agent anaesthesia (sevoflurane) [15].

One theory is that inhalational anaesthetics change the ratio of neuronal synapse excitation to inhibition, causing more emergence agitation than total intravenous anaesthesia [16].

Due to the analysis of total intravenous and inhalational anaesthetic agents, it may be difficult to determine ketamine's benefits. Excluding the two studies that used both inhalational and total intravenous anaesthetic agents from the sensitivity analysis, the ketamine group had lower emergence agitation, smaller confidence intervals, and less heterogeneity [17].

The incidence of PONV was low in this research, and postoperative respiratory depression, hypotension, and bradycardia were not clinically significant. Nalbuphine exhibits antagonist activity at receptors, which could account for its diminished propensity to induce nauseousness, vomiting, and psychostimulatory effects.

Using the MCHEOPS scale for postoperative pain [18], according to our findings, postoperative pain score was significantly higher in saline group (11%) in relation to nalbuphine group (2%) and the ketamine group (6%). Similar to our findings, Nan Zhao et al. found that Group N had lower postoperative pain scores than Group S.

6. Limitations

Some patients underwent tonsillectomy while others underwent adenotonsillectomy may have had an impact on the incidence of EA, which is one of the potential weaknesses of our study. Another significant drawback was the absence of long-term follow-up following discharge.

Despite finding no differences between the three groups, post-hospitalization nausea and vomiting due to nalbuphine's dual opioid agonist/antagonist action could be serious.

7. Conclusion

Among children undergoing sevoflurane anaesthesia, this study found that nalbuphine (0.1 mg/kg) and ketamine (0.25 mg/kg) were equally effective in reducing the risk of EA.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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