

Effect of Prophylactic Anti-emetics on Opioid-induced Nausea and Vomiting: A Retrospective Observational Cohort Study

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Abstract. *Background: The guidelines on pharmacotherapy for cancer-related pain advocate active measures against the adverse effects of opioids to increase adherence to medication. However, preventative therapy for the management of nausea and vomiting has not been specified. This study aimed to verify the effects of prophylactic anti-emetics in preventing opioid-induced nausea and vomiting. Patients and Methods: We conducted a retrospective analysis of cases at our hospital in which oral opioids or patches were initiated for the management of pain due to malignant tumours from January 2017 to September 2019. Results: Strong opioids were initiated for 349 patients; of these, data for 298 patients were analysed. A total of 193 patients were on anti-emetic prophylaxis. We found that the group that did not receive anti-emetic prophylaxis was significantly more likely to be prescribed an additional anti-emetic. Conclusion: Prophylactic administration of anti-emetics at the time of initiating opioid analgesics may reduce gastrointestinal toxicity.*

For patients with advanced cancer, opioids are very important drugs for the control of pain. Gastrointestinal toxicities, such as constipation and nausea, are the typical adverse effects of opioids. Controlling these adverse effects is important to improve adherence to medication. Guidelines for pharmacotherapy of cancer pain suggest that aggressive measures should be taken to control the adverse side effects and improve compliance. Prophylactic administration of drugs is recommended for constipation; however,

prophylactic administration of anti-emetics has not been recommended because few prospective trials have been conducted so far (1-3). Nausea is said to occur in about 40% of patients after the initiation of opioid therapy (4), but there are few recommendations on opioid-induced nausea and vomiting (OINV) (5); therefore, preventive measures against nausea are considered important.

We report the findings from a retrospective observational study with the primary objectives of estimating the incidence of nausea and understanding the efficacy of anti-emetic prophylaxis during initiation of opioids for the treatment of cancer pain.

Patients and Methods

Study design and patient selection. This was a single-centre retrospective observational study conducted to understand the incidence of OINV in Japanese patients with cancer pain who were initiated on strong opioid therapy (morphine, oxycodone, hydromorphone, and fentanyl). The study was approved by the relevant Institutional Review Board (National Hospital Organization Iwakuni Clinical Center Institutional Review Board, Iwakuni, Yamaguchi, Japan) (no. 0175) and was conducted in compliance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects. Informed consent was obtained using the opt-out option on our hospital website.

The data of patients who were prescribed strong opioids for cancer pain were extracted from their medical records. Patients were excluded when strong opioids had been initiated before the observation period or when they had received strong opioids at other centres. Patients with difficulty in oral intake were also excluded.

Statistical methods. We evaluated the number of patients who required additional anti-emetic medications among those who received no prophylactic anti-emetic drugs. Cases in which an additional anti-emetic was prescribed within 28 days after the initiation of the strong opioid were defined as receiving an additional prescription. Differences between the groups were assessed using the chi-squared test and Fisher's exact test. The Kaplan-Meier method was used to evaluate the period until the use of anti-emetics. Gray's test was used to evaluate the cumulative incidence of additional use of anti-emetics and death within 1 month from the use of opioids. Age, sex, primary site of cancer, prescribed opioid types and dosage, history of tramadol administration,

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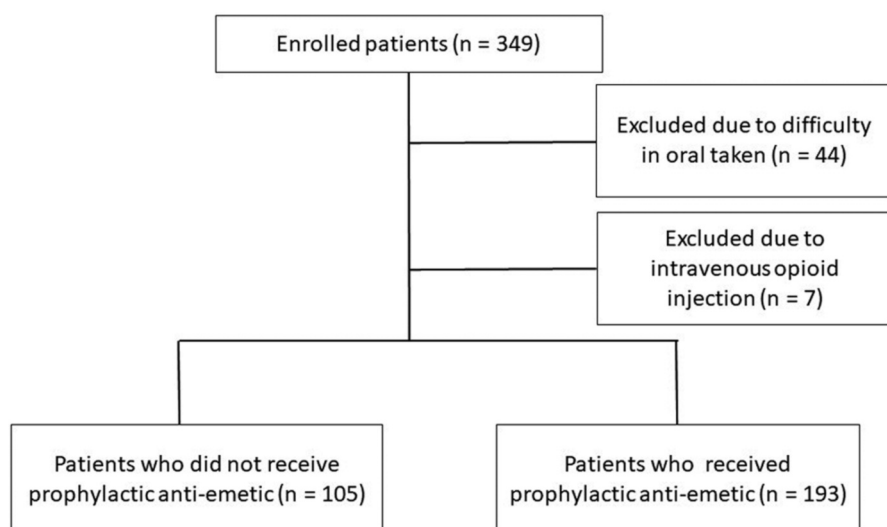


Figure 1. Flow chart showing recruitment of patients in this study.

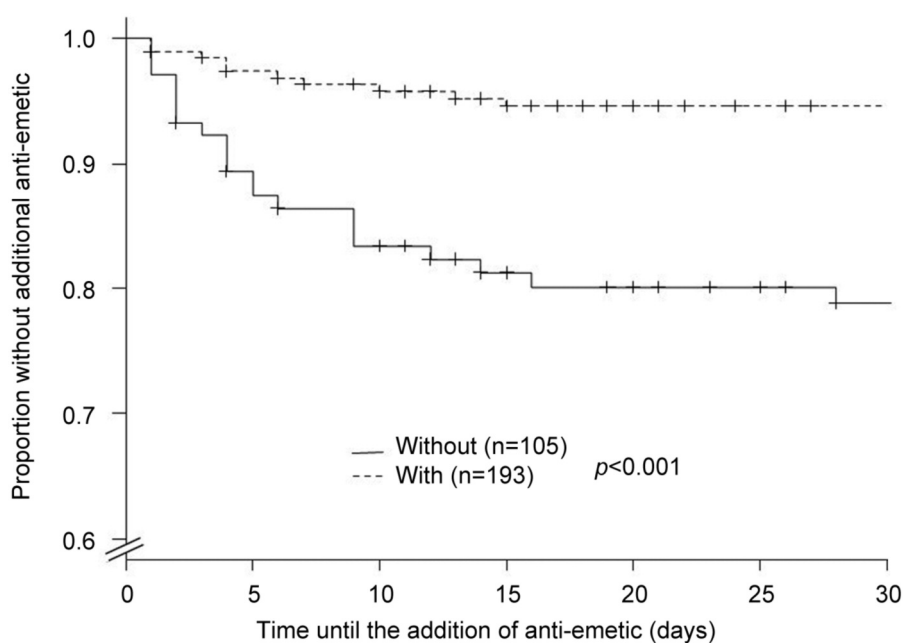


Figure 2. Time to administration of additional anti-emetic medicine. Time-to-event endpoints were analysed using Kaplan-Meier methods and were tested using the log-rank test.

subsequent administration of anticancer drugs, and outpatient opioid introduction were adjusted for in the multivariate analysis. All statistical tests were performed on observed values with a two-sided significance level of 0.05 without multiplicity considerations. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients. Between January 5, 2017 and September 30, 2019, 349 patients with cancer pain were started on strong opioids. Of the 349 patients, 44 were excluded from this study due to difficulty in oral intake, and a further seven were excluded because they received intravenous opioid

Table I. Demographic and baseline clinical characteristics of the patients.

Variable	Prophylactic anti-emetic		<i>p</i> -Value
	Without (n=105)	With (n=193)	
Age, years			
Median (range)	69 (37-89)	71 (35-94)	0.559
Gender, n (%)			
Male	60 (57.1)	118 (61.1)	0.537
Female	45 (42.9)	75 (38.9)	
Opioid type, n (%)			
Morphine	5 (4.8)	30 (15.5)	<0.001
Oxycodone	58 (55.2)	129 (66.8)	
Hydromorphone	8 (7.6)	12 (6.2)	
Fentanyl (patch)	34 (32.4)	22 (11.4)	
Primary tumor, n (%)			
Digestive tract	31 (29.5)	24 (12.4)	<0.001
Other	74 (70.5)	169 (87.6)	
Chemotherapy after opioid induction, n (%)			
Yes	35 (33.3)	77 (39.9)	0.317
No	70 (66.7)	116 (60.1)	
History of weak opioid administration, n (%)			
Yes	44 (41.9)	85 (44)	0.807
No	61 (58.1)	108 (56)	
Status within 1 month, n (%)			
Alive	78 (74.3)	142 (73.6)	>0.99
Dead	25 (23.8)	47 (24.4)	
Unknown	2 (1.9)	4 (2.1)	
Opioid rotation within 1 month, n (%)			
Yes	78 (74.3)	122 (63.2)	0.128
No	25 (23.8)	67 (34.7)	
Unknown	2 (1.9)	4 (2.1)	
Opioid introduction in outpatient setting, n (%)			
Yes	94 (89.5)	151 (78.2)	0.017
No	11 (10.5)	42 (21.8)	
Median dose (morphine equivalent), mg	15 (7.5-60)	15 (10-75)	<0.001

Fisher's exact test was used to compare the two groups, and *t*-test was used to test the continuous variables. Statistically significant *p*-values are shown in bold.

injection. The data for the remaining 298 patients were retrospectively analysed (Figure 1). The anti-emetics used in our study were prochlorperazine and metoclopramide. The patients' demographic and baseline clinical characteristics are shown in Table I. The patients in the group that received no anti-emetic prophylaxis had significantly advanced gastrointestinal tract carcinoma, used fentanyl more often, had received opioids more often at the Outpatient Department, and were initiated on opioids at lower doses than those in the group that received prophylactic anti-emetic.

Table II. Results of the multivariate analysis for the need of an additional anti-emetic.

Variable	OR	95% CI	<i>p</i> -Value
Age			
>70 Years	0.706	0.3080-1.620	0.409
Gender			
Male	0.39	0.1720-0.886	0.0246
Primary tumor			
Digestive tract	0.59	0.1800-1.930	0.384
Opioid			
Fentanyl patch	0.541	0.1770-1.660	0.283
Morphine	0.65	0.1430-2.950	0.576
Opioid introduction in outpatient setting			
Yes	0.367	0.0784-1.720	0.203
History of weak opioid administration			
Yes	2.33	0.9370-5.810	0.0686
Prophylactic anti-emetic			
Yes	0.212	0.0857-0.524	0.0008
History of chemotherapy after opioid induction			
Yes	1.06	0.4460-2.520	0.894
Opioid dose			
>15 mg	1.27	0.4555-3.530	0.651

CI: Confidence interval; OR: odds ratio. Logistic regression analysis was used for multivariate analysis. Statistically significant *p*-values are shown in bold.

Incidence of additional anti-emetic medications. The cumulative incidence of the need for additional anti-emetics within 4 weeks was 20.0% (21 out of 105 patients) in the group that received no anti-emetic prophylaxis, and 5.2% (10 out of 193 patients) in the group that received prophylactic anti-emetics (odds ratio=0.220, 95% confidence interval=0.088-0.513, $p<0.001$). The duration from initiation of opioids to the need for additional anti-emetic treatment was shorter in the non-prophylactic group than that in the prophylactic group ($p<0.001$; Figure 2). Since it is difficult to evaluate whether additional anti-emetics were prescribed to patients who died early, the same test was performed while excluding patients who died within 2 weeks of the start of opioids and patients who died within 4 weeks of the start of opioids. The results showed that anti-emetics were added significantly earlier in the non-prophylactic group than in the prophylactic group, as observed in the overall cohort analysis (both $p<0.001$). Since it cannot be ruled out that the cumulative incidence of additional anti-emetics and premature mortality may be competing factors, Gray's test was performed. The results also showed that prophylactic anti-emetic use significantly suppressed the addition of anti-emetics and had no effect on death ($p<0.001$ and $p=0.902$, respectively; Figure 3). Multivariate analysis showed that an

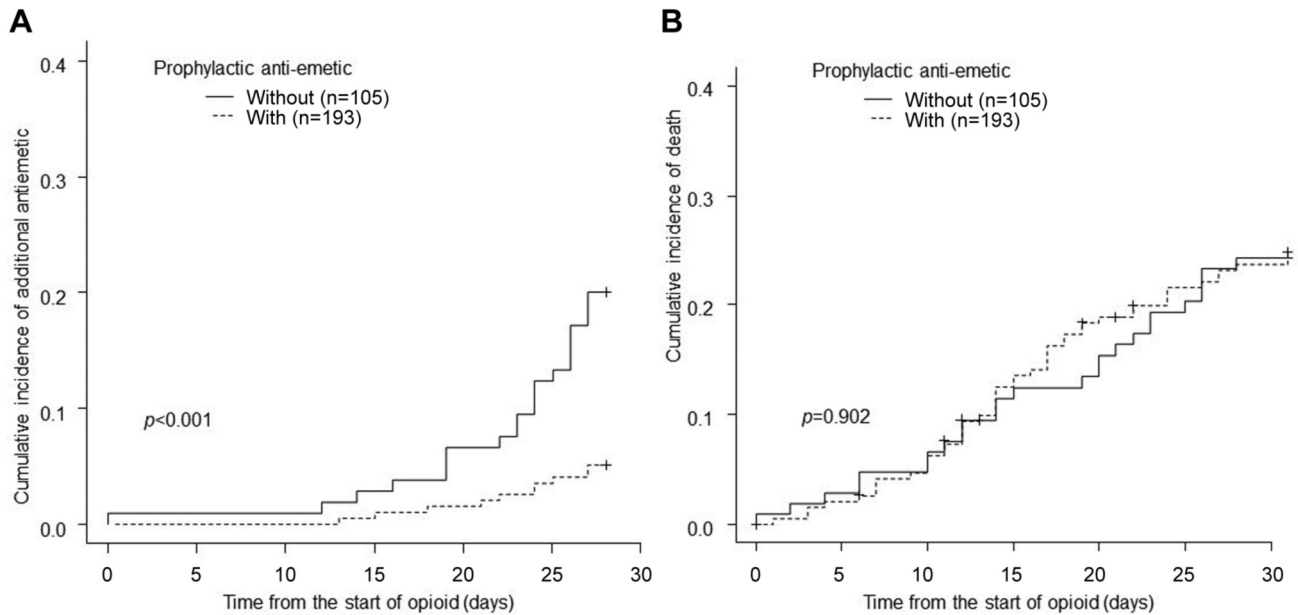


Figure 3. Cumulative incidence of additional use of anti-emetic (A) and death within 1 month (B) of opioid use according to treatment with and without prophylactic anti-emetic. The cumulative incidence of additional use of anti-emetics and death within 1 month was analysed using Gray's test.

additional anti-emetic was more often prescribed for females in the group without prophylactic anti-emetic, and for the patients who were switched from tramadol to strong opioids. These differences were found to be significant (Table II).

Discussion

Several studies have reported on prophylactic anti-emetic use for OINV. One study reported that 82% of Japanese physicians prescribed prophylactic anti-emetics at the initiation of opioid therapy, despite the lack of evidence regarding their prophylactic benefit (6). Another study reported that 45% of physicians in Italy reported using prophylactic anti-emetic drugs for OINV (7), which is much lower than the reported use in Japan. In our study, a prophylactic anti-emetic was administered to prevent OINV in 64.8% of the patients receiving strong opioids, which is less than that stated in a previous report in Japan (6). The lower rate of prophylactic anti-emetic use recorded in this study may be because this was a single-centre retrospective study.

In a previous single-centre study of 83 patients in Japan, prophylactic treatment with anti-emetics was reported to reduce the incidence of OINV (8). Several other retrospective studies reported that premedication with dopamine D2 blockers was not effective for preventing OINV (9-11). In our study, prophylactic anti-emetic use significantly reduced the need for additional anti-emetics (odds ratio 0.220, 95% confidence interval=0.0883-0.513, $p=0.0001$). However, a randomized, placebo-controlled, double-blind trial to evaluate

the efficacy and safety of prophylactic treatment with prochlorperazine for preventing OINV reported no prophylactic benefit of prochlorperazine, and the routine use of prochlorperazine as a prophylactic anti-emetic at the initiation of opioid treatment was not recommended (12). In addition to prochlorperazine, metoclopramide and olanzapine are used as treatment options for OINV but they are mainly dopamine D2 inhibitors. At the Emergency Department, ondansetron is often used to prevent OINV but a prospective observational study reported that ondansetron did not actually appear to be effective in preventing OINV (13). Hence, for the prevention of OINV, appropriate drugs need to be identified and evaluated in a prospective study.

Our study had several limitations. Firstly, no outcomes have been established for use in clinical trials to assess the efficacy of any medication to prevent OINV. We evaluated outcomes regarding the need for an additional anti-emetic in this study but the validity of our method cannot be confirmed. Moreover, it would have been helpful to evaluate whether the patients developed nausea, but because our study was retrospective, using data from the medical records, it was not possible to make a detailed evaluation of the symptoms of nausea. Furthermore, we did not evaluate whether nausea was actually the reason for opioid switching.

Gastrointestinal tract tumours were more common in the group that did not receive prophylactic administration of anti-emetics, and there was also a difference in the type of opioid used (Table I). Patients with primary gastrointestinal

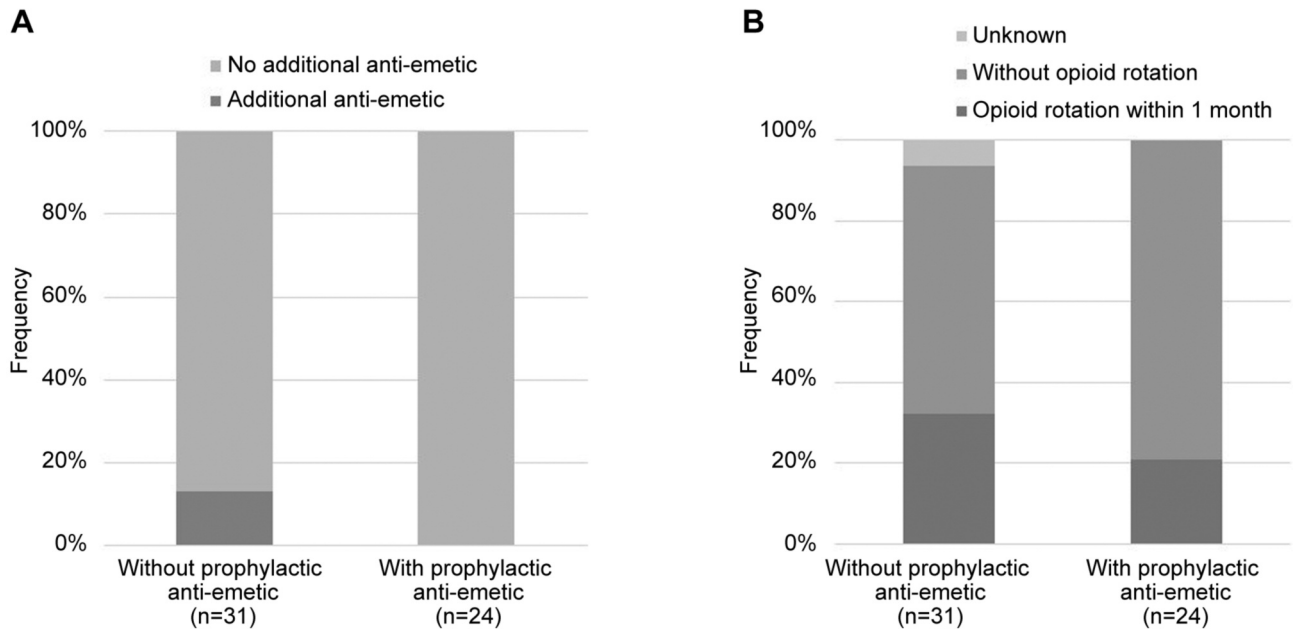


Figure 4. Incidence of the need for additional anti-emetics (A) and short-term opioid rotation (B) in patients with gastrointestinal tumour.

tumours were less likely to be prescribed prophylactic anti-emetics and more likely to receive fentanyl. Although no significant difference was found in the multivariate analysis, it cannot be denied that the difference in primary lesions may have led to the need for additional prescription of anti-emetics. In addition, patients who were introduced to opioids as outpatients were less likely to receive prophylactic anti-emetics, and the non-preventative group tended to be prescribed lower doses of opioids at the time of introduction. We think it is unlikely that this caused the additional prescription. In patients with gastrointestinal tumour, there was no significant difference between the groups with and without prophylactic anti-emetic regarding the use of additional anti-emetics and short-term opioid rotation ($p=0.123$ and 0.364 , respectively; Figure 4).

On multivariate analysis, the use of prophylactic anti-emetic agents, and sex were independent factors that influenced the need for additional anti-emetic drugs (Table I). There were many males in the prophylactic anti-emetic group but there was no significant difference in sex between the two groups. Previous studies have also shown that female sex is a risk factor for OINV, and it cannot be ruled out that this study may have influenced the results (11, 14). Interestingly, although there was no significant statistical difference, patients who were switched from tramadol were more likely to be prescribed additional anti-emetics. A separate study reported that the adverse effects of strong opioids were more pronounced in patients with a history of tramadol treatment (15). Similar results were obtained in our

study. Despite limited research results, prophylactic administration of anti-emetic drugs seems to be effective in preventing OINV.

The results of this study demonstrate that prophylactic administration of anti-emetics at the initiation of opioid analgesics might reduce OINV. Routine use of prophylactic anti-emetics at the initiation of opioid treatment is not recommended, but some patients might benefit from prophylactic anti-emetics. Further research is necessary to select suitable anti-emetics for prophylactic administration to prevent OINV.

Conflicts of Interest

The Authors declare no conflicts of interest in regard to this study.

Authors' Contributions

Tamura T wrote the article, Tamura T, Kawakado K, Makimoto G, Nakanishi M contributed to all aspects of the study's design, Kuyama S supervised the article and prepared the final version of the article. All listed Authors contributed to the arguments of the article and read and approved the final submission.

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