RESEARCH ARTICLE

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Efficacy of Premedication Protocol without Ranitidine for Taxane Regimen: A Multicenter Non-Randomized Historical Controlled Study

Chaichana Chantharakhit[1]*, Tanarat Ruchakorn[2], Somprattana Mungkornkaew[3], Pichyanin Amorntrakoon[4], Siwadonn Tassanamethee[5], Pathra Theeratrakul[1], Nantapa Sujaritvanichpong[1]

Abstract

Objective: To study the efficacy of the prevention of immediate hypersensitivity reactions (HSRs) from omitting ranitidine in the premedication protocol in patients who had chemotherapy with taxane regimen. **Methods:** This was a Multicenter, Ambispective Non-Randomized Historical Controlled Cohort Study. The incidence of HSRs in the patients who had the modified premedication without ranitidine were collected to compare with the historical group who had the standard premedication protocol with ranitidine. The relationships of each HSRs in the experimental group were compared with the historical control group using a multilevel regression analysis with the random-effects model. **Result:** A total of 441 patients were enrolled and analyzed in this study. 221 patients received the modified premedication protocol compared with 220 patients who received the standard premedication protocol in the historical group. HSRs were observed in 6 of 768 cycles of chemotherapy (0.78%) in a group of patients with the modified premedication protocol. Moreover, it was found in 4 of 761 cycles of chemotherapy (0.52%) in a group of patients with the standard premedication protocol. When comparing the relationship of the HSRs incidence between the groups using multilevel regression analysis with the random-effects model, there were no differences with a statistical significance (regression coefficients = 0.008, p-value = 0.30). **Conclusion:** The results of the study comprised evidence-based medicine supporting the safety of omitting ranitidine from the premedication protocol for the patients who had a taxane regimen and had a similar rate of HSRs to the use of ranitidine.

Keywords: Taxane- Hypersensitivity reactions (HSRs)- Ranitidine- Premedication

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Introduction

Paclitaxel and docetaxel are used for chemotherapy in the Taxane regimen, which are anti-microtubules used for cancer treatment, including non-small cell lung cancer, breast cancer, ovarian cancer, endometrial cancer, esophageal cancer, head and neck cancer, etc. The records indicated that there were 10-40% of hypersensitivity reactions (HSRs) from Taxane regimen, particularly paclitaxel, at a mild to moderate level, while 1% was at a severe level (Picard and Castells, 2015; Picard, 2017; Tsao et al., 2021) . The mechanism of immediate HSRs to taxane is generally attributed to the surfactants used in their formulation (Cremophor EL for paclitaxel and polysorbate 80 for docetaxel), which is a pharmaceutical chemical solvent used at a high level compared to other medicines (Sendo et al., 2005; Adams et al., 1993). Therefore, the incidence of HSRs in the patients who had taxane was higher than those who had other medicines. From previous studies, it was found that there were three mechanisms of HSRs (Weiss et al., 1990; Gelderblom et al., 2001; van Zuylen et al., 2000). The first mechanism was IgE-mediated mast-cell degranulation/ Type I hypersensitivity via immunity activation from the reaction of IgE on the mast cell to the stimulant to release the histamine to stimulate H1 receptor and H2 receptor, and resulted in the abnormal response. The second mechanism was Non-IgE-mediated idiosyncratic mast-cell degranulation, which had not been through IgE. The last mechanism was the complement activation of the body, the severity of which was related to the level of cremophor EL in the body.

*[1]Division of Medical Oncology, Department of Internal Medicine, Buddhasothorn Hospital, Chachoengsao, Thailand. [2]Vibharam Amatanakorn Specialized Cancer Hospital, Chonburi, Thailand. [3]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Buddhasothorn Hospital, Chachoengsao, Thailand. [4]Medical Oncology Clinic, Medical Department, Vibharam Hospital, Bangkok, Thailand. [5]Department of Surgery, Buddhasothorn Hospital, Chachoengsao, Thailand. *For Correspondence: Chaichana.MD@gmail.com*

Immediate HSRs to paclitaxel and docetaxel occur in approximately 10% of patients despite premedication and are severe in 1% (Sánchez-Muñoz et al., 2011; Broyles et al., 2020). Hypersensitivity symptoms generally develop within the first 10–15 minutes after infusion. The prevention of HSRs in the standard protocol comprises prolongation of infusion time, premedication combination drugs, which are drugs including dexamethasone, diphenhydramine (H1 antagonist), and H2 antagonist, which is ranitidine or famotidine (Rowinsky and Donehower, 1995; Boulanger et al., 2014). Ranitidine is widely used in the standard premedication protocol.

In January 2020, the United States Food and Drug Administration (US FDA) announced the withdrawal of ranitidine from the market after the discovery of N-nitrosodimethylamine (NDMA) as an ingredient of ranitidine; NDMA is a harmful chemical to health (White and Hernandez, 2021). For this reason, ranitidine was withdrawn from the market and production was canceled. As a result, there was no supply of ranitidine worldwide. Previous data showed that there was no higher risk of HSRs in the patients who received paclitaxel with premedication protocol without ranitidine when compared to those who had the standard premedication protocol (Gelderblom and Zwaveling, 2021; Cox et al., 2021). Moreover, some studies showed that evidence of using ranitidine to prevent HSRs was not as obvious as the use of steroid premedication.

The mechanism of ranitidine, which is an H2 antagonist restraining H2 receptor, affected gastric acid secretion when it was activated via IgE. For the server HSRs, the patients would have bronchospasm, dyspnea, and hypotension, which was through the mechanism H1 receptor pathway. Therefore, there was little evidence concerning the use of ranitidine in the premedication protocol to prevent HSRs. Further, the retrospective data showed that omitting ranitidine did not increase the incidence of HSRs. For this reason, the researcher would like to study the efficacy of the premedication protocol without ranitidine (modified premedication protocol) in patients who received taxane regimen to prevent HSRs due to the unavailability of ranitidine.

Materials and Methods

This therapeutic research comprised a non-concurrent controlled study, in which the control group included patients who had the premedication by the standard protocol with ranitidine and received taxane regimen (Historical controlled), while the intervention group included patients who had the modified premedication protocol without ranitidine. Thus, the method design was an ambispective non-randomized historical controlled cohort study. The objective was to study the efficacy of the prevention of HSRs incidence in the modified premedication protocol without ranitidine. The research steps were as follows.

1. Collect data on the incidence of HSR in patients treated with taxanes, i.e. paclitaxel and docetaxel, from May 2020 to December 31, 2020, which was the same period when the Pharmacy Department collected the data of HSRs incidence and had the premedication by the standard protocol with ranitidine. The data were collected from the database of the Pharmacy Department, Bhuddasothorn Hospital, including age, sex, cancer type, chemotherapy regimen with paclitaxel or docetaxel, dosage of paclitaxel or docetaxel, cycle, and incidence of HSRs. The severity of immediate HSRs was graded, as previously described in Table 1.(Brown, 2004)

2. Determine the new modified premedication protocol without ranitidine due to the unavailability of ranitidine to apply to patients with cancer who had the taxane regimen, paclitaxel and docetaxel. Patients were treated at the Division of Medical Oncology, Division of Gynecologic Oncology, and Department of Surgery, Buddhasothorn Hospital, Chachoengsao, Thailand, as well as the co-hospitals, i.e. Vibharam Amatanakorn Specialized Cancer Hospital, Chonburi, Thailand and Vibharam Hospital, Bangkok, Thailand.

Patients

Historical data of the patients were obtained from the Pharmacy Department, Buddhasothorn Hospital, who had the taxane regimen from May 2020 to December 31, 2020, which was the same period when the Pharmacy Department collected the data of HSRs incidence. The standard premedication protocol with ranitidine was applied as the historical control group.

Data from the patients who received the paclitaxel or docetaxel by the modified premedication protocol without ranitidine were collected and analyzed. The endpoint focused on the efficacy of the prevention of HSRs. The sample size, one study group, was determined using the statistical parameters from the known population incidence of 1.5% and anticipated incidence study group 5%, where the probability of Type I Error was at the alpha 0.05, the probability of Type II Error. The ability to detect a difference between groups (when a difference exists) was at the power of 80%, while the probability of non-response or dropout was 20%. A total of 200 samples who received the taxane was obtained.

Inclusion criteria

1. Being a patient aged over 18 years
2. Having cancer that required standard treatment with the taxane regimen, i.e. paclitaxel and docetaxel

Exclusion criteria

1. A patient with a history of severe hypersensitivity reactions from taxane, such as bronchospasm, hypotension, etc.
2. Have a severe hepatic impairment; the bilirubin >5xULN or AST/ALT >10xULN

Withdrawal criteria for individual participants

1. Have severe hypersensitivity reactions from taxane, such as bronchospasm and hypotension Approximately 80% of the population were at Buddhasothorn Hospital, which was the main center, while 20% were at the network center, including Vibharam Amatanakorn Specialized Cancer Hospital and Vibharam Hospital.

We conducted this study in compliance with the

principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board of Buddhasothorn Hospital (number BSH-IRB 010/2564). The study was registered by the Thai Registry of Clinical Trials with identification number TCTR20210322004. All participants signed written informed consent as endorsed by the Ethics Committee.

Statistical analyses

The relationship of the incidence of hypersensitivity reactions (HSRs) between the treatment group who had the standard premedication protocol (Historical control group) and modified premedication protocol without ranitidine (Intervention group) was analyzed. The HSRs were influenced by the intervention effect and time effect (chemotherapy cycle numbers). They were repeated measures of correlation data. Therefore, they were analyzed by multilevel regression analysis with the random-effects model. Imbalance confounding factors were adjusted in the regression model. A value of $p<0.05$ was considered statistically significant. Statistical analyses were performed using STATA version 16 (StataCorp, TX, USA).

Results

A total of 235 patients were eligible for participation in the eligible criteria, while fourteen patients were excluded (4 had severe hepatic impairment, 6 had severe renal impairment, and 4 refused chemotherapy). Therefore, 221 patients participated in the study and received the modified premedication protocol without ranitidine (Table 2) to compare with 220 patients in the historical control group who received the standard premedication protocol, as shown in Figure 1. Patients in the modified premedication protocol group received 768 chemotherapy treatments, while patients in the historical control group received 761 chemotherapy treatments. None of them withdrew from the study.

Baseline characteristics of patients in both groups

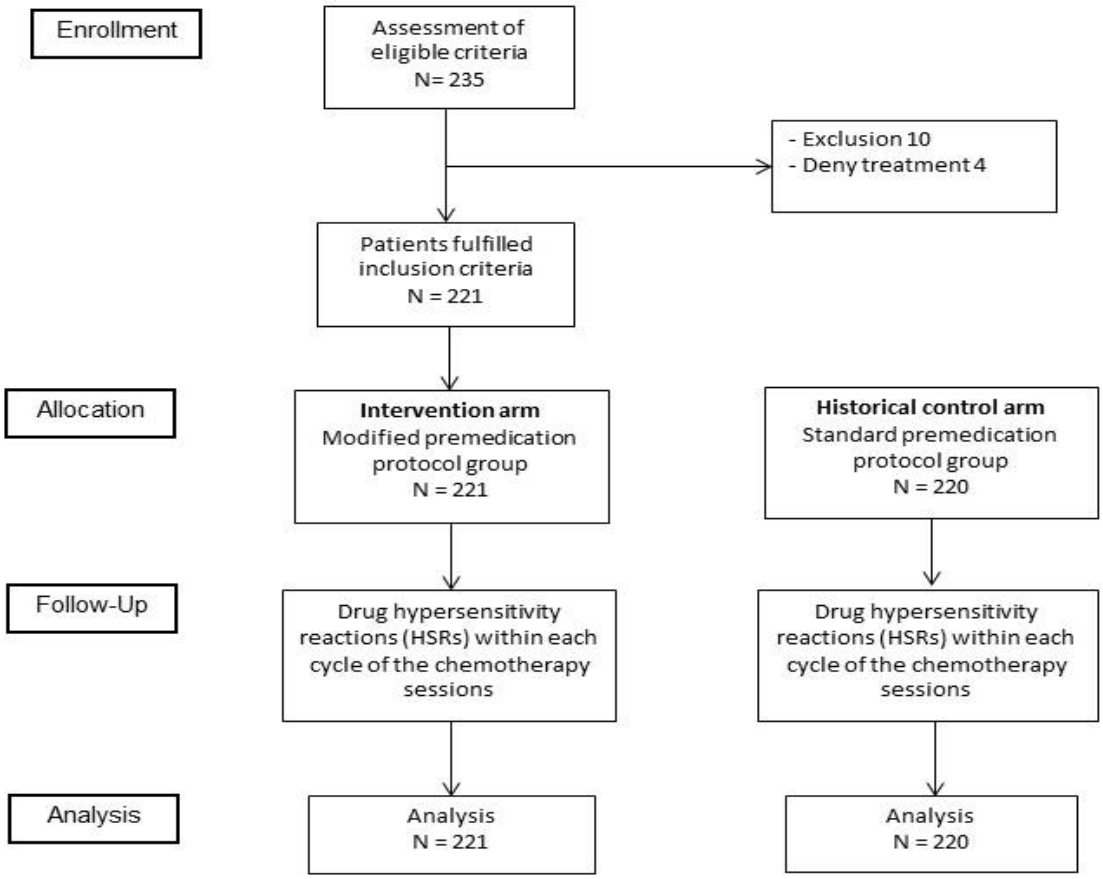

Figure 1. The CONSORT Flow Diagram

Table 1. Severity Grading System for Immediate HSRs

Grade	Severity	Description
1	Mild	Symptoms are limited to the skin (e.g., flushing) or involve a single organ/system and are mild (e.g. mild back pain).
2	Moderate	Symptoms involve at least 2 organs/systems (e.g. flushing and dyspnea), but there is no significant decrease in blood pressure or oxygen saturation.
3	Severe	Symptoms typically involve at least 2 organs/systems, and there is a significant decrease in blood pressure (systolic <90 mm Hg and/or syncope) and/or oxygen saturation (<92%).

Table 2. Protocols for Standard Premedication and Modified Premedication without Ranitidine

Schedule	Schedule
Standard premedication protocol	Modified premedication protocol
Dexamethasone 20 mg intravenous	Dexamethasone 20 mg intravenous
Ondansetron 8 mg intravenous	Ondansetron 8 mg intravenous
Ranitidine 50 mg intravenous	None (omit ranitidine)
Diphenhydramine 50 mg oral	Diphenhydramine 50 mg oral
Chlorpheniramine maleate 10 mg intravenous	Chlorpheniramine maleate 10 mg intravenous

showed no differences in age, sex, chemotherapy regimen, or number of cycles of chemotherapy. In terms of cancer type, they were similar; only breast cancer and ovarian cancer showed differences between the two groups. There were also no differences between the two groups for the combination chemotherapy. Only trastuzumab, the monoclonal antibody to HER2 gene, differed, as shown in Table 3.

It was also found that the patients who had the modified premedication protocol had HSRs 6 times out of 768 cycles of chemotherapy treatment (0.78%). Meanwhile, the patients in the historical control group who used the standard premedication protocol had HSRs 4 times out of 761 cycles of chemotherapy treatment (0.52%). Most of them were HSRs grade 1-2; there was only one HSRs grade 3 in the historical control group (Figure 2).

Table 3. Patient Characteristics

Characteristics	Standard premedication protocol N=220	Modified premedication protocol N= 221	p value
Age (year)			
Mean (+SD)	57.04 (11.81)	55.58 (10.94)	0.18
Gender, N (%)			
Male	54 (24.55)	47 (21.27)	0.24
Female	166 (75.45)	174 (78.73)	0.24
Cancer type, N (%)			
Lung	61 (27.73)	53 (23.98)	0.22
Breast	77 (35.00)	101 (45.70)	0.01*
Upper GI tract	6 (2.73)	10 (4.52)	0.23
Head and neck	4 (1.82)	6 (2.71)	0.38
Ovary	27 (12.27)	15 (6.79)	0.04*
Cervix	19 (8.64)	25 (11.31)	0.22
Endometrium	9 (4.09)	6 (2.71)	0.3
Skin	3 (1.36)	1 (0.45)	0.31
Sarcoma	4 (1.82)	1 (0.45)	0.19
Prostate	6 (2.73)	2 (0.90)	0.14
Anus	1 (0.45)	1 (0.45)	0.75
Hepatocellular carcinoma	2 (0.91)	0 (0.00)	0.25
Penis	1 (0.45)	0 (0.00)	0.5
Chemotherapy regimen, N (%)			
Paclitaxel	182 (82.73)	190 (86.36)	0.18
Docetaxel	38 (17.27)	30 (13.64)	0.18
Combination agent			
Carboplatin	117 (53.18)	105 (47.73)	0.15
Trastuzumab	6 (2.73)	17 (7.73)	0.02*
The number of cycles of chemotherapy (cycles)	761	768	0.92

*Statistically significant p-values

The analysis results on the relationship of HSRs incidence between the two groups indicated that the incidence of HSRs was affected by the intervention effect and time effect. It was the repeated measures of correlation data. For this reason, the multilevel regression analysis with the random-effects model was necessary to control the effects. Besides, the study design was a non-randomized controlled study, so the imbalance of prognostic factors by indication and contraindication was preliminary. However, the data of baseline patient characteristics, as shown in Table 3, indicated the balance of prognostic factors between both groups. However, breast cancer, ovarian cancer, and the receiving of trastuzumab were different. Nevertheless, these factors were not the prognostic factors by indication and contraindication. Only the factor relevant to the combination agent would be used in the regression analysis.

The results of multilevel regression analysis with the random-effects model with confounding factors adjustment shown in Table 4 revealed that the regression coefficient of HSRs of the standard premedication protocol was -0.002, whereas that of the modified premedication protocol was -0.005. Therefore, the HSRs between the two groups showed no statistically significant difference (regression coefficients = 0.008, p-value = 0.30).

Table 4. Multilevel Regression Analysis with the Random-Effects Model for Repeated Measures Correlation Data with Confounding Factor Adjustment

HSRs	coefficient	95% Confidence Interval	p value
Modified premedication protocol	0.008	-0.008, 0.024	0.34
Adjusted interaction of each cycle			
Standard premedication protocol	-0.002	-0.006, 0.001	0.19
Modified premedication protocol	-0.005	-0.009, -0.001	0.01
Regimen chemotherapy	-0.002	-0.007, 0.003	0.54
Random-effects Parameters			
patient: Independent	Estimate	95% Conf. Interval	
var (cycle)	3.56E-28	3.74e-30, 3.40e-26	
var (_cons)	0.001	0.001, 0.001	
var (Residual)	0.006	0.005, 0.006	
HSRs between standard protocol group and modified protocol group when adjusted for random-effects parameters and confounding factor		chi2 = 1.09, p-value = 0.30	

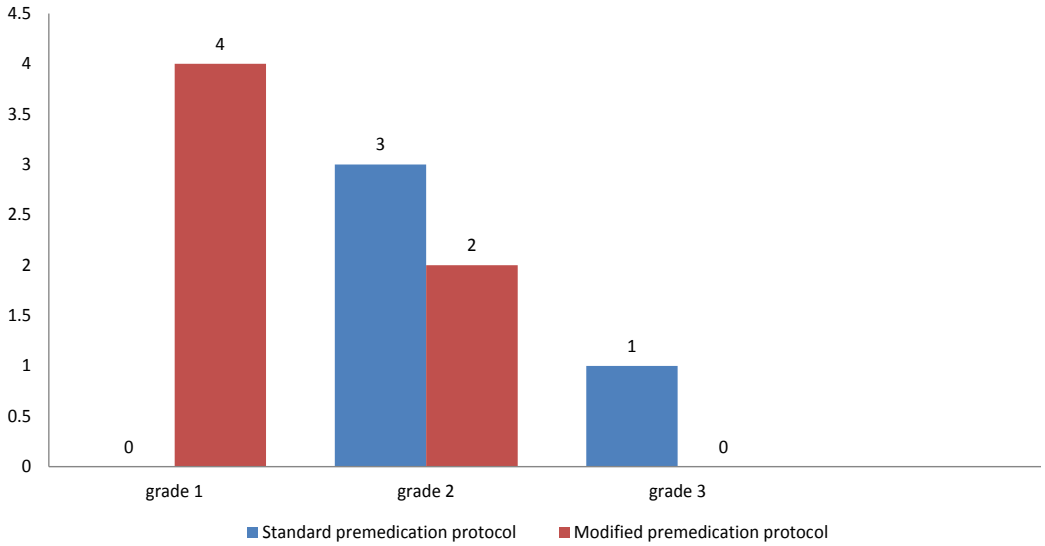

Figure 2. Comparison of Incidence for HSRs Severity from Taxane between the Standard Premedication Protocol and Modified Premedication Protocol without Ranitidine

Discussion

This study found that premedication without ranitidine had sufficient efficacy to prevent HSRs in patients who received the taxane regimen, which was not different from premedication with ranitidine. This was consistent with the theoretical data of the cremophor EL and polysorbate 80, which were the major causes of HSRs by activating the three mechanisms, which were IgE-mediated mast-cell degranulation/type I hypersensitivity, non-IgE-mediated idiosyncratic mast-cell degranulation, and complement activation. The use of ranitidine, which was the H2 antagonist, prevented H2 receptor suppression only in the IgE mechanism. In addition, previous studies only investigated the use of corticosteroids to prevent HSRs, thus offering little evidence concerning the use of ranitidine (Slimano et al., 2016; Lansinger et al., 2021; O'Cathail et al., 2013). Moreover, reports of omitting ranitidine from the premedication protocol without increasing the incidence of HSRs were developed after the unavailability of ranitidine worldwide (Gelderblom and Zwaveling, 2021; Cox et al., 2021). However, they were only retrospective studies, not comparative studies between the two clinical trial groups. Pretreatment with acetylsalicylic acid and montelukast has been reported to reduce the severity of HSRs during rapid desensitization in patients who developed HSRs to platinum chemotherapy (Breslow et al.,2009). Aspirin inhibits the synthesis of prostaglandins and montelukast blocks the receptor for cysteinyl leukotrienes, which are important activated mast cells and basophils. From the data, the efficacy of acetylsalicylic acid and montelukast in the premedication protocol for patients receiving taxane chemotherapy should be further explored in clinical trials.

Hence, the non-randomized design was the strength of this research because it studied and compared the patients who received the taxane regimen after the unavailability of ranitidine to the historical group. Moreover, the statistics were analyzed with the multilevel regression analysis approach because the occurrence of HSRs was influenced by the receipt of chemotherapy, which was independent, so the effect was different each time. The intervention effect and time effect were considered, which were the main confounders that comprised the correlated measurement data. None of the previous studies compared the relationship of HSRs between groups with such a method. Thus, it was the strength of this study. Nevertheless, the limitations in this study included the comparison of the historical groups to the non-randomized control study because the records of HSRs in the past were retrospective data, which might be incomplete.

In conclusion, the results of the study support the safety of omitting ranitidine from the premedication protocol in patients receiving chemotherapy with a taxane regimen and had a similar rate of HSRs to the use of ranitidine.

Author Contribution Statement

Chaichana Chantharakhit: Designed the study, reviewed the paper, central contact, facility contact information, collected data, analyzed data, draft manuscript preparation, edited the final version. Tanarat Ruchakorn: Designed the study, site sub-investigator, collected data; Somprattana Mungkornkaew: Collected data; Pichyanin Amorntrakoon: Collected data; Siwadonn Tassanamethee: Collected data; Pathra Theeratrakul: Edited the final version; Nantapa Sujaritvanichpong: Site sub-investigator; All authors read and approved the final version.

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funding statement to declare.

Funding Statement

The authors confirm that there are no relevant financial or non-financial competing interests to report and no conflicts of interest to declare.

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