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Effect of Timing of Intravenous Fentanyl Administration on the Incidence of Posttonsillectomy Nausea and Vomiting

Hye Jin Kim, MD; Min-Soo Kim, MD, PhD; Ha Yan Kim, MS; Wyun Kon Park, MD, PhD; Won Shik Kim, MD, PhD; Sungmi Kim, MD; Hyun Joo Kim, MD, PhD

Objective/Hypothesis: Fentanyl is commonly administered toward the end of tonsillectomy to prevent emergence delirium and reduce postoperative pain. However, it can delay emergence from anesthesia and increase the risk of postoperative nausea and vomiting (PONV). The goal of our study was to compare the risk of PONV based on the timing of fentanyl administration at the end of tonsillectomy in children.

Study Design: Prospective, double-blind, randomized controlled trial.

Methods: One hundred forty patients aged 3 to 7 years undergoing tonsillectomy were divided into two groups. Fentanyl (1 μg/kg) was administered at the end of surgery in group 1 (n = 70) and at 10 to 15 minutes before the end of surgery in group 2 (n = 70). Time to regular breathing and time to emergence from anesthesia were measured from the end of surgery. PONV and pediatric anesthesia emergence delirium scale scores were assessed every 10 minutes after admission to the anesthesia care unit.

Results: Incidences of PONV (2.9% vs. 2.9%, P > .99) and emergence delirium (11.4% vs. 5.7%, P = .23) were not significantly different between the two groups. Time to regular breathing (mean difference = 2.3 minutes; 95% confidence interval [CI]: 0.9 to 3.7 minutes) and time to emergence (median difference = 6.5 minutes; 95% CI, 2.5 to 10.5 minutes) were significantly longer in group 1 than in group 2.

Conclusions: Although there was no beneficial effect on PONV, recovery of regular breathing and consciousness was quicker with earlier fentanyl administration. Emergence delirium was well-controlled, similar to that with fentanyl administration at the end of surgery.

Key Words: Postoperative nausea and vomiting, fentanyl, tonsillectomy, emergence delirium, pain, postoperative.

Level of Evidence: 1b

INTRODUCTION

Adenoidal tonsillectomy is one of the most common otorhinolaryngology surgeries performed worldwide in the preschool age group1 and is associated with a high incidence (40%–60%) of emergence delirium (ED)2,3 and severe postoperative pain, resulting in slower turnover times and increased burden of patient care4 in the postanesthesia care unit (PACU). Additionally, crying accompanied by ED and pain after tonsillectomies may induce bleeding from the surgical site, resulting in difficult situations such as hypotension, hypoxemia, and difficult airway.5

For these reasons, fentanyl is commonly used in tonsillectomies,6,7 However, the administration of fentanyl is associated with an increased incidence of postoperative nausea and vomiting (PONV),2,3,8 which occurs in a dose-dependent manner by the activation of the mu-opioid receptor in the chemoreceptor zone and the direct stimulation of the vestibular apparatus.9 Moreover, delayed recovery from anesthesia is another cause for concern.

Some previous studies demonstrated that compared with fentanyl, short-acting opioids such as remifentanil and alfentanil reduced the incidence of PONV and induced faster recovery because of rapid systemic elimination.10,11 In contrast, in some studies, short-acting opioids did not reduce the incidence of PONV.12,13 However, the above studies compared different opioids. Comparing equipotent doses of different opioids for pain does not necessarily imply that PONV can be effectively compared as well. Therefore, a study using a single drug could explain the relationship more clearly than a comparison performed using plasma concentrations of different drugs. A recent meta-analysis suggested that the earlier administration of fentanyl reduces the incidence of PONV and also optimally controls ED.14

In this prospective randomized controlled trial, an extension of the aforementioned meta-analysis, we aimed...
to investigate the effect of the timing of fentanyl administration on PONV incidence in children undergoing tonsillectomy. We hypothesized that fentanyl administration at 10 to 15 minutes before the end of surgery would reduce the incidence of PONV compared with that at the end of surgery. The primary outcome was the incidence of PONV. Secondary outcomes were the incidence and severity of ED and time taken for recovery from anesthesia.

**MATERIALS AND METHODS**

**Study Design**

This prospective, double-blind, randomized study was performed at Severance Hospital, Yonsei University Health System, Seoul, Korea in accordance with the Declaration of Helsinki, and it was approved by the institutional review board (IRB) of Severance Hospital, Yonsei University Health System, Seoul, Korea (IRB no. 4-2017-0813, October 23, 2017) and registered at ClinicalTrials.gov (number: NCT03343002). Written informed consent was obtained from the parents. Pediatric patients aged 3 to 7 years with American Society of Anesthesiologists class I–II scheduled for tonsillectomy with or without adenoidectomy from November 2017 to August 2018 were included in the study. Patients with developmental disorders, cognitive impairment, cerebral palsy, history of seizures except simple febrile convulsions, anticipated difficult airway, upper respiratory infections, and a history of adverse reactions to fentanyl were excluded.

After patients were enrolled, an anesthesiologist who was not involved in the administration of anesthesia during the surgery performed the group assignment according to random allocation using a random number generator in Microsoft Excel 2016 (Microsoft, Redmond, WA) with a fixed block size of 4 and a 1:1 ratio. All patients were assigned to one of the following two groups according to the timing of fentanyl administration: group 1, fentanyl administration at the end of surgery; group 2, fentanyl administration 10 to 15 minutes before the end of surgery. The same anesthesiologist labeled the 2-mL syringes as 1 and 2. Each syringe labeled 1 and 2 contained fentanyl 1 μg/kg or an equivalent amount of saline according to the random table. The surgeon, patient, anesthesiologist who administered anesthesia for tonsillectomy, and anesthesiologist who examined the patient in PACU were blinded to the randomization order.

Patients were not premedicated before entering the operating room. All patients were monitored using devices, including a three-lead electrocardiography monitor, noninvasive blood pressure monitor, and pulse oximeter. After the monitors were attached, glycopyrrolate 4 μg/kg was intravenously administered.

Anesthesia was induced with propofol 2 to 3 mg/kg and fentanyl 1 μg/kg. Endotracheal intubation was performed after achieving neuromuscular relaxation with atracurium 0.5 mg/kg or rocuronium 0.3 to 0.6 mg/kg. Before the start of surgery, dexmedetomidine 0.1 mg/kg was intravenously administered. Anesthesia was maintained using sevoflurane 2.0 vol% to 3.0 vol% with a fraction of inspired oxygen of 0.5. The quality of induction was evaluated as follows: 1) crying and needs restraint, 2) moderate fear and reassured with difficulty, 3) slight fear but reassured easily, and 4) asleep or calm or awake and cooperative, and accepting the mask. Fentanyl (0.5 μg/kg) was administered when the heart rate or systolic blood pressure increased by more than 30% during the surgery compared with the baseline value before the start of anesthesia induction, and the increase lasted more than 5 minutes.

When the surgeon informed the anesthesiologist that the surgery would end in 10 to 15 minutes, the medication contained in the syringe labeled 1 was intravenously administered. At the end of the surgery, the medication contained in the syringe labeled 2 was intravenously administered. The flow rate of oxygen was increased to 6 L/min, and the fraction of inspired oxygen was increased to 1.0; sevoflurane was discontinued. The time of the end of the surgery was defined as the time when the surgeon inserted the hemostatic pack and removed the mouth gag.

When the patients opened their eyes or made a purposeful movement and an appropriate tidal volume of more than 6 mL/kg was detected with regular breathing, tracheal extubation was performed after gentle suctioning of the oropharynx. After extubation, oxygen (8 L/min) was provided via a facemask. Time to regular breathing was defined as the time from the end of surgery to the detection of regular breathing with a tidal volume of 6 mL/kg. Time to extubation was defined as the time from the end of surgery to tracheal extubation. Time to emergence was defined as the time from the end of surgery to the first response to verbal command. If the patient did not respond to verbal commands in the operating room, the emergence time was evaluated at 5-minute intervals in the PACU.

The occurrence of PONV was recorded at 10-minute intervals in PACU. Nausea was defined as the feeling of the urge to vomit. Vomiting was defined as retching and any expulsion of liquid gastric contents. When the patient needed rescue medication for PONV, ondansetron 0.1 mg/kg was intravenously administered.

The Pediatric Anesthesia Emergence Delirium (PAED) Scale was used as the main tool to determine the severity and incidence of ED. In addition, the five-step Emergence Agitation (EA) Scale was used to evaluate the severity and incidence of ED. The PAED scale consisted of five items as follows: 1) makes eye contact with caregiver, 2) purposeful actions, 3) aware of surroundings, 4) restless, and 5) inconsolable. Items 1 to 3 were scored from 4 (not at all) to 0 (extremely), whereas items 4 and 5 were scored in the reverse order (from 0 to 4). The total scores ranged from 0 to 20. A total PAED scale score above 12 was considered as the presence of ED. The five-step EA Scale was scored as follows: 1) obtunded with no response to stimulus, 2) asleep but responsive to movement or stimulation, 3) awake and responsive, 4) crying, and 5) thrashing behavior requiring restraint. A five-step EA Scale score of more than 3 was considered as the presence of ED.

Postoperative pain was measured using the Face, Legs, Activity, Cry, Consolability (FLACC) Scale. If the FLACC Scale score was 4 or higher or if the patient complained of pain, additional fentanyl (0.5 μg/kg) was intravenously administered. If pain was not relieved, another additional dose of fentanyl (0.5 μg/kg) was administered. Vital signs, including heart rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation, as well as the evidence of side effects, such as airway obstruction, reintubation, desaturation, drowsiness, pruritus, hypotension, and bradycardia, were recorded in the operating room and PACU.

The patients were evaluated by the anesthesiologist at 30 minutes of PACU stay and were discharged from the PACU when the following criteria were satisfied: no bleeding, no PONV, pain scores less than 4 on the FLACC scale, stable vital signs, spontaneous eye opening, and modified Aldrete score of 9 or more. If the criteria for discharge from PACU were not met, PACU stay was extended until 60 minutes.

**Statistical Analysis**

The primary outcome measured was the incidence of PONV. Secondary outcomes were the incidence and severity of
ED and time to recover from anesthesia (time to regular breathing, extubation, and emergence). In a previous study, the incidence of PONV was 23.6% when fentanyl was administered at the end of tonsillectomy. Another study reported the incidence of PONV as 5% when fentanyl was administered at 10 minutes before the end of tonsillectomy. Assuming that the incidence of PONV according to the time of fentanyl administration would be different based on the results of the previous studies, we estimated that 63 patients per group would be required for an α of 0.05 and a power of 80%. Considering a dropout rate of 10%, 70 patients were enrolled in each group.

Data analysis was performed in patients who had records of PONV and ED. Continuous variables were analyzed using the two-sided t test or Mann-Whitney U test, with P < .05 considered statistically significant based on the results of the Shapiro-Wilk test for normality. Categorical variables were analyzed using the χ² test or Fisher exact test. Univariate logistic regression analysis was performed to assess the impact of rescue fentanyl on PONV and ED as a confounder. All analyses were performed using SPSS for Windows (version 23; IBM, Armonk, NY) and SAS (version 9.4, SAS Institute, Cary, NC). Intent-to-treat

Table 1: Preoperative Patient Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Group 1, n = 70</th>
<th>Group 2, n = 70</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean (SD)</td>
<td>5.4 (1.1)</td>
<td>5.2 (1.3)</td>
<td>0.2 (−0.2 to 0.6)</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>19 (27.1)</td>
<td>28 (40)</td>
<td>−13 (−28 to 3)</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
<td>115 (10)</td>
<td>115 (8)</td>
<td>0.1 (−2.8 to 3.0)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>22 (5)</td>
<td>21 (4)</td>
<td>0.4 (−1.1 to 2.0)</td>
</tr>
<tr>
<td>Induction quality, median (IQR)</td>
<td>3.0 (2.0–3.0)</td>
<td>2.0 (2.0–3.0)</td>
<td>1.0 (0.0 to 1.0)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD), median (IQR), or number of patients (percentage).

Intent-to-treat

Fig. 1 Flowchart of patient enrollment. Among 182 patients who were initially scheduled for tonsillectomy with or without adenoidectomy from November 2017 to August 2018 in the institution, 42 were excluded. Of the 42 patients who were excluded, 13 declined to participate, 14 did not meet the inclusion criteria, and 15 changed their surgery appointment. One hundred forty patients were randomized into two groups according to the timing of fentanyl administration as follows: group 1, fentanyl administration at the end of surgery and group 2, fentanyl administration at 10 to 15 minutes before the end of surgery.
RESULTS

In total, 182 patients were initially screened, and 140 patients completed the study (Fig. 1). There were no missing data or dropouts among the enrolled patients. Patient characteristics, including age, gender, height, and weight, were similar between the groups; group 1 had better induction quality than group 2 (Table I).

The duration of surgery and anesthesia and total fentanyl dose were not significantly different between the

<table>
<thead>
<tr>
<th>TABLE II.</th>
<th>Intraoperative Parameters and Anesthetic Profiles in the Operating Room.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of anesthesia, min, median (IQR)</td>
<td>65.0 (55.0–80.0)</td>
</tr>
<tr>
<td>Duration of surgery, min, mean (SD)</td>
<td>37.6 (16.7)</td>
</tr>
<tr>
<td>Total dose of fentanyl during anesthesia, μg, median (IQR)</td>
<td>46.0 (40.0–56.0)</td>
</tr>
<tr>
<td>Total dose of fentanyl during anesthesia, μg/kg, median (IQR)</td>
<td>2.0 (2.0–2.2)</td>
</tr>
<tr>
<td>Time to regular breathing, min, mean (SD)</td>
<td>14.9 (4.4)</td>
</tr>
<tr>
<td>Time to extubation, min, mean (SD)</td>
<td>16.4 (4.6)</td>
</tr>
<tr>
<td>Time to emergence, min, median (IQR)</td>
<td>24.5 (18.0–34.0)</td>
</tr>
<tr>
<td>Airway obstruction, no. (%)</td>
<td>2 (2.9%)</td>
</tr>
<tr>
<td>Reintubation, no. (%)</td>
<td>1 (1.4%)</td>
</tr>
</tbody>
</table>

Values are mean (SD), median (IQR), or number of patients (percentage).

<table>
<thead>
<tr>
<th>TABLE III.</th>
<th>Postoperative Data in the Postanesthesia Care Unit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of PONV, no. (%)</td>
<td>2 (2.9%)</td>
</tr>
<tr>
<td>PAED scale</td>
<td></td>
</tr>
<tr>
<td>Incidence of EA, no. (%)</td>
<td>8 (11.4%)</td>
</tr>
<tr>
<td>Mean score of PAED scale, median (IQR)</td>
<td>2.0 (0.0–4.0)</td>
</tr>
<tr>
<td>Maximum score of PAED scale, median (IQR)</td>
<td>3.5 (0.0–7.0)</td>
</tr>
<tr>
<td>Score at PACU admission, median (IQR)</td>
<td>4.0 (0.0–8.0)</td>
</tr>
<tr>
<td>Score at 10 minutes after PACU admission, median (IQR)</td>
<td>2.0 (0.0–4.0)</td>
</tr>
<tr>
<td>Score at 20 minutes after PACU admission, median (IQR)</td>
<td>2.0 (0.0–4.0)</td>
</tr>
<tr>
<td>Score at 30 minutes after PACU admission, median (IQR)</td>
<td>2.0 (0.0–4.0)</td>
</tr>
<tr>
<td>Five-step EA scale</td>
<td></td>
</tr>
<tr>
<td>Incidence of EA, no. (%)</td>
<td>11 (15.7%)</td>
</tr>
<tr>
<td>FLACC scale</td>
<td></td>
</tr>
<tr>
<td>Mean score, median (IQR)</td>
<td>1.5 (0.0–2.5)</td>
</tr>
<tr>
<td>Maximum score, median (IQR)</td>
<td>2.0 (0.0–4.0)</td>
</tr>
<tr>
<td>Length of PACU stay, min, median (IQR)</td>
<td>32.5 (30.0–37.0)</td>
</tr>
<tr>
<td>No. of patients who received rescue fentanyl in the PACU, no. (%)</td>
<td>3 (4.3%)</td>
</tr>
<tr>
<td>No. of patients who received rescue ondansetron in the PACU, no. (%)</td>
<td>2 (2.9%)</td>
</tr>
</tbody>
</table>

Values are mean (SD), median (IQR), or number of patients (percentage).

*Mean difference of normally distributed data and median difference of data not normally distributed were used as continuous variables. Risk difference was used as categorical variable.

CI = confidence interval; IQR = interquartile range; SD = standard deviation.

Analysis was performed even if the agent in the syringe labeled 1 was not administered exactly 10 to 15 minutes before the end of surgery owing to an inaccurate estimate by the surgeon. Numerical data are presented as means (standard deviation [SD]) if the data showed a normal distribution. If not, data are presented as medians (interquartile range [IQR]). Categorical variables are presented as numbers of patients and percentages. The risk difference and its 95% confidence interval (CI) are reported.
two groups (Table II). Time to regular breathing (mean [SD] = 14.9 [4.4] minutes vs. 12.6 [3.7] minutes, difference = 2.3 minutes; 95% CI: 0.9 to 3.7 minutes), extubation (mean [SD] = 16.4 [4.6] minutes vs. 14.1 [4.0] minutes, difference = 2.3 minutes; 95% CI: 0.8 to 3.7 minutes), and emergence (median [IQR] = 24.5 [18.0–34.0] minutes vs. 18.0 [14.0–26.0] minutes, difference = 6.5 minutes; 95% CI: 2.5 to 10.5 minutes) were significantly longer in group 1 than in group 2. Two cases of airway obstruction occurred in group 1 and one case in group 2. In the above three cases, immediately after extubation, chest expansion by spontaneous breathing was not adequate, and resistance was felt on manual ventilation via a mask with 30 to 40 cm H₂O positive pressure. In two cases, the resistance was reduced, and adequate chest expansion was restored with 10 positive pressure ventilations; ventilatory support with a mask was provided until the patients’ spontaneous respiration recovered. In one patient in group 1, in whom resistance did not decrease and adequate chest expansion was not restored, reintubation was performed.

All patients were discharged from PACU within 60 minutes of admission. The postoperative parameters in the PACU are shown in Table III. The incidence of PONV (2.9% vs. 2.9%, difference = 0%; 95% CI: -0.06% to 0.06%) was not significantly different between the two groups. The incidence of ED based on the PAED Scale (risk difference = 5.7%; 95% CI: -0.8% to 15%) or the five-step EA Scale and the mean and maximum PAED Scale scores were not significantly different between the two groups. There were no significant differences between the two groups with regard to the mean and maximum FLACC scale scores, length of PACU stay, occurrence of adverse events, vital signs, or fentanyl use in the PACU.

In the univariate analysis, the number of patients rescued with fentanyl during surgery and PACU stay showed no statistically significant correlation with PONV (P = .998 and .714, respectively) or EA occurrences (P = .999 and .585, respectively).

**DISCUSSION**

Fentanyl is widely used for postoperative pain after tonsillectomy, and it can reduce the incidence of ED. However, anesthesiologists are reluctant to use sufficient amounts of fentanyl owing to concerns about adverse effects such as delayed awakening, respiratory depression, and PONV. Considering the dose dependency of opioids and the fact that the most likely pathophysiology is mu-opioid receptor activation in the brainstem, the occurrence of PONV might be linked to the duration of action and the remnant effect of opioids. Thus, adjusting the timing of fentanyl administration might help prevent both ED and PONV. Therefore, in this study, the effects of fentanyl administration at two different timings were compared; however, we observed that the incidence of PONV was similar regardless of the time of fentanyl administration. Triggering of the vomiting reflex by a fentanyl-induced decrease in gastric motility is another possible mechanism of PONV occurrence. Further studies on the relationship between fentanyl concentrations in the plasma, brain, and other sites of action and PONV occurrence are needed.

The overall incidence of PONV in this study was as low as 3%. Dexamethasone and anesthetics that are free of nitrous oxide might have contributed to this result. Dexamethasone 0.1 mg/kg to 0.5 mg/kg is strongly recommended for children undergoing tonsillectomy because of its beneficial effects on pain and PONV but not in a dose-dependent manner. It achieves its effect through direct central action at the solitary tract nucleus, interaction with the neurotransmitter serotonin, anti-inflammatory effects, and reduction in opioid-related nausea and vomiting when used with opioids. In the study by Moss et al. reporting a similar incidence, more aggressive PONV prevention was achieved with dexamethasone 0.5 mg/kg and ondansetron 0.1 mg/kg as additional antiemetics, but nitrous oxide was used for anesthesia, which is a risk factor of PONV. PONV could be effectively prevented by dexamethasone, free of nitrous oxide, but further benefits can be expected by adding ondansetron.

In our study, the incidence of ED was not significantly different according to the timing of fentanyl administration. This result is consistent with the that of the meta-analysis by Kim et al. Fentanyl has a duration of action of 30 to 60 minutes for its potent analgesic effect and slight sedative effect. Therefore, even with administration at 10 to 15 minutes before the end of surgery, as in our study, pain reduction and effects on ED might be optimal. The suggested mechanisms by which fentanyl reduces the incidence of ED are through pain control, sedative effects, and a mu-opioid receptor–mediated depression of the hypothalamic hypocretin/orexin arousal system; however, the exact mechanism is unclear.

In addition to fentanyl, propofol prior to emergence and pre- or intraoperative dexmedetomidine have been reported to reduce the incidence of ED. Comparisons and identification of synergy as multimodal therapy will be valuable in future studies.

An interesting finding in this study was that the administration of fentanyl 10 to 15 minutes earlier allowed significantly quicker recovery of regular breathing and early extubation. Moreover, the time to emergence decreased by 7 minutes. Several studies have shown that the administration of fentanyl at the end of surgery delays awakening. Considering the turnover time in the operating room, this is a significant advantage for saving time and increasing efficiency in clinical practice, especially in ambulatory surgeries with operation times of <30 minutes.

Fentanyl has the undesired side effect of respiratory depression. In the study by Stoekel et al., minute ventilation could not reach normal levels within 25 minutes of administration of a 0.5-mg fentanyl bolus. Gelberg et al. reported that ventilation did not normalize after 15 minutes of a 1-μg/kg fentanyl bolus. This suggests that full recovery from ventilatory depression cannot be assumed when the patient is awakened around 15 minutes after the administration of fentanyl at the end of surgery. In our study, one patient in group 1 had a time to extubation of 16 minutes and had to be reintubated. However, no reintubation was required in
group 2. The results of our study cannot verify that earlier administration can reduce the incidence of reintubation because the incidence of reintubation was very low (1.4%). However, the significant difference in the time to recovery and the similar incidence of ED and pain scores between the two groups suggest that adequate plasma concentrations of fentanyl at emergence can be achieved by earlier administration of fentanyl, which ensures analgesia without clinically significant respiratory depression.

Our study had some limitations. First, there was no control group in which fentanyl was not used or nonopioid medications were used. The use of opioids for posttonsillectomy pain is the standard analgesic regimen in our center. Moreover, previous studies have shown that nonopioid medications do not reduce the degree of postoperative pain. Therefore, the administration of fentanyl at the end of surgery may result in quicker recovery of regular breathing and consciousness. ED and postoperative pain were well controlled, similar to when fentanyl was administered at the end of surgery. This finding is beneficial in short-duration ambulatory surgeries such as tonsillectomy.

Acknowledgments
The authors thank Dr. Park, Department of Otorhinolaryngology, Yonsei University, College of Medicine, for performing the surgeries.

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