



# Effect of Remifentanil on Postoperative Vomiting After Strabismus Surgery in Preschool Children: A Prospective Randomized Controlled Trial

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## Abstract

**Background:** Strabismus surgery and the use of opioid are risk factors of postoperative vomiting. We evaluated whether there is a dose-dependent effect of remifentanil on the incidence of postoperative vomiting.

**Methods:** Sixty pediatric patients who were scheduled for strabismus surgery were enrolled. Patients were randomly divided into three groups; Group H (high-dose remifentanil group), Group L (low-dose remifentanil group), and Group C (control group). After endotracheal intubation, patients in the Group H and L received an intravenous bolus dose of remifentanil of 1.0  $\mu\text{g}/\text{kg}$  and 0.5  $\mu\text{g}/\text{kg}$  over 2 min, respectively. Group H and L patients received a continuous infusion of remifentanil (0.1  $\mu\text{g}/\text{kg}/\text{min}$ ) during the surgery. The patients in Group C did not have any dose of remifentanil. Intravenous fentanyl (1  $\mu\text{g}/\text{kg}$ ) was administered to the patients for postoperative pain control.

**Results:** The primary outcome was a difference of the incidence of postoperative vomiting within 24 hours after surgery. There was no significant difference in incidence of postoperative vomiting between three groups. The degree of emergence agitation and postoperative pain did not show any significant difference between three groups.

**Conclusions:** The intraoperative administration of remifentanil did not show dose-dependent effect on postoperative vomiting in pediatric strabismus surgery.

**Keywords:** Children, Postoperative Vomiting, Remifentanil, Strabismus Surgery

## 1. Background

Postoperative nausea and vomiting (PONV) are common adverse events in the postoperative period. Several factors affect occurrence of postoperative vomiting (POV) (1). Pediatric strabismus surgery is associated with a high incidence of POV (2).

Remifentanil is an ultra-short-acting opioid. Context sensitive half time (CSHT) of remifentanil is 3 - 4 minutes, and it is independent of infusion duration. It is known that the use of fentanyl leads to increase the incidence of POV (3). The association between different doses of remifentanil and the incidence of POV has not been sufficiently evaluated. Therefore, this study aimed to evaluate whether different doses of remifentanil affect POV in pediatric strabismus surgery.

The primary outcome was a difference of the incidence of POV within 24 hours after surgery between different remifentanil dosage. The secondary outcome was the de-

gree of emergence agitation and postoperative pain between three groups.

## 2. Methods

This study was approved by the institutional review board of Haeundae Paik Hospital (protocol number:129792-2015-024) and registered at <https://clinicaltrials.gov> (protocol number: NCT02455401). This study was performed in accordance with the principles stated in the Declaration of Helsinki. Written informed consent was obtained from the parents of pediatric patients.

Sixty-preschool children who underwent strabismus surgery from May 2015 to November 2016 were included in this study. Patients who did not want to participate in the study, patients with a history of POV and motion sickness, and patients who received anti-emetics within 24 hours before surgery were excluded. Assigned patients were ran-

domly divided into three groups; Group H, Group L, and Group C. Midazolam (0.1 mg/kg) was intravenously administered to the patients at waiting room. After the patients had entered the operating room, standard monitoring was applied. During face mask ventilation with an oxygen flow of 6 L/min, general anesthesia (GA) was induced with intravenous administration of atropine (0.01 mg/kg), lidocaine (1 mg/kg), propofol (2 mg/kg) and rocuronium (0.6 mg/kg). Endotracheal intubation was done and anesthesia was maintained using sevoflurane. The patients in the Group H and Group L received an intravenous bolus dose of remifentanyl of 1.0  $\mu\text{g}/\text{kg}$  and 0.5  $\mu\text{g}/\text{kg}$  over 2 min, respectively. After that, continuous infusion of remifentanyl (0.1  $\mu\text{g}/\text{kg}/\text{min}$ ) was administered to the patients during surgery. The patients in Group C did not have any dose of remifentanyl. The administration of sevoflurane was discontinued at the end of the surgery, and fentanyl (1  $\mu\text{g}/\text{kg}$ ) was intravenously administered to the patients.

The incidence of POV was evaluated within 24 hours after the completion of the surgery. If nausea persisted in a patient even after the patient had vomited, 0.1 mg/kg of metoclopramide was intravenously administered to the patient.

Emergence agitation (evaluated using the Pediatric Anesthesia Emergence Delirium [PAED] Scale)(4), and postoperative pain (evaluated using the Faces Pain Scale [FPS] score)(5) were evaluated after endotracheal extubation; 0, 20, 40, and 60 min after extubation at the post-anesthetic care unit (PACU). Intravenous ketorolac (1 mg/kg) was administered to patients who had severe emergence agitation (4) or severe postoperative pain (FPS score  $\geq$  5). If emergence agitation in a patient did not subside even after ketorolac had been administered to the patient, 0.5  $\mu\text{g}/\text{kg}$  of fentanyl was intravenously administered to the patient.

Systolic BP and HR were recorded after the patients had entered the operating room (T1), after the induction of GA (T2), after endotracheal intubation (T3), 2 min after bolus injection of remifentanyl (T4), after the start of surgery (T5), 10 min after the start of the continuous infusion of remifentanyl (T6), 20 min after the start of the continuous infusion of remifentanyl (T7), 30 min after the start of the continuous infusion of remifentanyl (T8), and after endotracheal extubation (T9). When the oculocardiac reflex (OCR; defined as a 15% decrease in HR as compared to baseline HR) occurred, we requested to stop the surgery and injected intravenous atropine (0.01 mg/kg) if the OCR lasted for more than 5 seconds.

The sample size for this study was determined based on the findings of a previous study (6). The number of patients was calculated for reducing the incidence of POV

from 49% to 10%. For a power of 80% and significance level of 0.05, we found that 18 patients would be needed for each group. We calculated 20 patients would be needed for each group including a dropout rate of 10%. Information regarding the baseline parameter values and clinical characteristics for each patient were summarized through descriptive statistics. After a descriptive analysis had been performed, in order to identify differences among the three groups, the chi-squared test or Fisher's exact test was used for the analysis of categorical variables, and analysis of variance (ANOVA) or the Kruskal-Wallis was used for the analysis of continuous variables. Normality testing was carried out using the Shapiro-Wilk test. Repeated measures ANOVA (RM-ANOVA) was used to compare the groups and repeated measurements within each group, and the Bonferroni correction was used for a post hoc analysis. When sphericity could not be assumed, RM-ANOVA was used with the Huynh-Feldt correction. In this study, for each statistical analysis, version 25.0 of IBM® SPSS® Statistics was used (IBM, Armonk, NY, USA). With respect to hypothesis testing, P values  $<$  0.05 were considered statistically significant.

### 3. Results and Discussion

The demographic characteristics of the patients have been described in Table 1. There were significant differences in the heights of the patients ( $P = 0.036$ ); the post hoc analysis showed that the patients in Group H were taller than those in Group C. There were also significant differences in operation times ( $P = 0.039$ ); the post hoc analysis revealed that the operative time for the patients in Group C was longer than that for the patients in Group H.

The incidence of POV in the three groups did not significantly differ (Group H = 5%, Group L = 5%, and Group C = 10%,  $P = 1.000$ ). The overall incidence of POV was 6.7% ( $n = 4/60$ ). Metoclopramide had been intravenously administered to two patients in Group C and Group H. The cumulative dose of remifentanyl was 124.9 (interquartile range [IQR]; 104.3 - 198.0  $\mu\text{g}$ , 114.4 (IQR; 101.8 - 137.4)  $\mu\text{g}$ , and 0  $\mu\text{g}$  in Group H, L and C, respectively ( $P <$  0.00001).

There were no significant differences of PAED Scale and FPS score among the three groups ( $P >$  0.05). The three groups also did not significantly differ with respect to the total dose of ketorolac and fentanyl. The percentage of children with received intravenous ketorolac administration was 15%, 5%, and 10% in Group H, L and C, respectively ( $P = 0.57$ ). Also, the percentage of children with fentanyl was 0%, 5%, and 0% in Group H, L, and C, respectively ( $P = 0.56$ ).

There was no statistically significant difference of systolic BP among the three groups ( $P = 0.572$ ). In addition,

**Table 1.** Patients' Baseline Characteristics<sup>a</sup>

Variable	Group C (N = 20)	Group L (N = 20)	Group H (N = 20)	P Value	Post Hoc <sup>b</sup>
Age (year)	4.95 ± 1.15	5.25 ± 1.07	5.20 ± 1.11	0.618 <sup>c</sup>	
<b>ASA classification</b>				0.361 <sup>d</sup>	
I	20	19	20		
II	0	1	0		
<b>Sex</b>				0.215 <sup>d</sup>	
Male	4	8	9		
Female	16	12	11		
<b>Height</b>	108.73 ± 10.41	112.33 ± 8.74	116.25 ± 7.43	0.036 <sup>e</sup>	Group H > Group C
<b>Weight</b>	19.41 ± 4.96	20.86 ± 4.48	22.58 ± 4.63	0.054 <sup>c</sup>	
<b>DOS (min)</b>	46.75 ± 18.16	41.75 ± 11.27	35.75 ± 8.78	0.039 <sup>c</sup>	Group C > Group H
<b>DOA (min)</b>	89.75 ± 20.49	82.25 ± 14.64	77.25 ± 13.13	0.135 <sup>c</sup>	
<b>Time to extubation (min)</b>	20.75 ± 7.12	18.50 ± 7.09	18.75 ± 8.25	0.616 <sup>c</sup>	
<b>Type of surgery</b>					
Recession	19 (95.0)	17 (85.0)	19 (95.0)	0.603 <sup>f</sup>	
Transposition	4 (20.0)	3 (15.0)	1 (5.0)	0.505 <sup>f</sup>	
Myomectomy	1 (5.0)	2 (10.0)	1 (5.0)	1.000 <sup>f</sup>	
Advancement	0 (0.0)	1 (5.0)	0 (0.0)	1.000 <sup>f</sup>	
<b>No. of muscles repaired</b>				0.216 <sup>f</sup>	
1	8	13	13		
2	10	7	7		
3	2	0	0		

Abbreviations: ANOVA, analysis of variance; ASA, American Society of Anesthesiologist; DOA, duration of anesthesia; DOS, duration of surgery.

<sup>a</sup> Shapiro-Wilk's test was employed for test of normality assumption.

<sup>b</sup> For post-hoc pairwise comparison for categorical variables, Scheffe's or Dunn's method was applied to adjust significance level of alpha due to the multiple testing.

<sup>c</sup> By Kruskal-Wallis test.

<sup>d</sup> By chi-square test.

<sup>e</sup> By ANOVA.

<sup>f</sup> By Fisher's exact test.

there was no difference of HR between three groups except for the T9 time point, which is the time after endotracheal extubation; the post hoc analysis showed that the HR of the Group L patients were higher than those of the Group C patients ( $P = 0.025$ ). The OCR occurred in only two patients of Group L.

This study showed that intraoperative remifentanyl administration had no dose-dependent effect on the incidence of POV after pediatric strabismus surgery. The severity of emergence agitation and postoperative pain also did not significantly differ according to dosages of remifentanyl.

There are several articles that have studied POV and intraoperative opioid use in pediatric populations. When comparing remifentanyl and alfentanil, there was no significant difference between the incidence of POV (31% vs. 26%) in strabismus surgery (7). Comparing the groups

with and without remifentanyl under desflurane anesthesia, the incidence of POV was not different even though the administration of desflurane was different (8). Oh et al. (9) evaluated the incidence of PONV after pediatric strabismus surgery with sevoflurane or remifentanyl-sevoflurane, both using 50% N<sub>2</sub>O/O<sub>2</sub>. The authors found that combining remifentanyl with sevoflurane did not further increase the incidence of PONV. Intraoperative use of fentanyl leads to increase the occurrence of POV (3). On the other side, intravenous fentanyl (1 µg/kg) administration before end of surgery reduced agitation from 63.3% to 36.7% after sevoflurane anesthesia in children (10). Emergence agitation as well as POV are common in pediatric strabismus surgery (11). Therefore, the patients had an intravenous administration of fentanyl for reducing of emergence agitation in this study.

Several factors could have caused the low incidence

(6.7%) of POV. The patients with a history of POV and motion sickness had been excluded. A history of previous vomiting is a major risk factor for reoccurrence of POV (2,12). And, nitrous oxide was not used during GA in this study. The use of nitrous oxide has been reported to be a strong risk factor for POV (12) and avoiding the use of nitrous oxide can reduce the risk of PONV (13). The use of midazolam, which was administered to the patients included in this study for the reduction of separation anxiety, is known to cause a decrease in the occurrence of POV in children after strabismus surgery (14). Due to the short CSHT of remifentanyl (15), it is highly probable that the blood level of remifentanyl was very low in children after an average extubation time of 19.3 min in our study.

It is not easy to separate emergence agitation from postoperative pain. So, the management of postoperative pain is recommended to reduce emergence agitation in pediatric patients (16). Intervention of intravenous fentanyl was effective for reducing of emergence agitation than non-intravenous fentanyl (17). Greater than 0.25 mcg/kg/min of remifentanyl infusion rate are associated with higher tolerance, and above than 0.2 mcg/kg/min are characterized by lower pain thresholds (18). Infusion rate of 0.1 mcg/kg/min of remifentanyl seems to avoid tolerance and hyperalgesia problems in this study.

The present study has some limitations. First, we did not use intravenous anesthesia because there is no commercially available flexible open target-controlled infusion pump in our hospital. Second, the three groups of patients differed with respect to the heights of the patients and durations of surgery for the patients. There was a delay from the start of anesthesia to the start of the surgery because surgeon's condition. The duration of remifentanyl infusion was not significantly different between three groups. There is an interesting study on dexmedetomidine, as a non-opioid agent and ginger, as a non-pharmaceutical agent in recent studies (11, 19). Researches about PONV has been studied for a long time, but it is still an unknown area. In the future, more research is needed with a new design.

#### 4. Conclusions

The intraoperative use of remifentanyl did not have dose-dependent effect on POV in pediatric patients undergoing strabismus surgery. Increasing dosage of remifentanyl did not further increase the incidence of POV and decrease the severity of emergence agitation and postoperative pain. Intraoperative remifentanyl infusion combining

prophylaxis atropine can help to maintain stable hemodynamic GA.

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#### Footnotes

**Authors' Contribution:** Study design: Ki Hwa Lee and Hyun-Seong Lee; Data collection: Hyun-Seong Lee and Byeongcheol Lee; Analysis of data: Sung Hyun Shin and Daeseok Oh; Preparation, review and approval of the manuscript: Hyun-Seong Lee, Ki Hwa Lee and Yei Heum Park.

**Clinical Trial Registration Code:** NCT02455401 (<https://clinicaltrials.gov>)

**Conflict of Interests:** There is no conflict of interests.

**Data Reproducibility:** The data presented in this study will be available to the reviewers or the EIC upon their request as a part of the review process.

**Ethical Approval:** This study was approved by the institutional review board of Haeundae Paik Hospital (protocol number: 129792-2015-024).

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**Informed Consent:** Written informed consent was obtained from the parents of pediatric patients.

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