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Research Article

Analysis of Antiemetic Premedication Administration Timing on Nausea and Vomiting Incidence among Breast Cancer Patients Receiving Chemotherapy

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Abstract

The risk factors affecting chemotherapy-induced nausea and vomiting (CINV) include antiemetic premedication time pattern, and this study investigates the capability of enhancing this in breast cancer patients receiving high emetogenic chemotherapy (HEC). Furthermore, this observational research was implemented at the oncology unit of Dr. Soetomo General Hospital Surabaya over a three-month period involving 69 female patients. The results showed unspecific antiemetic premedication timing in comparison to those with recommended timeframes, was connected with greater occurrence of both acute nausea in all cycles of chemotherapy ($p<0.05$), and acute vomiting in second and third cycles ($p<0.05$) but not in the first cycle ($p=0.49$). However, specific time administration of antiemetic treatment was linked with lower incidence of delayed nausea in all cycles ($p<0.05$), and less delayed vomiting in second and third cycles ($p<0.05$) but not in first cycle ($p=0.10$). These findings indicate specific time administration of antiemetic drugs causes significant advantages in mitigating CINV among breast cancer patients treated with emetogenic chemotherapy, and significantly lessened the occurrence of acute and delayed nausea and vomiting.

Keywords: Antiemetic premedication timing, breast cancer, CINV, nausea and vomiting

Analisis Waktu Pemberian Premedikasi Antiemetik terhadap Kejadian Mual Muntah pada Pasien Kanker Payudara yang Mendapatkan Kemoterapi

Abstrak

Kemoterapi dapat menginduksi mual muntah (*chemotherapy-induced nausea and vomiting*, CINV) yang dipengaruhi oleh beberapa faktor. Salah satu faktornya adalah waktu pemberian premedikasi antiemetik yang dapat meningkatkan kejadian CINV pada pasien kanker payudara yang menerima kemoterapi. Studi ini menganalisis waktu pemberian premedikasi antiemetik terhadap kejadian mual dan muntah yang terjadi pada pasien kanker payudara yang mendapatkan kemoterapi dengan tingkat emetogenik yang tinggi. Penelitian ini merupakan penelitian observasional prospektif dilakukan di Poli Onkologi Satu Atap RSUD Dr. Soetomo Surabaya selama periode pengambilan data tiga bulan dan melibatkan 69 wanita kanker payudara yang mendapat kemoterapi dengan tingkat emetogenik yang tinggi. Pemberian premedikasi antiemetik dengan waktu yang tidak spesifik, meningkatkan kejadian mual akut pada semua siklus dengan $p<0,05$ dan pada kejadian muntah akut pada siklus kedua dan ketiga ($p<0,05$), namun tidak pada siklus pertama kemoterapi ($p=0,49$). Pemberian premedikasi antiemetik dengan waktu spesifik dapat menurunkan kejadian mual tertunda di siklus pertama hingga ketiga ($p<0,05$) dan pada kejadian muntah tertunda pada siklus kedua dan ketiga ($p<0,05$), namun tidak pada siklus pertama ($p=0,10$). Penelitian ini memberikan bukti bahwa premedikasi antiemetik yang diberikan dengan waktu spesifik memberikan manfaat dalam mengurangi kejadian CINV yang berpotensi pada pasien kanker payudara yang mendapatkan kemoterapi dengan tingkat emetogenik tinggi.

Kata kunci: CINV, kanker payudara, mual dan muntah, waktu pemberian premedikasi antiemetik

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Introduction

One of the most prevalent types of neoplasm is breast cancer. About 50% of Indonesian women suffered from breast cancer have their disease diagnosed at an advanced stage.[1,2] The standard treatment for breast cancer involves the use of chemotherapy.[3] Combination chemotherapy regimens are associated with higher response rates compared to single-agent therapies. In addition, it is often associated with chemotherapy induced nausea and vomiting (CINV), serious adverse effect that is able to negatively impact upon patients quality of life (QoL) and how they could allow and comply with therapy.[4–6] The known patient-related risk factors involves young age, female gender, low alcohol intake history, and prior adverse experience with chemotherapy.[7–9] Anthracycline-based chemotherapy is categorized as a highly emetogenic chemotherapy (HEC).[10] Some chemotherapy drugs are highly emetogenic (>90% frequency of emesis, for instance, cisplatin and combination anthracycline with cyclophosphamide), moderate emetic risk (30–90% frequency of emesis, for instance, cyclophosphamide, carboplatin, and epirubicin), low emetic risk (10–30% frequency of emesis, for instance, etoposide) and minimal emetic risk (<10% frequency of emesis, for instance, bleomycin).[11–13] The combinations of several chemotherapeutics agents can increase CINV activity. CINV prevention and treatment is a prevention against CINV and antiemetic given to patients receiving chemotherapy.[14]

CINV is associated with significant decline in their life quality and is perceived by patients as one of the most important adverse effects associated with cancer treatment.[6] Risk factors for developing CINV are classified as patient or treatment-related. Meanwhile, some variability could be observed in patient risk factors on the basis of chemotherapy regimen, the common patient-related factors including younger age, female, lower history of alcohol use (<5 standard drinks per week), emesis with prior chemotherapy and a dosing schedule of premedication antiemetic that covers both acute and delayed emesis.[7,8] CINV can be subdivided as acute and delayed. Acute onset nausea and vomiting usually follow within a few minutes to several hours after drug administration. In addition, this commonly resolves within the first 24 hours. After 5 to 6 hours, the intensity of acute emesis generally is at its peak. The incidence of acute emesis related to CINV is high on younger women with lower ethanol usage and had experienced CINV before. The dose of emetogenic agent and antiemetic regimen also contribute to the incidence of CINV. On the other hand, delayed nausea and vomiting usually occurs in the period 24–120 hours after chemotherapy.[8,10,15]

National Comprehensive Cancer Network (NCCN) guidelines provide a classification that addresses the likelihood of CINV that is primarily related to the emetogenic potential of the specific chemotherapeutic agents applied. Patient who got acute emesis and did not take any antiemetic prophylaxis, therefore the chemotherapeutic agents can be classified into four types. The first is high emetic risk (higher than 90% of patients experiencing acute emesis: e.g. combination of anthracycline and cyclophosphamide, cisplatin, and cyclophosphamide >1500 mg/m^2); the second one is moderate emetic risk (30–90% of patients suffering acute emesis: e.g. carboplatin, cyclophosphamide 1500 mg/m^2, daunorubicin, doxorubicin, epirubicin, and ifosfamide); the third one is low emetic risk (10–30% of patients with acute emesis: e.g. cytarabine 100–200 mg/m^2, docetaxel, etoposide, 5-fluorouracil, gemcitabine, and paclitaxel); and the fourth is minimal emetic risk (fewer than 10% of patients experience acute emesis: e.g. bleomycin, vinblastine,

vincristine, and vinorelbine).[8,13,15] The common way to prevent chemotherapy-induced nausea and vomiting is by performing antiemetic therapy before chemotherapy. The antiemetic therapy should also be continued for the same period as the duration of the emetic activity of the chemotherapeutic agent being used.[16] The acute CINV occurs within 1–2 hours of chemotherapy administration and can last for up to 24 hours, the delayed CINV presents more than 24 hours until 120 hours periods after chemotherapy administration.[17] The antiemetic premedication has reduced the vomiting prevalence considerably, but the evaluation shows that approximately 60.7% of patients still undergo either acute or delayed nausea following the chemotherapy.[18]

At oncology unit of Dr. Soetomo General Hospital, antiemetic regimen used during highly emetogenic chemotherapy includes a 5-Hydroxytrptamine (5-HT3) receptor antagonist (ondansetron), a corticosteroid (dexamethasone), an antihistamine (diphenhydramine) and an H2 receptor antagonist (ranitidine). Dr. Soetomo General Hospital adopts antiemetic premedication protocol of NCCN version 2.2017 guideline. The protocol is applied on cancer patients receiving high emetogenic chemotherapy (HEC), namely 5-HT_3 (ondansetron 8–16 mg intravenous administration), antagonist NK-1 (aprepitant 125 mg per oral administration), and dexamethasone 12 mg (intravenous or per oral administration).[19] However, antagonist NK-1 (aprepitant) is not widely available in Indonesia, therefore the protocol is modified by adding ranitidine and diphenhydramine. Ranitidine inhibits H2 receptors and minimizes gastric acids secretion resulting in preventing nausea and vomiting, while diphenhydramine inhibits H1 receptors and to reduce vestibular stimulation and thus preventing nausea and vomiting.[20] Although this type of regimen is known to be effective in preventing nausea and vomiting by chemotherapy with low emetogenic potential, previous study suggests that this approach may not be effective for patients who received chemotherapy with moderate and high emetogenic levels.[13,19]

Antiemetic premedication timing is one of the risk factors increasing CINV incidence. According to US National Cancer Institute, antiemetic premedication (ondansetron) must be administered within 15–30 minutes before chemotherapy to prevent nausea and vomiting.[21] The administration timing is determined based on ondansetron onset of action to prevent nausea and vomiting. Based on this introduction, this study analyzes whether specific time administration of antiemetic premedication can reduce nausea and vomiting incidence of breast cancer patients receiving high emetogenic chemotherapy.

Methods

This was a prospective observational study analyzing antiemetic premedication administration timing on nausea and vomiting incidence of breast cancer patients, who receiving high emetogenic chemotherapy at oncology unit of Dr. Soetomo General Hospital Surabaya. However, the purpose of this study was not to investigate differential effect of antiemetic premedication timing on nausea and vomiting incidence. This study was declared ethical by the health research ethics committee of Dr. Soetomo General Hopital Surabaya with approval number 100/Pan.KKE/II/2016.

The participants recruited in this study were women with breast cancer underwent their first chemotherapy cycle with antiemetic premedication as prophylaxis between March to April 2016. The inclusion criteria of this study were breast cancer patients receiving chemotherapy since the first cycle, who never done any chemotherapy before and receiving

antiemetic premedication as prophylaxis of emesis. All patients were observed from first until the third cycle of chemotherapy and interviewed from the first cycle through the third cycle of chemotherapy. The exclusion criteria were breast cancer patients that receives chemotherapy without antiemetic premedication and the breast cancer patients receiving chemotherapy but not from the first cycle. Meanwhile, the drop out criteria were breast cancer patients who passed away during the research, withdrawing their participation from this research, and those who were not continuing their chemotherapy treatment.

Antiemetic premedication (ondansetron) was given 15 until 30 minutes before chemotherapy which was considered specific time, while less than 15 minutes and more than 30 minutes of antiemetic administration was considered unspesific time. Antiemetic premedication administration time refers to the interval between the end of antiemetic (ondansetron) administration to the start of chemotherapy. The subjects were followed from first until third chemotherapy cycle and underwent structured interview by a pharmacist to evaluate the response to antiemetic treatment. After completing each cycle of chemotherapy, patient filled questionnaire. The observation was conducted for five days after chemotherapy being held. The interview was carried out on every cycle of chemotherapy (first cycle, second cycle, and third cycle). The patients are interviewed twice per cycle, namely 24 hours after chemotherapy (acute CINV) and 120 hours after chemotherapy (delayed CINV) (Figure 1). Then, the analysis of antiemetic premedication timing on nausea and vomiting was performed. The incidence of nausea and vomiting that occurred during the acute and delayed time frames was assessed using a shortened Indonesian language version of the

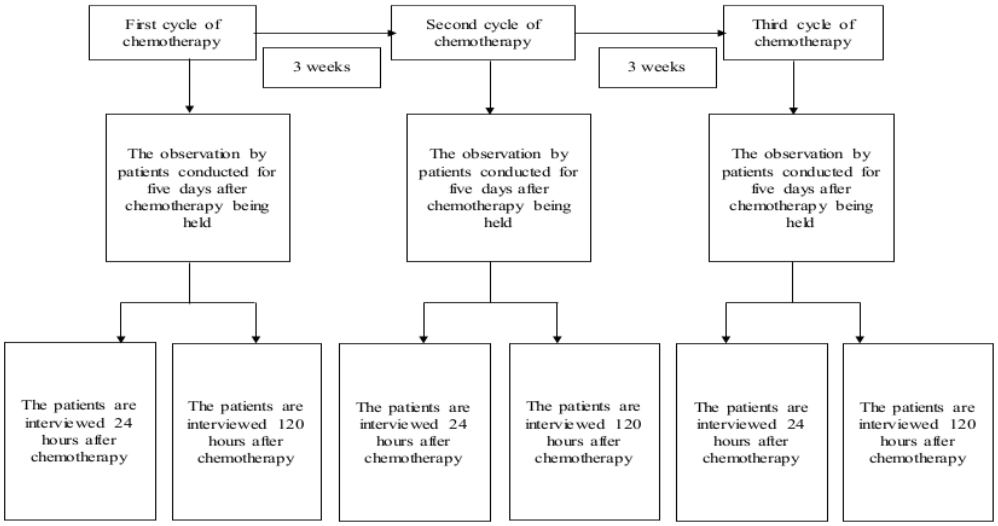

Figure 1 The Observation Workflow during Collecting Patient's Data with Acute and Delayed Nausea Vomiting after Chemotherapy

Patient interview was carried out on every cycle of chemotherapy (first cycle, second cycle, and third cycle). The patients were interviewed twice per cycle, namely 24 hours after chemotherapy (acute chemotherapy induced nausea and vomiting (CINV)) and 120 hours after chemotherapy (delayed CINV).

assessment of antiemetic efficacy and safety questionnaire with NCI-CTCAE version 4.03 guideline to assess the grade of nausea and vomiting.[10,22,23] Mann-Whitney test was used to analyze each variable between the groups. Statistical analysis were computed on a significance level of 5%.

Results

During the data capture period, 72 women proceeded to receive chemotherapy, with 3 subjects who dropped out (one deceased, two declining interview) leaving 69 patients who proceeded to evaluation. All patients were women, with 17% aged <40 years old, 74% aged 40–60 years old, and 9% aged >60 years old. A variety of chemotherapy regimens were used, all of which were classified as highly emetogenic (85% was treated using Cyclophosphamide, Adriamycin, Fluorouracil; 12% using Cyclophosphamide, Epirubicin, Fluorourcil; or 3% using Cyclophosphamide, Adriamycin). All patients received the same antiemetic premedication combination. First, ranitidine 50 mg in 8 ml normal saline was given intravenous bolus injection. Second, diphenhydramine 10 mg in 4 ml normal saline was given intravenous bolus injection. Third, dexamethasone 20 mg in 100 ml D5% with intravenous drips for 15 minutes. The fourth, ondansetron 8 mg in 50 ml normal saline administered through intravenous drips for 10 minutes (Table 1).

The distribution of timing for the administration of antiemetic premedication was highly variable. The range of antiemetic premedication administration time was within 15 minutes until more than 2 hours before chemotherapy. Most of patients received unspecific antiemetic premedication timing, whereas only small amount of patients that had specific time administration of antiemetic premedication.

The analysis of antiemetic premedication timing on the prevalence of acute nausea and vomiting at first, second, and third cycles of chemotherapy could be seen at Table 2, 3, 4, and 5. Those tables showed that either in acute or delayed CINV, unspecific antiemetic premedication timing significantly increased the acute and delayed nausea and vomiting. Unspecific antiemetic premedication timing was associated with a greater prevalence of acute nausea all cycles of chemotherapy ($p<0.05$) and with a greater prevalence of acute vomiting in second and third cycles ($p<0.05$) but not in first cycle of chemotherapy ($p=0.49$). Specific time administration of antiemetic treatment was associated with a lower prevalence of delayed nausea in all cycles ($p<0.05$), as well as a lower prevalence of delayed vomiting in second and third cycles ($p<0.05$) but not in first cycle of chemotherapy ($p=0.10$).

Discussion

Breast cancer is a common malignancy in Indonesia and around the world.[24] CINV associated with cytotoxic chemotherapy in this context has a potentially major role upon well being, treatment tolerability and overall treatment outcomes.[6] The use of chemotherapy can produce nausea and vomiting. These particularly unpleasant impressions continue be a problem despite better antiemetic.[25,26] The main objective of this study was to analyze antiemetic premedication administration timing on nausea and vomiting incidence of breast cancer patients, who received high emetogenic chemotherapy in oncology unit in Dr. Soetomo General Hospital Surabaya. This prospective observational study was carried out due to the limited number of nurses working at chemotherapy ward and the time difference between antiemetic premedication and chemotherapy regimens transfer from pharmacy unit to chemotherapy wards. The time difference caused interval between

Table 1 Patients Characteristic

Characteristics	Total	Percentage (%)
Age		
<40 years	12	17.00
40–60 years	51	74.00
>60 years	6	9.00
(Average±SD)	(48±8.92)	
(Range min-max)	(22–66)	
Gender		
Female	69	100.00
Male	0	0.00
Type of Cancer		
Breast cancer	69	100.00
Chemotherapy Regimen		
Cyclophosphamide, Adriamycin, Fluorouracil (CAF)	59	85.00
Cyclophosphamide, Epirubicin, Fluorourcil (CEF)	8	12.00
Cyclophosphamide, Adriamycin (CA)	2	3.00
Level of Emetogenic Chemotherapy		
High emetogenic chemotherapy	69	100.00
Moderate emetogenic chemotherapy	0	0.00
Low emetogenic chemotherapy	0	0.00
Minimal emetogenic chemotherapy	0	0.00
Dose of Chemotherapy		
CAF 600/60/600	1	1.45
CAF 600/70/750	1	1.45
CAF 605/60/600	1	1.45
CAF 700/70/700	12	17.39
CAF 750/75/750	16	23.18
CAF 790/79/790	1	1.45
CAF 800/70/750	4	5.80
CAF 800/70/1000	6	8.69
CAF 800/75/750	1	1.45
CAF 800/80/800	14	20.29
CAF 850/85/850	1	1.45
CAF 900/90/900	1	1.45
CA 70/800	2	2.90
CEF 700/70/700	2	2.90
CEF 750/75/750	2	2.90
CEF 800/80/800	2	2.90
CEF 850/85/850	1	1.45
CEF 1000/80/1000	1	1.45
Combination Antiemetic Premedication		
Ranitidine 50 mg in 8 ml normal saline Diphenhydramine 10 mg in 4 ml normal saline Dexamethasone 20 mg in 100 ml D5% Ondansetron 8 mg in 50 ml normal saline	69	100.00

Different doses of chemotherapy did not significantly affect emetogenic level of the chemotherapy. All chemotherapy combinations administered were categorized as high emetogenic chemotherapy.

Table 2 The Analysis of Antiemetic Premedication Timing on Incident of Acute Nausea

Cycle	Antiemetic Premedication Timing	Nausea	Negligible	p
		n (patient)	n (patient)	
1	Specific time	0	6	<0.05
	Unspecific time	36	27	
2	Specific time	0	13	<0.05
	Unspecific time	32	24	
3	Specific time	2	29	<0.05
	Unspecific time	25	13	

*This research used Mann-Whitney test; Unspecific antiemetic premedication timing was associated with a greater prevalence of acute nausea all cycles of chemotherapy with p<0.05.

antiemetic premedication (ondansetron) and chemotherapy drugs administration. This study also intended to observe and evaluate the nurses awareness of the important of time interval between antiemetic premedication and chemotherapy regimens administration.

This study controlled several risk factors including all patients were female breast cancer patients, and all of them received HEC. This observation was carried out starting from the first cycle of chemotherapy in order to have the same history of CINV, and all patients received the same antiemetic premedication. This was controlled to obtain homogeneous patients thereby reducing the bias. This research has demonstrated that unspecific time administration of antiemetic premedication was associated with compromised antiemetic treatment efficacy, to some extent in the acute stage and more prominently in the late phase.

Dr. Soetomo General Hospital adopts antiemetic premedication protocol of NCCN version 2.2017 guideline, which is applied on cancer patients receiving HEC, namely 5-HT_3 (ondansetron 8–16 mg intravenous administration), antagonist NK-1 (aprepitant 125 mg per oral administration), and dexamethasone 12 mg (intravenous or per oral administration).[19] Since aprepitant is not available in Indonesia, Dr. Soetomo General Hospital adjusts antiemetic premedication protocol by administering 5-HT_3 (ondansetron 8 mg), dexamethasone 20 mg, H2 blocker (ranitidine 50 mg), and (diphenhydramine 10 mg). Ranitidine and diphenhydramine are modifications added to antiemetic premedication protocol to prevent nausea and vomiting incidence on patient. Ranitidine inhibits H2 receptors and minimizes gastric acids secretion resulting in preventing

Table 3 The Analysis of Antiemetic Premedication Timing on Incident of Acute Vomiting

Cycle	Antiemetic Premedication Timing	Vomiting	Negligible	p
		n (patient)	n (patient)	
1	Specific time	0	6	0,498
	Unspecific time	11	52	
2	Specific time	0	13	<0.05
	Unspecific time	16	40	
3	Specific time	0	31	<0.05
	Unspecific time	8	30	

*This research used Mann-Whitney test; Unspecific antiemetic premedication timing was associated with a greater prevalence of acute vomiting in second and third cycles of chemotherapy with p<0.05, but not in first cycle of chemotherapy with p=0.498.

Table 4 The Analysis of Antiemetic Premedication Timing on Incident of Delayed Nausea

Cycle	Antiemetic Premedication Timing	Nausea	Negligible	p
		n (patient)	n (patient)	
1	Specific time	3	3	<0.05
	Unspecific time	59	4	
2	Specific time	6	7	<0.05
	Unspecific time	53	3	
3	Specific time	21	10	<0.05
	Unspecific time	35	3	

*This research used Mann-Whitney test; Specific time administration of antiemetic treatment was associated with lower prevalence of delayed nausea all cycles chemotherapy with p<0.05.

nausea and vomiting, while diphenhydramine inhibits H1 receptors and to reduce vestibular stimulation and thus preventing nausea and vomiting.[20] It was confirmed that the administration of antiemetic premedication was not effective on HEC. However, the administration of antiemetic premedication at a specific time might reduce nausea and vomiting incidence on patients.

These findings are similar to those seen in previous research. It has previously been observed that the administration of high emetogenic chemotherapy frequently caused delayed CINV rather than acute CINV. The administration of antiemetics in controlling delayed CINV might work less optimally. Complete protection from acute and delayed nausea in the initial cycle of chemotherapy were 60% and 45%, accordingly, for great emetic risk chemotherapy and the rates were advanced in the whole cycles.[27–30] The incidence of acute and delayed CINV during first, second, and third cycles of chemotherapy could reduce the occurence and severity of acute nausea but not delayed nausea. In the incidence of vomiting, the regimentation could also reduce the incidence and severity of both acute and delayed vomiting (the response is greater than in nausea). Patient at high risk for CINV failed to achieve good nausea control.[31] The use of premedication antiemetic has reduced the incidence of vomiting, but 30–60% of the patients still experienced either acute or delayed nausea.[4] This study focused on the timing of antiemetic premedication for the incidence of acute CINV and delayed CINV. Breakthrough CINV is nausea and vomiting incidence

Table 5 The Analysis of Antiemetic Premedication Timing on Incident of Delayed Vomiting

Cycle	Antiemetic Premedication Timing	Vomiting	Negligible	p
		n (patient)	n (patient)	
1	Specific time	0	6	0.100
	Unspecific time	26	37	
2	Specific time	2	11	<0.05
	Unspecific time	26	30	
3	Specific time	8	23	<0.05
	Unspecific time	23	15	

*This research used Mann-Whitney test; Specific time administration of antiemetic treatment was associated with lower prevalence of delayed vomiting in second and third cycles chemotherapy with p<0.05, but not in first cycle of chemotherapy with p=0.100.

for 5 days on patients receiving emetic prophylaxis that requires rescue antiemetic as additional therapy to control nausea and vomiting incidence. Breakthrough CINV will not be discussed in this study. Anticipatory CINV is nausea and vomiting incidence that occurs between the cycles of chemotherapy and is associated with previous CINV.[32] Anticipatory CINV was also excluded from the discussion because it occured before each cycle of chemotherapy which was beyond our observation time period.

The research findings here provide further evidence that specific time administration of antiemetic drugs produces important benefits in reducing CINV among people treated with emetogenic chemotherapy for breast cancer. The results emphasize the need to schedule workflows to improve the timeliness of antiemetic treatment provided in this setting. Possible approaches to explore could involve schedule workflow for dispensing and delivery of antiemetic drugs, more involvement from pharmacists in the processes of preparing the medications for administration (currently undertaken by nursing staff), greater education for nursing and medical staff about the importance of specific antiemetic treatment timing, and greater standardization of practices overall. The effects of scheduled workflow and changes to practice should be re-assessed in future research. If more specific time administration of the antiemetic drugs cannot produce a more robust response in reducing delayed phase CINV, especially in cycles after the initial treatment, it is also possible that changes to the antiemetic treatment regimen may need to be considered and evaluated.

This research study has a range of limitations. The sample size was small and some participants declined to participate. The study design did not explore or document the reasons for unspecific time administration of antiemetic treatments, and the protocol was not sufficiently powered to allow detailed exploration of the effects associated with different category of chemotherapy regimens. Randomized controlled trial (RCT) study was not carried out since the objective of this study was to analyse the effect of antiemetic premedication timing on nausea and vomiting incidence with the limited number of nurses. Future research studies could be designed to address these limitations and to provide additional data to explore these aspects of this clinically important issue.

Conclusion

Specific time administration of antiemetic premedication may minimize the incidence of nausea and vomiting. This study suggests that scheduled workflow and other approaches to increase the timeliness of antiemetic treatment may enhance protection against CINV for people treated with emetogenic chemotherapy for breast cancer, potentially improving quality of life and improving outcomes.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12