



Determination of Independent Risk Factors Associated with Nausea and Vomiting Induced by Intravenous Tramadol Patient-controlled Analgesia after Spine Surgery

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Background: Nausea and vomiting are common side effects of tramadol. We conducted a retrospective study to identify the risk factors associated with nausea and vomiting induced by intravenous (IV) tramadol patient-controlled analgesia (PCA). **Methods:** Four hundred and sixty-one patients who received intravenous tramadol PCA after spine surgery were enrolled in our retrospective study. Patients' demographics, total doses of tramadol administered, and types of adjuvant agents including metoclopramide pretreatment and addition of ketorolac to the PCA solution were recorded. Associations between individual variables and the IV tramadol PCA-induced nausea and vomiting were analyzed statistically. Further logistic regression analysis was used to determine the independent risk factors of each variable. **Results:** The independent risk factor associated with IV tramadol PCA-induced nausea and vomiting was female gender (adjusted odds ratio [OR] 2.5, 95 % confidence interval [CI] 1.4-4.6). The addition of ketorolac to PCA solution resulted in decreased nausea and vomiting (adjusted OR 0.4, 95 % CI 0.2-0.7). **Conclusions:** Our study demonstrated that, after spine surgery, females could be associated with IV tramadol PCA-induced nausea and vomiting, and that addition of ketorolac to the PCA solution might decrease its incidence. These findings suggest that adding ketorolac to tramadol PCA solution may help in the management of IV tramadol-induced nausea and vomiting after spine surgery.

Key words: risk factor, nausea, vomiting, tramadol PCA, spine surgery

INTRODUCTION

Tramadol is a synthetic centrally acting opioid with no severe respiratory or cardiovascular side effects.¹ Its analgesic action is mediated by 2 major synergic mechanisms: a weak μ opioid effect and the inhibition of serotonin and norepinephrine reuptake. It has been shown to be effective in the management of postoperative pain by means of intravenous (IV) patient-controlled analgesia (PCA).^{2,3} However, IV tramadol PCA often results in a higher incidence of nausea and vomiting,^{1, 4-6} which

may offset its usefulness and lessen patients' satisfaction. There is no available information about the risk factors for nausea/vomiting induced by IV tramadol PCA. In the present study, we carried out a retrospective investigation on the probable risk factors associated with nausea and vomiting induced by IV tramadol PCA for pain management after spine surgery.

METHODS

The protocol of this retrospective study was examined and approved by the Institutional Ethics Committee of Taichung Armed Forces General Hospital. We collected the data of 461 patients who had received IV tramadol PCA after spine surgery for at least 3 days between March 2005 and February 2006. Exclusion criteria included missing demographic data of patients and/or their transfer to the intensive care unit. All patients underwent general anesthesia with volatile anesthetics. The regimen of IV tramadol PCA (tramadol 10 mg/ml) was carried out

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Table I Demographic characteristics and anesthetic/analgesic technique-related findings of patients with and without nausea/ vomiting

Demographic characteristics	Patients with N/V (n=133)	Patients without N/V (n=328)	P value
Age (yr)	54.7±19.3	54.0±17.9	0.710
Male/ female	29/104	153/175	<0.001
Female	104 (78.2 %)	175 (53.3 %)	
Height (cm)	157.0±8.9	159.9±10.0	0.004
Weight (kg)	59.0±9.0	60.9±9.1	0.042
Body mass index (kg/m ²)	24.0±3.7	23.9±3.6	0.789
Metoclopramide pretreatment	78(58.6 %)	256(78.0 %)	<0.001
Total tramadol consumption (mg)	573.5±217.8	556.2±202.7	0.417
Ketorolac-containing PCA solution	32(24.1 %)	152(46.3 %)	<0.001
Intraoperative tramadol loading	130(97.8 %)	321(97.9 %)	0.762

N/V, nausea/vomiting; PCA, patient-controlled analgesia

with a background dose of 0.2-1 ml/h, lockout interval of 10 min, and a demand dose of 0.3-1.5 ml. The dosage was decided based on each patient's age and body weight. Some of the patients received a loading dose of tramadol (1-2 mg/kg) intraoperatively or received a PCA solution with ketorolac (tramadol 8 mg/ml, ketorolac 3 mg/ml) or metoclopramide pretreatment (10 mg IV). All patients were taught to use the PCA machine preoperatively, and were visited twice a day for 3 days postoperatively. Complaints of nausea, vomiting, and other adverse events were recorded.

Patient characteristics that were recorded included age, sex, height, weight, and body mass index (BMI). In addition, intraoperative tramadol loading, metoclopramide pretreatment, ketorolac dose added to the PCA solution, and total tramadol consumption were recorded.

Statistical analysis

The group data are presented as the mean±standard deviation, number, or percentage. To compare data between the groups of patients with or without nausea/vomiting induced by IV tramadol PCA, categorical data were analyzed using chi-squared test; while continuous data were analyzed by means of a t-test. A *p* value<0.05 was considered statistically significant. The relative magnitudes of the associations between individual variables and the likelihood of nausea/vomiting were compared using calculated crude odds ratios (OR). The significance

Table II Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) of potential factors related to nausea/vomiting

Possible risk factors	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age (yr)	1.002 (0.991-1.013)	0.700	0.999 (0.998-1.000)	0.943
Female	2.842 (1.800-4.487)	<0.001	2.546 (1.404-4.619)	0.002
Height (cm)	0.969 (0.948-0.990)	0.004	0.985 (0.831-1.169)	0.866
Weight (kg)	0.976 (0.954-0.999)	0.039	1.009 (0.801-1.272)	0.939
Body mass index (kg/m ²)	1.007 (0.953-1.064)	0.812	0.932 (0.529-1.639)	0.806
Total tramadol consumption (mg)	1.000 (0.999-1.001)	0.443	0.999 (0.998-1.000)	0.090
Metoclopramide pretreatment	0.473 (0.309-0.724)	0.001	0.605 (0.361-1.014)	0.056
Ketorolac-containing PCA solution	0.367 (0.233-0.577)	<0.001	0.376 (0.216-0.654)	0.001
Intraoperative tramadol loading	1.083 (0.283-4.148)	0.907	2.584 (0.638-10.464)	0.183

OR, odds ratio; CI, confidence intervals; PCA, patient-controlled analgesia.

of the estimated OR was evaluated by 95% confidence interval (CI). All candidate variables were further analyzed by logistic regression, and an adjusted OR with 95% CI was obtained. The statistics program used for the analysis was SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

Of the 461 patients investigated, 133 exhibited IV tramadol PCA-induced nausea/vomiting. A consideration of the demographic characteristics of patients with or without nausea/vomiting revealed that the potential risk factors of nausea/vomiting were female gender (*p* < 0.001), body height (*p* = 0.004), and weight (*p* = 0.042) (Table I). With respect to analgesic adjuvants, patients receiving metoclopramide pretreatment or ketorolac-containing PCA solution (*p* < 0.001, *p* < 0.001, respectively) showed a lower incidence of nausea/vomiting (Table I).

Table II displays the crude OR and adjusted OR with 95% CI for each factor. The results exhibited by crude OR were similar to those shown in Table I. However, after controlling for all variables, the adjusted OR results were found to differ from crude OR results. Female gender (adjusted OR 2.5, 95% CI 1.4-4.6) was shown to be a significant independent risk factor associated with IV tra-

madol PCA-induced nausea/vomiting. Moreover, patients who received ketorolac-containing PCA solution showed a decreased risk of nausea/vomiting (adjusted OR 0.4, 95% CI 0.2-0.7).

DISCUSSION

Our study showed that female gender is an independent risk factor for the development of IV tramadol PCA-induced nausea/vomiting, and patients who received ketorolac-containing PCA solution had a decreased risk of nausea/vomiting.

Our data showed high incidence of IV tramadol PCA-induced nausea/vomiting (29%). The analgesic effect of tramadol is a result of it being a weak μ opioid agonist and an inhibitor of serotonin and norepinephrine reuptake. Pharmacologically, opioid, serotonin, and norepinephrine^{7,8} may stimulate the chemoreceptor trigger zone in the area postrema of the medulla, leading to nausea/vomiting. This may explain the high incidence of nausea/vomiting induced by tramadol.

In our study, we found that female gender was associated with a higher incidence of IV tramadol PCA-induced nausea/vomiting. A similar finding was also reported in patients receiving epidural fentanyl PCA.⁹ It is well established that female gender is the risk factor for postoperative nausea and vomiting (PONV).¹⁰ This accumulated information makes it reasonable to suggest that prophylactic antiemetics should be prescribed to female patients who are scheduled to receive postoperative PCA with opioids.

We also found that adding ketorolac to PCA solution could reduce the incidence of nausea/vomiting. Kim et al.¹¹ reported that ketorolac combined with lower doses of fentanyl caused less nausea and vomiting after thyroid surgery. Thagaard et al.¹² also demonstrated that IV ketorolac (30 mg) provided better analgesia and less PONV after ambulatory surgery compared with either dexamethasone (4 mg) or betamethasone (12 mg). In addition, a small randomized trial by Lepri et al.¹³ showed that patients receiving a combination of ketorolac with tramadol in the PCA solution could decrease nausea/vomiting compared with those receiving tramadol alone, although these results were not statistically significant. The results of these previous reports are consistent with our study.

Several striking demographic and analgesic technique-related factors were found to be unrelated to the probability of IV tramadol PCA-induced nausea/vomiting. First, we observed no influence of weight, height, or BMI on the probability of PCA-induced nausea/vomiting in

this study. Some studies have investigated whether BMI could be a risk factor for PONV, but the results were controversial.^{14,15} The effect of BMI on nausea/vomiting requires further investigation. Second, there was no effect of age on the incidence of nausea/vomiting. This finding is consistent with the study by Lee et al.¹⁶ Third, before variable-controlled analysis, metoclopramide pretreatment significantly reduced the incidence of nausea/vomiting. However, logistic regression excluded metoclopramide pretreatment as an independent risk factor. A metaanalysis revealed that an IV dose of 10 mg metoclopramide had no significant preventive effect on PONV.¹⁷ However, Wallenborn et al.¹⁸ showed that the preventive effect of metoclopramide on PONV was dose-dependent, and a dose of at least 25 mg was effective. Thus, an inadequate dose of metoclopramide in this study may explain the insignificant effectiveness of metoclopramide pretreatment on reducing nausea/vomiting.

In addition, intraoperative loading of tramadol was found not to be related to IV tramadol PCA-induced nausea/vomiting. It has been reported that intraoperative loading of tramadol decreased IV tramadol PCA-induced nausea/vomiting.¹⁹ However, similar results were not found in our study. This might be due to the high percentage of intraoperative loading (97%) in both our study groups, which could have made it difficult to find a significant difference.

Total tramadol consumption was not significantly different between the groups with or without nausea/vomiting. This finding conflicts with the theory that less consumption of tramadol may lead to less nausea/vomiting. This result is quite doubt-struck. A retrospective study, like ours, has certain unavoidable drawbacks such as uncontrolled variables and conditions that may influence the results. For example, nausea/vomiting may cause patients to avoid using PCA, thereby resulting in decreased total tramadol consumption in the nausea/vomiting group.

There are some limitations to our study. It was limited to patients who had undergone spine surgery, so the results might not be representative of the general population. In addition, some explanatory variables associated with nausea/vomiting, such as smoking status and history of PONV, were not included in this study.

In conclusion, after spine surgery, female patients may be more susceptible to IV tramadol PCA-induced nausea/vomiting. The addition of ketorolac to the tramadol PCA solution is suggested in order to reduce these side effects.

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