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# Effects of remifentanil versus nitrous oxide on postoperative nausea, vomiting, and pain in patients receiving thyroidectomy

## Propensity score matching analysis

Min Kyoung Kim, MD, PhD, Myung Sub Yi, MD, Hyun Kang, MD, PhD, MPH*, Geun-Joo Choi, MD, PhD

**Abstract**

Remifentanil and nitrous oxide ($N_2O$) are 2 commonly used anesthetic agents. Both these agents are known risk factors for postoperative nausea and vomiting (PONV). However, remifentanil and $N_2O$ have not been directly compared in a published study. Remifentanil can induce acute tolerance or hyperalgesia, thus affecting postoperative pain. The objective of this retrospective study is to compare the effects of remifentanil and $N_2O$ on PONV and pain in patients receiving intravenous patient-controlled analgesia (IV-PCA) after thyroidectomy.

We analyzed the electronic medical records of 992 patients receiving fentanyl-based IV-PCA after thyroidectomy at Chung-Ang University Hospital from January 1, 2010 to April 30, 2016. We categorized the patients according to anesthetic agents used: group $N_2O$ (n=745) and group remifentanil (n=247). The propensity score matching method was used to match patients in the 2 groups based on their covariates. Finally, 128 matched subjects were selected from each group.

There were no differences between groups for all covariates after propensity score matching. The numeric rating scale for nausea (0.55±0.88 vs 0.27±0.76, $P$=0.01) was higher and complete response (88 [68.8%] vs 106 [82.8%], $P$=0.001) was lower in group $N_2O$ compared with group remifentanil on postoperative day 0. However, the visual analog scale score for pain (3.47±2.02 vs 3.97±1.48, $P$=0.025) was higher in group remifentanil than group $N_2O$ on postoperative day 0.

In patients receiving IV-PCA after thyroidectomy, postoperative nausea was lower but postoperative pain was higher in group remifentanil.

**Abbreviations:** CR = complete responder, IV-PCA = intravenous patient-controlled analgesia, $N_2O$ = nitrous oxide, NRS = numeric rating scale, POD = postoperative days, PONV = postoperative nausea and vomiting, SD = standard deviation, STD = standardized difference, VAS = visual analog scale.

**Keywords:** nitrous oxide, pain, postoperative, postoperative nausea and vomiting, remifentanil

### 1. Introduction

A characteristic complication of general anesthesia is postoperative nausea and vomiting (PONV). PONV can induce both postoperative pain and surgical wound dehiscence.[1] Moreover, PONV can reduce overall patient satisfaction and increase both the length of hospital stay and the overall medical cost by increasing the risk of pulmonary aspiration, electrolyte abnormality, and dehydration.[2,3] The risk factors for PONV include patient-related factors (female, nonsmoker, and history of PONV or motion sickness), perioperative opioid usage, anesthetic methods, and surgical type.[4]

Thyroidectomy patients constitute a high-risk group for PONV. Indeed, the incidence of PONV is higher (63–84% of thyroidectomy patients) than that in patients who underwent other surgeries.[5] Thus, many studies have investigated the effects of various pharmacologic agents, combinations of pharmacologic agents, and anesthetic or surgical methods for reducing PONV in these patients.[6–11]

Remifentanil and nitrous oxide ($N_2O$) are commonly used anesthetic agents. Remifentanil is an ultra-short acting opioid used in anesthetic practice for relieving pain and improving hemodynamic stability during anesthetic and surgical management.[12] However, remifentanil is known to significantly increase the risk of PONV, although reports concerning the effects of this agent are inconsistent.[13,14] In addition, continuous infusion of remifentanil may induce acute opioid tolerance or hyperalgesia.[15]

$N_2O$ has been widely used as an adjuvant to clinical anesthetic practice. The analgesic properties and general properties of this gas that render it suitable for this purpose include its low solubility, rapid onset and short half-life, and low cost. Like remifentanil, $N_2O$ is also a well-known risk factor for PONV, especially in cases where patients were exposed to $N_2O$ for a prolonged time.[16,17] However, no comparative study evaluating

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Department of Anesthesiology and Pain Medicine, Chung-Ang University College of Medicine, Dongjak-gu, Seoul, Republic of Korea.

* Correspondence: Hyun Kang, Department of Anesthesiology and Pain Medicine, Chung-Ang University College of Medicine, Dongjak-gu, Seoul, Korea (e-mail: roman00@naver.com).

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PONV and postoperative pain in remifentanil- and $N_2O$-based anesthetic methods has been reported. In the present retrospective study, we aim to compare the effects of remifentanil and $N_2O$ on PONV in patients undergoing thyroidectomy and using opioids for postoperative pain management.

## 2. Methods

### 2.1. Study design

This retrospective study was approved and informed consent was exempted by the Institutional Review Board of Chung-Ang University Hospital. All data were anonymized and de-identified at the start of the study. We analyzed the electronic medical records of 992 patients receiving fentanyl-based intravenous patient-controlled analgesia (IV-PCA) after thyroidectomy at Chung-Ang University Hospital from January 1, 2010 to April 30, 2016. The STROBE (Strengthening the Reporting of Observational Studies in epidemiology) checklist was used for constructing this manuscript.[18] We excluded cases where the patient was under 19 years old, cases with missing data for variables or outcome measures, cases in which the patient did not receive fentanyl-based IV-PCA or prior participation into other randomized controlled trials. We categorized the patients according to anesthetic agents used: group $N_2O$ (n=745) and group remifentanil (n=247).

### 2.2. Data collection

We collected and sorted data regarding risk factors for PONV related to patient characteristics (age, gender, height, weight, and history of smoking, PONV or motion sickness), risk factors related to anesthetic use (operation time, use of glycopyrrolate as premedication, and type of anesthetic agents used [desflurane vs sevoflurane vs propofol]), and risk factors related to PCA (dosage of fentanyl, use of nefopam, palonosetron, and ramosetron in IV-PCA). Postoperative variables included severity of nausea and pain, number of incidences of vomiting, incidence of headache, usage of rescue antiemetics, usage of rescue analgesics, and incidence of complete response (CR). These variables were measured on postoperative days (POD) 0 and 1. CR was defined as no nausea, no vomiting, and no requirement of antiemetic during the postoperative period at POD 0 or 1. The severity of pain was recorded on a 10-point visual analog scale (VAS) while the severity of nausea was recorded on a numerical rating scale (none=0/mild=1/moderate=2/severe=3/worst imaginable=4).

### 2.3. Statistics

Because this was a retrospective cohort study, patients were not randomized prior to intervention. For this reason, we used the propensity score matching method to reduce the bias due to confounding factors. The propensity score was calculated using logistic regression analysis, and accounting for covariates such as age, gender, height, weight, history of smoking, PONV or motion sickness, operation time, use of glycopyrrolate as premedication, type of anesthetic agents used, dosage of fentanyl, and use of nefopam, palonosetron, and ramosetron in IV-PCA. We adopted the nearest available match between the 2 groups according to propensity score similarities (caliper radius of 0.001). We subsequently calculated standardized differences (STDs) for covariates to evaluate the balance between each matched group. STD is defined as the difference in means between 2 groups in units of standard deviation (SD). When the value of STD is lower than 20%, a good comparison between the groups is considered to have been achieved.[19]

For continuous variables, the data distribution was first evaluated for normality using the Shapiro–Wilk test. Normally distributed data were then compared using parametric methods and non-normally distributed data were analyzed using nonparametric methods. Prior to matching, an unpaired *t* test or Mann–Whitney *U* test was used for comparing continuous variables, and a chi-squared analysis or Fisher exact test was used for comparing descriptive variables. After matching, statistical differences between the remifentanil group and $N_2O$ group were evaluated using a paired *t* test, Wilcoxon signed-rank test, and McNamara test. Continuous variables were expressed as mean ± SD and descriptive variables were expressed as absolute number (%).

$P$ value <0.05 was considered statistically significant. All analyses of data were conducted using the Statistical Package for the Social Sciences software suite (version 23; IBM Corp., Armonk, NY).

## 3. Results

The records of 992 patients receiving fentanyl-based IV-PCA after thyroidectomy at Chung-Ang University Hospital from January 1, 2010 to April 3, 2016 were collected and categorized into group $N_2O$ (n=745) or group remifentanil (n=247). Table 1 shows the overall demographic characteristics of all patients (and also the characteristics of the matched cohorts).

### 3.1. Group $N_2O$ versus group remifentanil in the overall series

Before propensity score matching, 5 variables among 15 confounding variables showed poor STD scores. These variables were as follows: age, operation time, use of sevoflurane, desflurane, or propofol continuous infusion, and use of nefopam in IV-PCA (Table 1).

Except for VAS of pain on POD 0 and 1, the numeric rating scale (NRS) of nausea on POD 0, the number of vomiting episodes on POD 1, and complete responder on POD 0, there was no significant difference in variables between the 2 groups (Table 2).

### 3.2. Group $N_2O$ versus group remifentanil according to propensity score analysis

After matching, there were 128 patients in each group. All 15 confounding variables showed acceptable STDs (<20%), confirming that the matching procedure was efficient in creating a balance between the 2 groups (Table 1). The VAS score of pain ($3.47 \pm 2.02$ vs $3.97 \pm 1.48$, $P < 0.025$) and CR (88 [68.8%] vs 106 [82.8%], $P = 0.001$) on POD 0 were both higher in the remifentanil group. The NRS of nausea ($0.55 \pm 0.88$ vs $0.27 \pm 0.76$, $P = 0.01$) was higher in the $N_2O$ group than in the remifentanil group (Table 3).

## 4. Discussion

According to our study, the VAS score of pain and CR on POD 0 were both higher in patients receiving IV-PCA using general anesthesia with remifentanil than in patients receiving IV-PCA using general anesthesia with $N_2O$ after thyroidectomy. The NRS of nausea was lower using remifentanil than when using $N_2O$.

**Table 1**

**Patients' characteristics in total and matched cohorts.**

| | Total set | | | | Matched set | | | |
|---|---|---|---|---|---|---|---|---|
| Characteristics | Group $N_2O$ (n=745) | Group remifentanil (n=247) | STD, % | *P* | Group $N_2O$ (n=128) | Group remifentanil (n=128) | STD, % | *P* |
| Patients' characteristics | | | | | | | | |
| Age, y | 47.77±12.51 | 44.814±13.53 | −23.15 | 0.002*,† | 46.23±13.99 | 47.78±14.43 | 10.91 | 0.382‡ |
| Gender, M:F | 149:596 | 47:200 | 16.09 | 0.740 | 31:97 | 28:100 | 9.5 | 0.656 |
| Height, cm | 161.58±13.72 | 161.58±7.40 | 0 | 0.995 | 162.20±8.14 | 161.69±7.81 | −6.39 | 0.606 |
| Weight, kg | 62.07±11.39 | 60.67±11.40 | 13.17 | 0.093 | 61.37±11.64 | 62.23±11.53 | 7.42 | 0.550 |
| Smoking | 75 (10.1) | 23 (9.3) | 8.25 | 0.730 | 13 (10.2) | 12 (9.4) | −7.84 | 0.833 |
| History of PONV or motion-sickness | 39 (5.2) | 15 (6.1) | 15.93 | 0.615 | 14 (10.9) | 12 (9.4) | −13.76 | 0.679 |
| Anesthetic factors | | | | | | | | |
| Operation time, min | 156.92±51.43 | 217.44±84.64 | 98.59 | <0.001*,† | 189.41±75.48 | 188.07±66.29 | −1.89 | 0.88‡ |
| Premedication | 200 (26.8) | 66 (26.7) | −0.37 | 0.969 | 37 (28.9) | 34 (26.6) | −7.95 | 0.675 |
| Sevoflurane | 362 (48.6) | 63 (25.5) | 62.35 | <0.001* | 50 (39.1) | 43 (36.3) | −7.16 | 0.363 |
| Desflurane | 383 (51.4) | 144 (58.4) | 12.75 | 0.06 | 78 (60.9) | 85 (66.4) | 9.03 | 0.363 |
| Propofol continuous infusion | 0 (0.0) | 40 (16.2) | 200 | <0.001* | 0 | 0 | N/A | N/A |
| PCA-related factors | | | | | | | | |
| PCA fentanyl, μg | 1038.37±145.12 | 1038.47±144.89 | 0.07 | 0.992† | 1055.94±127.98 | 1053.06±139.39 | −2.15 | 0.864 |
| Acupan | 383 (51.4) | 167 (67.6) | 27.23 | <0.001 | 84 (65.6) | 87 (68.0) | 3.66 | 0.691 |
| Palonosetron | 438 (58.8) | 162 (65.6) | 10.93 | 0.058 | 67 (52.3) | 73 (57.0) | 8.99 | 0.451 |
| Ramosetron | 223 (29.9) | 81 (32.8) | 9.25 | 0.398 | | | | |

Values are expressed as mean±standard deviation or absolute number (%).

F=female, M=male, N/A=not applicable, PCA=patient-controlled analgesia, PONV=postoperative nausea and vomiting, STD=standardized difference.

* $P<0.05$ between groups.

† Mann–Whitney *U* test.

‡ Wilcoxon signed-rank test was used because of abnormal distribution.

A common postoperative complaint of patients after thyroidectomy is PONV, which has a remarkably higher incidence following this procedure than following other surgeries.[5] There are various risk factors for PONV, including age, sex, and use of perioperative opioid. In particular, an important factor explaining the higher incidence of PONV in patients receiving thyroidectomy is surgical manipulation (especially manipulation involving vagus nerve stimulation).[4] Further, vomiting after thyroidectomy may cause serious complications, including postoperative bleeding and neck hematoma, which can lead to surgical wound dehiscence and potentially bleeding-induced upper airway obstruction.[20] Therefore, proper prophylaxis or treatment for PONV in these patients is very important. Although various pharmacological prophylactic methods have been studied extensively in patients undergoing thyroidectomy,[5,9–11] the effect of these methods is still controversial. Thus, it may be easier and more efficacious to identify and reduce modifiable risk factors, including anesthetic agents, for PONV.

Remifentanil continues to be extensively used in anesthetic practice, since it is rapidly degraded by tissue esterase and has a

**Table 2**

**Postoperative variables before matching.**

| | Group $N_2O$ (n=745) | Group remifentanil (n=247) | STD, % | *P* |
|---|---|---|---|---|
| Pain VAS at d 0 | 3.54±1.94 | 3.98±1.8 | −23.08 | 0.048* |
| Pain VAS at d 1 | 2.31±1.42 | 2.58±1.53 | −18.64 | 0.014* |
| Nausea NRS at d 0 (none=0/mild=1/moderate=2/severe=3/worst imaginable=4) | 0.48±0.9 | 0.31±0.76 | 19.6 | 0.016*,† |
| Nausea NRS at d 1 (none=0/mild=1/moderate=2/severe=3/worst imaginable=4) | 0.06±0.25 | 0.06±0.29 | 0 | 0.607† |
| Rescue antiemetic | 50 (6.7) | 26 (10.5) | 44.19 | 0.051 |
| Rescue analgesic | 46 (6.2) | 22 (8.9) | 35.76 | 0.141 |
| CR at d 0 | 560 (75.2) | 204 (82.6) | 9.38 | 0.016* |
| CR at d 1 | 703 (94.4) | 232 (93.9) | 0.53 | 0.799 |
| Number of vomiting at d 0 | 0.11±0.46 | 0.09±0.40 | 4.49 | 0.470† |
| Number of vomiting at d 1 | 0.02±0.14 | 0.00±0.06 | 16 | 0.041*,† |
| Dizziness at d 0 | 19 (2.6) | 4 (1.6) | 47.62 | 0.4 |
| Dizziness at d 1 | 11 (1.5) | 4 (1.6) | 6.45 | 0.873 |
| Headache at d 0 | 2 (0.3) | 2 (0.8) | 90.91 | 0.245 |
| Headache at d 1 | 5 (0.7) | 1 (0.4) | 54.55 | 0.64 |

Values are expressed as mean±standard deviation or absolute number (%).

CR=complete responder, NRS=numeric rating scale, STD=standardized difference, VAS=visual analog scale.

* $P<0.05$ between groups.

† Mann–Whitney *U* test was used because of abnormal distribution.

**Table 3**

**Postoperative variables after matching.**

| | Group $N_2O$ (n=128) | Group remifentanil (n=128) | STD, % | P |
|---|---|---|---|---|
| Pain VAS at d 0 | 3.47±2.02 | 3.97±1.48 | 28.24 | 0.025* |
| Pain VAS at d 1 | 1.84±1.22 | 2.03±1.33 | 14.89 | 0.222 |
| Nausea NRS at d 0 (none=0/mild=1/moderate=2/severe=3/worst imaginable=4) | 0.55±0.88 | 0.27±0.76 | −34.06 | 0.01*,† |
| Nausea NRS at d 1 (none=0/mild=1/moderate=2/severe=3/worst imaginable=4) | 0.05±0.23 | 0.05±0.21 | 0 | 0.777† |
| Rescue antiemetic | 13 (10.2) | 5 (3.9) | −61.76 | 0.051 |
| Rescue analgesic | 7 (5.5) | 12 (9.4) | 70.91 | 0.233 |
| CR at d 0 | 88 (68.8) | 106 (82.8) | 20.35 | 0.001* |
| CR at d 1 | 118 (92.2) | 122 (95.3) | 3.36 | 0.302 |
| Number of vomiting at d 0 | 0.14±0.59 | 0.08±0.37 | −12.18 | 0.307† |
| Number of vomiting at d 1 | 0.05±0.28 | 0.00±0.00 | −25.25 | 0.056† |
| Dizziness at d 0 | 4 (3.1) | 1 (0.8) | −94.19 | 0.175 |
| Dizziness at d 1 | 1 (0.8) | 2 (1.6) | 100 | 0.561 |
| Headache at d 0 | 2 (1.6) | 1 (0.8) | −50 | 0.561 |
| Headache at d 1 | 1 (0.8) | 0 (0.0) | −100 | 0.316 |

Values are expressed as mean±standard deviation or absolute number (%).

CR=complete responder, NRS=numeric rating scale, STD=standardized difference, VAS=visual analog scale.

* $P < 0.05$ between groups.

† Wilcoxon signed-rank test was used because of abnormal distribution.

short half-life. However, there is some controversy concerning the effect of remifentanil on PONV. Several previous studies[12,13] reported that remifentanil use increased the incidence of PONV, while other studies (remifentanil vs other opioids[21] and sevoflurane with remifentanil vs sevoflurane)[22] reported that remifentanil did not increase incidence of PONV. Since remifentanil can lead to acute tolerance and hyperalgesia,[15,23,24] remifentanil use during thyroidectomy may increase postoperative pain in the immediate period after surgery, and in consequence result in higher postoperative rescue analgesic requirements after infusion of remifentanil has stopped.[25] These features of remifentanil may potentially cause a vicious cycle of PONV by increasing the need for use of postoperative narcotic analgesics.

$N_2O$ shares similar features with remifentanil. It has a rapid onset of action and a short half-life. It is known to increase the incidence of PONV via several different mechanisms, including stimulation of the central nervous system through catecholamine release,[26] induction of changes in middle ear pressure which subsequently influence the vestibular system,[27] and by an increase in abdominal bowel distension.[28] The association of $N_2O$ with severe PONV is especially strong in patients of Asian ethnicity.[16]

Although patients in our study have a high-risk factor for PONV (opioid was used in PCA, thyroidectomy is a high-risk surgery for PONV, the proportion of female gender [75.8% in $N_2O$ group vs 78.1% in remifentanil group, $P=0.656$] was high, and all patients were of Asian ethnicity), the percentage of patients who were not CR was 31.2% in the $N_2O$ group and 17.2% in the remifentanil group. Thus, incidence of PONV was lower in both groups in comparison with a previous study.[5] The prophylactic use of antiemetic before the end of surgery and also mixed in with PCA, routine use of more effective antiemetics (2nd generation antiemetics such as palonosetron and ramosetron were used), and reduced stimulation of the vagus nerve by the surgical team, might all have contributed to the lower incidence of PONV in our study compared with the earlier study.

In our comparison between the 2 groups, remifentanil, $N_2O$, and volatile anesthetics are all known risk factors of PONV. However, remifentanil use or $N_2O$ use effectively reduced the total usage of the intraoperative volatile anesthetics, and both remifentanil and $N_2O$ are eliminated very rapidly. Therefore, their effect on PONV may be expected to wear off promptly. However, while $N_2O$ was generally kept at a constant concentration during the maintenance of general anesthesia, the infusion rate of remifentanil was titrated in real-time according to the hemodynamic status and the somatic signs of the patient. In consequence, there was a further reduction in the usage of volatile agents in the remifentanil group relative to the $N_2O$ group. Since the total usage of intraoperative volatile anesthetic was more effectively titrated and consequently reduced in the remifentanil group in comparison with the $N_2O$ group, the risk factor for volatile anesthetic is higher in the $N_2O$ group. Indeed, this aspect may account for our result that NRS of nausea was lower and that there was a higher number of CR on POD 0 in the remifentanil group.

Conversely, the VAS of postoperative pain was higher with remifentanil than with $N_2O$, although this was observed only on POD 0. There was, however, no difference in rescue analgesic requirement between the 2 groups. Thus, remifentanil use has distinct disadvantages as well as advantages. The many advantages of remifentanil use include the short-acting nature and rapid recovery, while the major disadvantage is acute tolerance and hyperalgesia. Acute tolerance is induced rapidly after total dose of intraoperative opioid infusion is increased or when short acting opioids like remifentanil are used.[25] Opioid-induced hyperalgesia is increased when the total dose of opioid during surgery is increased, and the intensity of pain due to surgery is high.[15] The clinical effects of these characteristics are still controversial. Several previous studies[24,29] have reported that remifentanil-induced hyperalgesia increased the requirement of postoperative analgesia. However, in agreement with results reported in the present study, another study[30] reported no difference in rescue analgesic consumption. These discrepancies may be due to differences in the doses of intraoperative remifentanil infusion. However, additional confounding factors and bias that affect the results of these studies cannot be ruled out. Therefore, we assume that although remifentanil-induced hyperalgesia influences the degree of pain in patients, additional administration of rescue narcotic analgesic is not needed.

This study had several limitations. First, as in other retrospective studies, our data were imperfect, including missing or incomplete data. Since patients were asked to recall the severity or events of their nausea and vomiting at POD 0 or 1, recall bias may be a problem, and the incidence of PONV may be underestimated because less severe PONV may be ignored. Second, our study used data from a single-medical center. Hence, caution is advised in generalizing from the results presented in our study, and further randomized controlled trials should be performed.

In conclusion, the severity and incidence of PONV in patients receiving fentanyl-based IV-PCA after thyroidectomy under general anesthesia was lower in the remifentanil group. Although the postoperative pain was higher in the remifentanil group than that in the $N_2O$ group, there was no difference in the use of rescue narcotic analgesic between the 2 groups.

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