Randomised Controlled Trial

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Slower intravenous tramadol administration can prevent nausea and vomiting and predict postoperative nausea and vomiting: a randomized controlled trial

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Objective: Nausea and vomiting are the most common complications in patients who use tramadol for analgesia. This study evaluated the risk of nausea and vomiting related to intravenous tramadol administration.

Methods: In this study, 315 patients who received pre-analgesia before elective surgery were selected, and participants were divided into groups based on the Apfel risk assessment of nausea and vomiting, as follows: high risk (Apfel = 4), medium risk (Apfel = 2–3), and low-risk (Apfel = 1). Tramadol (1.5 mg/kg) was administered intravenously over a duration of 1 min, 2 min, or 3 min before anaesthesia induction to observe preoperative nausea and vomiting reactions within 10 min.

Results: In the low-risk group, the numeric rating scale for postoperative nausea scores and the incidence of nausea and vomiting were significantly lower in the 3-min group than those in the 1-min group, and the incidence of preoperative nausea and vomiting after intravenous administration of tramadol in the 1-min and 3-min groups were significantly related to the incidence of postoperative nausea and vomiting. The incidence of nausea and vomiting during pre-administration in the 1-min and 3-min groups was identified as an independent risk factor for postoperative nausea and vomiting.

Conclusions: In the clinical treatment of pain with tramadol, the slow intravenous application of tramadol within 3 min is worthy of being adopted and promoted by clinicians in their daily work.

Keywords: analgesia, Apfel risk, nausea and vomiting, rate of administration, tramadol

Introduction

Nausea and vomiting are patientive, unpleasant feelings resulting in discomfort to varying degrees in patients. They are an important cause of reduced perioperative satisfaction in patients receiving surgery. Determining a patient's risk of developing nausea and vomiting in advance and administering treatment is currently the common clinical approach, including choosing prophylactic and therapeutic regimens based on the Apfel risk assessment for nausea and vomiting[1]. Tramadol is a weak opioid analgesic, a serotonin and norepinephrine reuptake inhibitor, and is a μ opioid receptor agonist[2,3]. In clinical practice, tramadol is injected intravenously for the treatment of acute, chronic, moderate and severe pain and chills[4–6]. Nausea and vomiting are the most common complications in patients undergoing analgesia using tramadol, which can significantly affect patient comfort, aspiration pneumonia, and other complications[7,8]. Therefore, it is important to explore safe and effective methods to prevent nausea and vomiting caused by tramadol.

Generally speaking, there are three main management methods for nausea and vomiting caused by opioids: switching opioids (substituting one for another to reduce side effects), use of antiemetics, and changing the opioid administration route[9]. Previous studies have demonstrated that slowing the intravenous titration speed can minimize nausea and vomiting complications associated with oral tramadol and increase the patient's tolerance to tramadol[10,11]. However, there is still a lack of research on the

HIGHLIGHTS

- Intensity and the incidence of nausea and vomiting were significantly lower in the 3-min group than those in the 1-min group.
- Incidence of preoperative nausea and vomiting after intravenous administration of tramadol were significantly related to the incidence of postoperative nausea and vomiting.
- Slow intravenous application of tramadol within 3 min is worthy of being adopted and promoted by clinicians

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best speed of administration to prevent nausea and vomiting caused by intravenous tramadol in the perioperative period. Moreover, the best method for preventing nausea and vomiting induced by intravenous tramadol is likely to vary for patients with different degrees of nausea and vomiting risk.

This study included patients receiving tramadol for preanalgesia, explored the effects of different infusion speeds of intravenous tramadol on nausea and vomiting, and determined optimal administration rates for tramadol in patients with different risks of nausea and vomiting. The incidence of postoperative nausea and vomiting (PONV) was also followed up to explore how to predict the occurrence of PONV based on reactions caused by preoperative tramadol application and to provide a basis for the clinical prediction of PONV.

Material and methods

Patients and ethics

This study was a prospective randomized controlled study in accordance with the Consolidated Standards of Reporting Trials (CONSORT)[12]. This research was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee and registered in the registered website. And this study was registered in https://www.researchregistry.com/browse-the-registry#home/ (unique identifying number: researchregistry9730). Written informed consent was obtained from all patients before their inclusion in the study. All data from this study can be obtained from the corresponding author upon reasonable request.

Patients ($n = 315$) who underwent elective surgery with general anaesthesia from June 2021 to May 2022 were selected for the study. The inclusion criteria were as follows: age 18–65 years, $18.5 \leq$ body mass index (BMI) ≤ 28, American Association of Anesthesiologists Grade I–II, and an elective nature of the surgery. The exclusion criteria were: patients with chronic pain and those with long-term use of analgesics, psychotropic drugs, or alcohol; abnormal liver and kidney function; history of opiate allergy; use of sedatives or antiemetics 24 h before surgery; use of monoamine oxidase inhibitors or antidepressants within 15 days of surgery; high risk of complications such as reflux aspiration; history or family history of epilepsy; severe chronic obstructive pulmonary disease; severe or uncontrolled bronchial asthma; pulmonary infection; severe heart disease; pregnancy or breast feeding; and inability to cooperate with the study for any reason.

Randomization and blinding

This study adopted block randomization, and the patients were divided into high-risk, medium-risk, and low-risk groups according to the Apfel risk assessment of nausea and vomiting. Patients were randomly divided into groups with varying administration speeds of preoperative intravenous tramadol (1, 2, or 3 min). Randomization method was carried out using the sealed envelope method. The study implementer opened the envelope to determine the administration scheme, and then sealed the envelope again until the end of the study.

In this study, a single-blinded method was used to administer intravenous tramadol. The patients were not aware of their drug group. In addition, the researchers who participated in the follow-up after surgery were blinded to the grouping.

Experimental intervention and procedure

Physiological data of patients, including gender, height, weight, BMI, standard electrocardiogram, heart rate, blood pressure, and SPO_2 (Pulse oxygen saturation) were collected at baseline before drug administration. An intravenous infusion pathway was established by professional operating room nurses and doctors. After tramadol administration, if the patient's SPO_2 was lower than 85%, they were instructed to perform deep breathing. Tramadol was administered at 1.5 mg/kg intravenously, and administration was completed within 1 min, 2 min, or 3 min (based on group allocation) using a micropump. Heart rate, blood pressure, and SPO_2 were continuously monitored for 10 min after tramadol administration, and the occurrence of adverse reactions was recorded, including nausea, vomiting, sweating, and sedation. The degree of nausea was scored using the numerical rating scale for postoperative nausea (NRS; 0, no discomfort; 10, intolerable nausea). All patients were followed up 12 h and 24 h after surgery, and NRS scores and vomiting within 0–12 h and 12–24 h after surgery were recorded. The recorded NRS score of nausea and vomiting is the maximum NRS score of nausea and vomiting in this period.

Statistical analysis

The NRS scale scores within 10 min after intravenous tramadol administration were used as the primary outcome. In a pilot study, we observed that the average NRS score was 3.24 ± 2.72 after administration over 1 min and 1.45 ± 2.16 after 3-min administration. Power Analysis and Sample Size software (v. 11.0; NCSS, LLC) was used to determine sample size according to the parallel controlled study design with an α of 0.05 and test power of 0.8, considering a 10% loss to follow-up rate; this required a sample size of 35 patients in each group. For simultaneous exploration of tramadol administration rates in nausea and vomiting-risk groups, patients were grouped based on Apfel scores (0, 1–2, or 3). In this study, 105 patients were included in each of the different administration rate groups, for a total of 315 patients.

Statistical analysis was performed using SPSS software (v. 21.0; IBM Corp.). Normally distributed measurement data are expressed as mean ± standard deviation, non-normally distributed data as median (interquartile range), and qualitative variables as number (percentage). Comparisons between groups for continuous normally distributed variables were performed using one-way analysis of variance with Fisher's least significant difference test for multiple comparisons. Comparisons between groups for non-normally distributed data were performed using the Kruskal–Wallis or Mann–Whitney U test; comparisons of rate differences were performed using Pearson's χ^2 test, the corrected χ^2 test, or Fisher's exact test, as appropriate. Additional Pearson correlation coefficient and logistic regression analyses were used to explore the risk factors predicting PONV. A two-sided P less than 0.05 was considered significant.

Results

As shown in Fig. 1, 408 patients were initially screened in this study. Ninety-three patients were excluded due to a BMI greater than or equal to 30, suspicious difficult airways, untreated COPD, heart disease, or study withdrawal, and 315 patients were

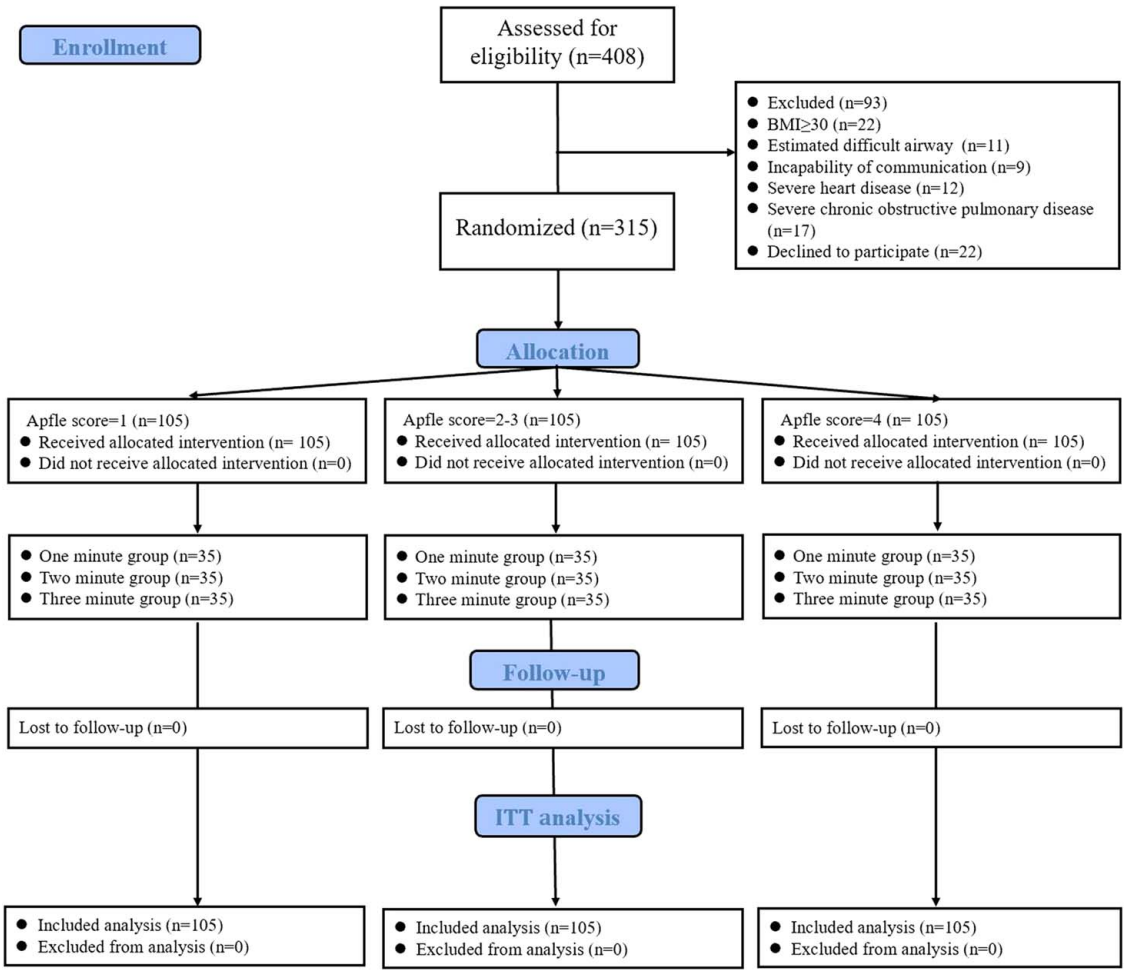

Figure 1. Flow chart of patient inclusion in the study.

finally included. The demographic and baseline characteristics of all included patients are shown in Table 1. There were no significant differences between the groups.

In low-risk patients (Apfel score = 1), it was observed that the NRS score of nausea and vomiting were significantly lower in the 3-min administration group than in the 1-min group ($P < 0.05$; Fig. 2A). However, in patients with moderate (Apfel score = 2–3; Fig. 2B) and high risk (Apfel score = 4; Fig. 2C), as well as in the whole patients (Fig. 2D) there was no significant difference in NRS scores between the tramadol administration rate groups.

In low-risk patients, the incidence of nausea and vomiting was significantly lower in the 3-min group than in the 1-min (8.6% vs. 28.6%, $P = 0.031$) and 2-min (8.6% vs. 37.1%, $P = 0.004$) groups (Fig. 3A). However, there was no significant differences in the moderate- and high-risk groups (Fig. 3B and C). Among the whole population combined risk groups, incidence of nausea and vomiting was significantly lower in the 3-min group than in the 1-min group (42.9% vs. 55.2%, $P = 0.049$; Fig. 3D).

The correlation between NRS scores after tramadol pre-analgesia in the 1-min, 2-min, and 3-min administration groups and NRS scores at 0–12 h (Fig. 4A), 12–24 h (Fig. 4B), and 0–24 h (Fig. 4C) are shown in Fig. 4. The NRS scores after pre-analgesia were significantly correlated with the postoperative NRS scores in the 1-min [0–12 h ($R = 0.529$, $P < 0.001$), 12–24 h ($R = 0.338$, $P < 0.001$), 0–24 h ($R = 0.544$, $P < 0.001$)] and 3-min administration groups [0–12 h ($R = 0.368$, $P < 0.001$), 12–24 h ($R = 0.305$, $P = 0.002$), 0–24 h ($R = 0.370$, $P < 0.001$)]. There was not a statistical difference in the correlation in the 2-min administration group.

In the multivariate regression analysis, the occurrence of PONV could be effectively predicted by pre-administration of tramadol for analgesia in the 1-min ($P < 0.01$) and 3-min groups ($P = 0.033$) but not in the 2-min group ($P = 0.923$). Thus, in the 1-min and 3-min tramadol administration groups, the occurrence of nausea after pre-administration was an independent risk factor for PONV (Table 2, Table 3).

Discussion

In the present study, we found that slowing the intravenous administration of preoperative tramadol can improve the nausea and vomiting reactions in low-risk patients caused by intravenous administration of tramadol. That is, intravenous administration over 3 min could significantly reduce the NRS scores and incidence of nausea in low-risk patients compared to administration over 1 min; however, no significant effects were observed in the

Table 1

Demographic and baseline characteristics for all included subjects

	Apfel score = 1			Apfel score = 2–3			Apfel score = 4		
	1 min ($n=35$)	2 min ($n=35$)	3 min ($n=35$)	1 min ($n=35$)	2 min ($n=35$)	3 min ($n=35$)	1 min ($n=35$)	2 min ($n=35$)	3 min ($n=35$)
Age (year)	42.0 ± 11.0	41.5 ± 10.2	44 ± 11.0	42.0 ± 12.0	39.3 ± 10.7	39 ± 9.4	43.0 ± 9.9	40.7 ± 10.4	44 ± 9.3
Sex (Male), *n* (%)	35 (100)	35 (100)	35 (100)	17 (48.6)	23 (65.7)	15 (42.9)	0	0	0
Weight (kg)	67.9 ± 8.5	70.5 ± 8.0	68.6 ±	62.1 ± 10.1	67.3 ± 7.9	65.7 ± 10.5	57.7 ± 6	56.4 ± 6	55.9 ± 7.46
Height (cm)	169.2 ± 4.7	169.9 ± 5.5	168.2 ± 5.9	163.3 ± 7.6	166.4 ± 7.4	165.2 ± 8.1	157.5 ± 4.9	157.4 ± 5.1	156.3 ± 4.5
BMI (kg/m^2)	23.7 ± 2.9	24.4 ± 2.3	24.2 ± 2.77	23.2 ± 2.56	24.3 ± 2.7	24 ± 2.53	23.3 ± 2.39	22.8 ± 2.9	22.9 ± 2.89
Smoking (yes), *n* (%)	35 (100)	35 (100)	35 (100)	2 (5.7)	6 (17.1)	4 (11.4)	0 (0.0)	0 (0.0)	0 (0.0)
History of PONV (yes), *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	9 (25.7)	6 (17.1)	35 (100)	35 (100)	35 (100)
Surgery type									
Gynaecological surgeyr, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	7 (20.0)	4 (11.4)	5 (14.3)	10 (28.6)	8 (22.9)	10 (28.6)
Abdominal digestive surgery, *n* (%)	16 (45.7)	11 (31.4)	9 (25.7)	9 (25.7)	15 (42.9)	16 (45.7)	9 (25.7)	10 (28.6)	10 (28.6)
Orthopaedic surgery, *n* (%)	6 (17.1)	10 (28.6)	8 (22.9)	2 (5.7)	8 (22.9)	6 (17.1)	3 (8.6)	3 (8.6)	4 (11.4)
Breast and thyroid surgery, *n* (%)	5 (14.3)	2 (5.7)	7 (20.0)	6 (17.1)	4 (11.4)	5 (14.3)	10 (28.6)	9 (25.7)	9 (25.7)
Other, *n* (%)	8 (22.9)	12 (34.3)	11 (31.4)	11 (31.4)	4 (11.4)	3 (14.3)	3 (8.6)	5 (14.3)	2 (5.7)
Surgery method (open), *n* (%)	15 (42.9)	21 (60.0)	14 (40.0)	12 (34.3)	19 (54.3)	14 (40.0)	12 (34.3)	19 (54.3)	14 (40.0)
MAP (mmHg)	97.2 ± 11	99.4 ± 12.8	97.6 ± 12.0	97.5 ± 11	100 ± 11.9	97.2 ± 11.5	96.4 ± 10.7	93.1 ± 11.7	96.8 ± 12.3
HR (bpm)	73.9 ± 12	71.8 ± 11.7	74.6 ± 13.3	77.4 ± 11.2	77.3 ± 11.8	77.9 ± 13.5	75.2 ± 10.9	74.3 ± 15.4	77.5 ± 11.8
S_PO2 (%)	98.9 ± 1.3	98.5 ± 1.3	98.4 ± 1.8	96.1 ± 1.5	98.5 ± 1.7	98.7 ± 1.48	98.9 ± 1.1	96.2 ± 1.5	99.4 ± 1.2
Surgery duration (h)	0.9 (0.7–2.0)	1.3 (0.8–2.0)	1.0 (0.6–1.7)	1.2 (0.8–1.9)	1.3 (0.7–2.1)	1.0 (0.6–1.7)	1.6 (1.0–2.1)	1.0 (0.6–2.5)	1.6 (1.1–2.5)

Data are presented as mean ± standard deviation, number (percentage), or median (interquartile range).

HR, heart rate; MAP, mean arterial pressure; PONV, postoperative nausea and vomiting.

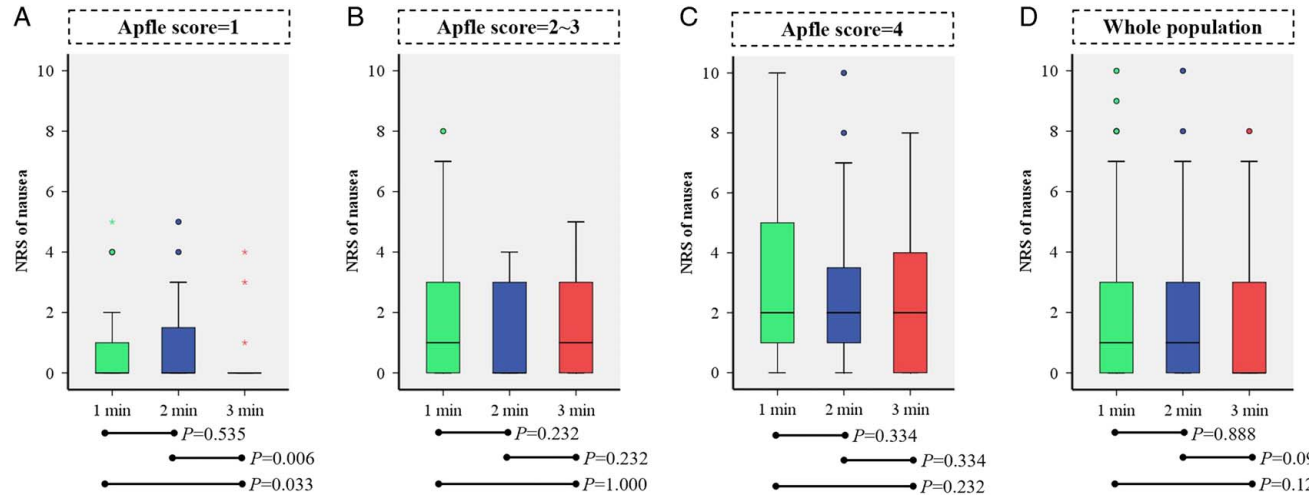

Figure 2. NRS, scores of nausea and vomiting in different Apfel risk groups [(A) Apfle score = 1; (B) Apfle score = 2–3; (C) Apfle score = 4] and the entire population (D) after intravenous tramadol administration. NRS, number rating scale.

medium-risk and high-risk groups. In addition, through secondary analysis, we found that NRS scores of nausea and vomiting caused by intravenous tramadol administration over 1 and 3 min were significantly correlated with the NRS score of PONV; thus, the preoperative analgesic administration rate could effectively predict PONV.

Nausea and vomiting are the most common reasons for discontinuing tramadol in clinical use[13,14]. Exploring methods to prevent nausea and vomiting induced by tramadol would be helpful for clinicians to formulate personalized pain treatment plans. The known non-drug methods to prevent nausea and vomiting include eating ginger, drawing attention away from symptoms, and use of deep breathing techniques[15]. Early research found that, in patients who took tramadol orally as an analgesic for a long time, slowing the titration speed of intravenous tramadol administration could improve patient tolerance to tramadol[11]. However, studies on the prevention of nausea and vomiting caused by transient intravenous tramadol use are few. In the present study, we found that the effects of slowing down tramadol administration speed on improving nausea and vomiting were limited. For patients with medium- and high risk of nausea and vomiting, reducing the administration speed had no significant effect on nausea and vomiting caused by intravenous tramadol. Therefore, to reduce the occurrence of nausea and

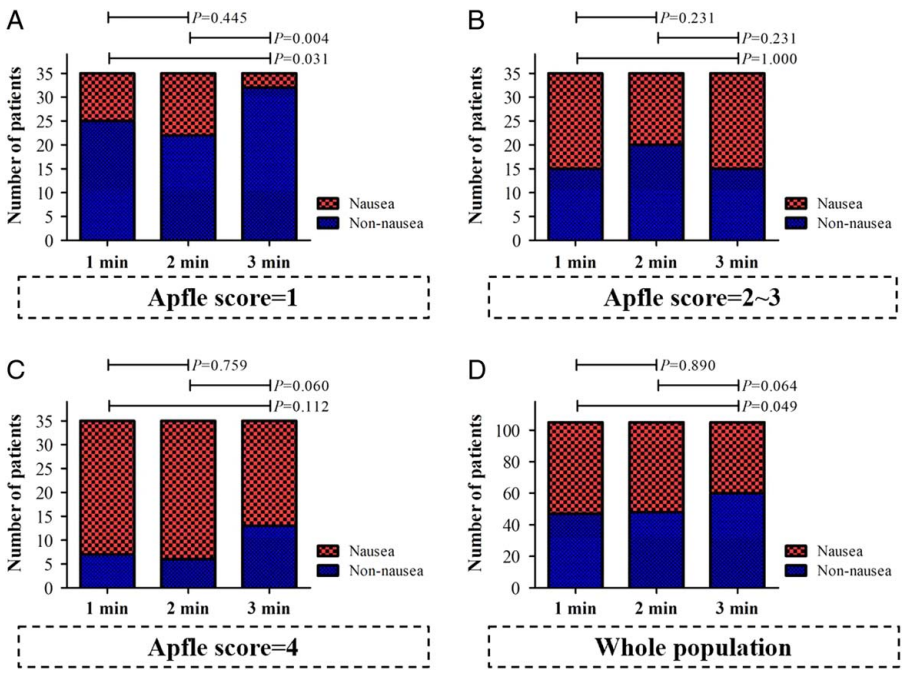

Figure 3. Incidence of nausea in different Apfel risk groups [(A) Apfle score = 1; (B), Apfle score = 2–3; (C) Apfle score = 4] and in the entire population (D) after intravenous tramadol administration.

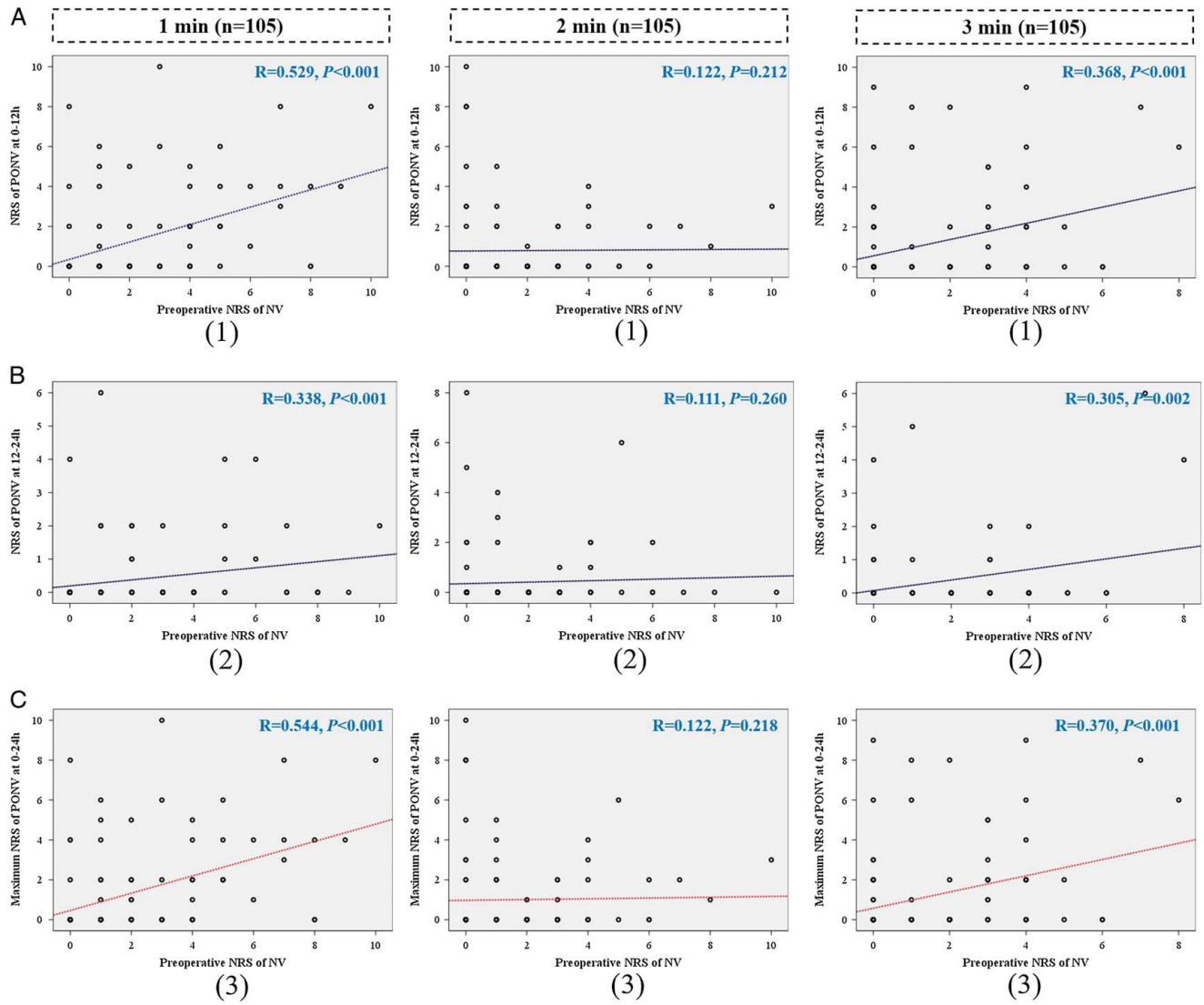

Figure 4. Correlation between NRS scores of nausea and vomiting caused by preoperative intravenous tramadol administration at different rates (1, 1 min; 2, 2 min; 3, 3 min) and NRS scores of nausea and vomiting within 0–12 h (A), 12–24 h (B), and 0–24 h (C) after surgery. NRS, number rating scale.

vomiting, other methods or multiple interventions may be required, such as the use of antiemetics[16] or increasing the tramadol administration rate even longer; however, this may lead to reduced efficiency. Notwithstanding, we found that, for low-risk patients, prolonging the administration to 3 min could effectively reduce nausea and vomiting. In the entire sample, the incidence of nausea and vomiting in the 3-min group was significantly lower than that in the 1-min group. Therefore, in general, increasing the administration time may be beneficial for some patients.

Clinical strategies for PONV mainly rely on two aspects: drug or non-drug intervention and early identification of potential high-risk patients. In this study, patients were followed up until 24 h after surgery. The NRS scores of nausea and vomiting after intravenous administration of tramadol in the 1-min and 3-min groups were significantly correlated with the NRS score of nausea and vomiting at 0–12 h and 12–24 h after surgery. The same phenomenon was observed in NRS scores for PONV in the overall patients. According to the Apfel risk assessment scale for nausea and vomiting, the most common risk indicators currently used are history of motion sickness, smoking, sex (male or female), and opioid exposure[17,18]. These factors were simultaneously included in the multivariate regression analysis in the present study. The regression analysis results showed that the occurrence of preoperative nausea after tramadol administration was an independent risk factor for PONV in the 1-min and 3-min administration duration groups. Thus, preoperative evaluation of nausea and vomiting risk can be used as an effective way to predict the occurrence of PONV, in addition to the Apfel risk assessment. Based on the evaluation of preoperative nausea, one can effectively predict the degree and probability of PONV, so as to formulate individualized prevention plans.

Several limitations should be considered when interpreting the current findings. Firstly, some important potential confounding factors such as anaesthesia methods and intraoperative medication are not completely standardized, thus the association between preoperative scores and PONV should be further explored when different anaesthesia strategy was applied. Secondly, future research could be further performed to explore

Table 2

Univariate logistic regression of preoperative risk variables for predicting postoperative nausea and vomiting

Population	Factors	Wald x^2	*P*
1 min ($n=105$)	Sex (male/female)	2.572	0.100
	History of motion sickness (yes/no)	0.161	0.689
	Smoking (yes/no)	2.869	0.090
	Surgery type (abdominal operation/other surgery)	0.000	0.985
	Nausea and vomiting during the tramadol treatment (yes/no)	13.355	< 0.001
	Time of surgery ≥ 2h (yes/no)	1.476	0.224
	PCIA (yes/no)	3.051	0.081
2 min ($n=105$)	Sex (male/female)	6.273	0.012
	History of motion sickness (yes/no)	2.181	0.140
	Smoking (yes/no)	0.616	0.433
	Surgery type (abdominal operation/other surgery)	3.359	0.067
	Nausea and vomiting during the tramadol treatment (yes/no)	0.009	0.923
	Time of surgery ≥ 2h (yes/no)	0.001	0.978
	PCIA (yes/no)	0.170	0.680
3 min ($n=105$)	Sex (male/female)	3.577	0.059
	History of motion sickness (yes/no)	0.878	0.349
	Smoking (yes/no)	0.605	0.437
	Surgery type (abdominal operation/other surgery)	0.641	0.424
	Nausea and vomiting during the tramadol treatment (yes/no)	4.527	0.033
	Time of surgery ≥ 2h (yes/no)	0.001	0.981
	PCIA (yes/no)	0.956	0.328

PCIA, patient-controlled intravenous analgesia.

Table 3

Overall logistic regression model based on significative factors for predicting for predicting postoperative nausea and vomiting

Population	Factors	Wald x^2	*P*	OR (95% CI)
1 min ($n=105$)	Sex (male/female)	11.145	0.001	0.17 (0.06–0.48)
	Nausea and vomiting during the tramadol treatment (yes/no)	16.385	< 0.001	0.08 (0.03–0.28)
2 min ($n=105$)	Sex (male/female)	15.211	< 0.001	0.13 (0.05–0.36)
3 min (n = 105)	Sex (male/female)	8.417	0.004	0.21 (0.07–0.60)
	Nausea and vomiting during the tramadol treatment (yes/no)	5.572	0.018	0.32 (0.12–0.82)

OR, odds rate.

the impact of tramadol administration on specific patient populations and different surgical procedures to validate the current findings. Thirdly, for each subgroup in this study the sample size is relatively small, and larger sample size study should be performed in future.

Conclusions

In summary, although administering tramadol for over 3 min showed no significant reduction of nausea and vomiting in patients with high and medium risk, the 3-min administration is recommended for low-risk patients. In addition, the 3-min administration had a significant predictive effect on the occurrence of PONV. Therefore, this study implies that, when tramadol is used for clinical pain treatment, slow intravenous application over 3 min should be adopted and promoted by clinicians in their daily work. This can effectively improve drug-related nausea and vomiting reactions in some patients and can also predict the occurrence of PONV while achieving preoperative analgesia.

Ethics approval and informed consent

This research was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (ID: 2021-047-1) and registered in the China Clinical Trial Registry (www.chictr.org.cn; ID: ChiCTR2100048284). Written informed consent was obtained from all patients before their inclusion in the study.

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Author contribution

W.G., X.Z., J.C., A.Y., Y.C. and J.C. contributed to data collection. W.G., J.C. and B.S. contributed to data analysis. W.G., X.Z., J.C. and G.D. contributed to drafting and revising the article. All authors have read and approved the final manuscript.

Conflicts of interest disclosure

The authors declare no competing interests.

Research registration unique identifying number (UIN)

This study was registered at Chinese Clinical Trial Registry (https://www.chictr.org.cn/) and the Research Registration Unique Identifying Number (UIN) is ChiCTR2100048284.

Guarantor

Jie Chen, Guangyou Duan.

Data availability statement

All data from this study can be obtained from the corresponding author upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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