Original Article

A Comparison of 5-HT3 Receptor Antagonist and Metoclopramide in the Patients Receiving Chemotherapeutic Regimens Including CMF, CAF and CHOP

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Abstract

Background: Chemotherapy- induced nausea and vomiting (CINV) occur frequently causing problems with an unacceptably high incidence that significantly affect patients' daily functioning and health-related quality of life. The present study was aimed to compare acute CINV for granisetron as 5-HT3 receptor antagonist and metoclopramide in the patients receiving chemotherapeutic regimens including cyclophosphamide and adriamycin. An attempt is made to examine whether it is possible to successfully replace granisetron with metoclopramide in control of acute CINV.

Methods: A total of 137 patients with breast cancer (78.8%) and lymphoma (17.5%) from two oncology departments in the first course of chemotherapy were enrolled. They received granisetron 3mg/IV and dexamethasone 8mg for the first referring and in the second referring metoclopramid 30mg/IV and dexamethasone 8mg/IV thirty minutes before chemotherapy and metoclopramide 20mg/IV during chemotherapy. The patients recorded the incidence of chemotherapy induced nausea and vomiting (CINV) and other side effects including headache, extra pyramidal manifestations and delayed nausea.

Results: Median age of studied patients was 49±15 year. The patients who received granisetron and dexamethasone had less acute nausea (during the first 24 hours after chemotherapy) than those who received metoclopramide. Also our study showed that controlled CINV episodes in patients who received CMF regimen were better than the regimen including adriamycin (CAF, CHOP) into both granisetron (p=0.06) and metoclopramid (p=0.04). The most common adverse event related to these drugs was extra pyramidal manifestations for 16 and 10 patients who had received granisetron and metoclopramide respectively. While the number of the patients who had sever delayed CINV (2-7 days after chemotherapy) episodes with granisetron (7 cases) was lower than those who took metoclopramide drug (14 cases). The number of patients who experienced extrapyramidal manifestations in metoclopramide group was lower than granisetron group.

Conclusion: There were not any significant clinically serious adverse events in any patients undergoing chemotherapy due to cancer. Thus, the safety profiles of granisetron and metoclopramide were comparable in this study. The patients who were treated with cyclophosphamide, and adriamycin, the efficacy of dexamethasone and metoclopramide in controlling acute nausea and vomiting nearly equaled to those of granisetron. Thus the present study supports the use of metoclopramide due to its lower cost and nearly the same efficacy and safety compared to granisetron in CMF regimen.

Keywords: granisetron, metoclopramide; Chemotherapy induced nausea and vomiting; Adriamycin; cyclophosphamide

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Introduction

Chemotherapy induced nausea and vomiting (CINV) occur as frequently problem with an unacceptably the most frequently high incidence that significantly affect patients' daily functioning and health-related quality of life [1] and is described by patients as a major adverse effect of the treatment [2]. Emesis control impairs the functional activity and quality of life for patients, increases the use of health care resources, and compromise adherence to treatment [3-5].

CINV is categorized into acute and delayed CINV according to the timing of its occurrence relative to the administration of chemotherapy. Acute CINV is considered the nausea or vomiting that occurs during the first 24 hours after chemotherapy administration and delayed CINV occurs after 24 hours following a dose of chemotherapy [6].

The development of the 5HT3 antagonists represents a significant advance in preventing CINV [7]. Antagonists for the 5-hydroxytryptamine (5-HT) receptor decrease the frequency of vomiting in patients receiving emetogenic chemotherapy. However, control of nausea, particularly delayed nausea experienced on the days after chemotherapy, remains elusive. For the patients receiving cytotoxic drugs, Granisetron hydrochloride, a selective serotonin (5-HT3) receptor antagonist, has been shown to be effective in the treatment of emesis [8].

Metoclopramide, a dopamine and serotonin receptor antagonist was discovered in 1988, while the first efficacy about its clinical safety in the prevention of post-operative nausea and vomiting (PONV) was in 1960 [5]. Also currently it is used widely as an agent for controlling of radiation-induced nausea and vomiting in the UK [9].

The present study was aimed to compare control of acute CINV for granisetron as 5-HT3 receptor antagonist and metoclopramide in the patients receiving chemotherapeutic regimens including cyclophosphamide and adriamycin. The intention was to examine whether it is possible to successfully replace granisetron with metoclopramide in control of acute CINV.

Materials and Methods

A total of 137 patients with breast cancer (78.8%) and lymphoma (17.5%) from two oncology departments in the first course of chemotherapy were enrolled. Inclusion criteria were patients aged 18 years or older who previously had not chemotherapy and were scheduled to receive first course of chemotherapy. The considered regimen were included one of these following regimens: CMF regimen (cyclophosphamide, methotrexate, and fluorouracil), CAF regimen (cyclophosphamide, doxorubicinhydrochloride, fluorouracil), CHOP (cyclophosphamide, hydroxydaunorubicin hydrochloride, Oncovin, Prednisolon). This study was designed to compare any change in the rate of acute CINV after the administration of granisetron and metoclopramide according to our center protocol. At first, a combination of granisetron 3mg/IV with dexamethasone 8mg was used for all patients. In the second course of chemotherapy regimen anti emetic protocol changed to metoclopramide 30mg/ IV and dexamethasone 8mg thirty minutes before chemotherapy, metoclopramide 20mg/ IV during chemotherapy.

Patients were observed for acute and delayed (starting from the second day until the seventh day) nausea. All episodes of CINV including nausea, vomiting and retching were recorded.

Nausea severity was classified into five categories; none, low (non tolerance to some food), moderate (retching), high (high vomiting), sever (sever and none controlled vomiting). Definition of retching was as the labored, spasmodic, rhythmic contraction of the respiratory muscles, including the diaphragm, chest wall, and abdominal wall muscles, without the expulsion of gastric contents [9]. The side effects including headache, extrapyramidal manifestations and delayed nausea were recorded. Also patients' satisfaction levels about granisetron or metoclopramide were assessed.

Statistical Analysis

The comparisons of efficacy in CINV control and tolerability were performed using the Fisher exact test in both groups (granisetron or metoclopramide). Evaluation of the patient characteristics in two groups were assessed using the chi-square test. We considered $P < 0.05$ as significant level for all statistical analysis. Statistical analysis was performed using SPSS software, version 11.5.

Results

From June 2009 to July 2010, 137 patients from two oncologic departments were enrolled to be studied in two groups (granisetron or metoclopramid). Patient characteristics and treatment regimens are listed in

Table 1. Baseline demographic and clinical characteristics of study patients

Characteristics		Frequency (percent)
Sex	Male	8 (13.1)
	Female	119 (86.9)
Cancer	Breast	108 (78.8)
	Lymphoma	24 (17.5)
	Other	5 (3.6)
Age	30-39	15 (10.9)
	40-49	59 (43.1)
	50-59	38 (27.7)
	60-69	14 (10.2)
	70	11(8)
Chemotherapy regimen	CMF	22 (16.1)
	CHOP	25 (18.2)
	CAF	90 (65.7)

Table 2. Assessment of severity Chemotherapy induced nausea and vomiting

Severity	Group	
	Metoclopramid (%)	Granisetron (%)
No	63 (46)	68 (49.6)
mild	30 (21.9)	36 (25.5)
Moderate	27 (19.7)	25 (18.2)
sever	14 (10.2)	7 (5.1)
Very sever	3 (2.2)	2 (1.5)

Table 3. Assessment of extrapyramidal manifestations in two studied patients

Severity	Extrapyramidal manifestations	
	metoclopramid (%)	granisetron (%)
No	127 (92.7)	121 (88.3)
mild	5 (3.6)	11 (8)
Moderate	3 (2.2)	3 (2.2)
sever	2 (1.5)	2 (1.5)
Very sever	--	--

table 1. The majority of patients were female (86.9%) with breast cancer (78.8%). Median age of studied patients was 49±15 year.

The severity of acute CINV in patients who received metoclopramide as anti-emetic was little more than granisetron (Table 2) and CINV episodes that controlled with granisetron were little better than metoclopramid (75% versus 68%) (p=0.04), although there was relatively poor control of nausea and vomiting with both antiemetic regimes. In this study, especially in those under 49 years with chemotherapy containing adriamycine, both antiemetic regimen did not have adequate control and there was a need for the addition of newer drugs to control CINV.

We considered cut of point 49 years old (as median age) for comparative analysis by CINV severity based on age. Our analysis showed that the severity of acute CINV was lower in older patients than in younger ones ($p<0.0001$). In evaluation of a relationship between age and satisfactory level, we found higher satisfactory level in older patients than younger ones ($p<0.0001$). Male subjects had less acute CINV episodes into metoclopramid regimen than female ones ($p=0.041$), but in granisetron regimen was not significant ($p<0.39$).

Analysis of chemotherapy regimen showed that control of acute CINV episodes in patients who received CMF regimen was better than patients with regimen including Adriamycin (CAF, CHOP) in both granisetron ($p=0.06$) and metoclopramid group ($p=0.04$). Also the delayed CINV rates were in accordance to acute CINV rate, so control of sever delayed CINV episodes with granisetron was better than metoclopramid. Surprisingly patients who experienced extrapyramidal manifestations in metoclopramide group were lower than granisetron group ($p<0.05$) (Table3).

Discussion

The primary goal of this study was to compare controlling of acute CINV for granisetron as 5-HT3 receptor antagonist and metoclopramide in the patients receiving chemotherapeutic regimens including cyclophosphamide and adriamycin. This study wanted to examine whether it is possible to successfully replace granisetron with metoclopramide in control of acute CINV.

The etiology of nausea and vomiting after chemotherapy is multi factorial and such factors are considered to affect the incidence of CINV. Two of these factors include sex and age, female patients [10] and younger patients are at greater risk [11, 12], in line with our result. Our analysis showed that the severity of acute CINV was lower in older patients than younger ones.

In the present study, the treatment groups were the same, as we changed the considered chemotherapy regimen (granisetron) to another

(metoclopramide) for all studied cases. In the literature Granisetron has been shown to be an effective therapy for nausea and vomiting induced by cancer chemotherapy [13]. In another study that evaluate granisetron against nausea and vomiting by induced anticancer drugs more patients receiving granisetron were emesis free 24 hours after administration of study, this compared with patients who received metoclopramide. In patients who experienced nausea, the severity of nausea was significantly lower in the patients who had received granisetron than metoclopramide, although this difference was not significant. There were not any significant adverse events occurred in any patients. Thus, the safety profiles of granisetron and metoclopramide were comparable in this study [14]. The same in present study, patients who treated with cyclophosphamide, and adriamycin, the efficacy of dexamethasone and metoclopramide in controlling acute nausea and vomiting nearly equaled to granisetron with marginally better with granisetrone.

Like our study design, Tsavaris et al evaluated ondansetron (OND) as antagonists for the 5-hydroxytryptamine (5-HT) receptor like granisetron vs metoclopramide and in mild and moderately emetogenic chemotherapy on 76 patients. They found that after switching to metoclopramide, they had adequate control of nausea and vomiting. Extrapyramidal manifestations occurred in 3 (5%) of patients receiving metoclopramide. Diarrhea was noted in 3 (2%) of cycles with OND and in 28 (18%) with metoclopramide. In this study, the number of patients who were emesis free (no nausea, retching, or vomiting) was higher in patients who received granisetron (75%) than in those who received metoclopramide (68%). In patients who experienced nausea, the severity of nausea was significantly lower than granisetron compared with metoclopramide [15].

Also Levitt M et al found that the patients who received dexamethasone and metoclopramide had significantly less nausea during the first 24 hours after chemotherapy than OND with dexamethasone. There were no statistically significant differences in efficacy between these regimens. Finally they concluded that for women with breast cancer who are being treated with cyclophosphamide, methotrexate, and fluorouracil, the efficacy of dexamethasone and metoclopramide in controlling nausea and vomiting equaled or exceeded that of OND as hydroxytryptamine (5-HT) receptor [16]. This result is the same with present study, as the analysis of chemotherapy regimen showed that control of acute CINV episodes in patients who received CMF regimen was better than patients with regimen including Adriamycin (CAF, CHOP) in both granisetron (p=0.06) and metoclopramid group (p=0.04). Here, the most common adverse event related to these study drugs was extrapyramidal manifestations for 16 and 10 patients who had received granisetron and metoclopramide respectively.

Conclusion

There were not any significant clinically serious adverse events in any patients undergoing chemotherapy due to cancer. Thus, the safety profiles of granisetron and metoclopramide were comparable in this study. Number of patients who experienced extrapyramidal manifestations in metoclopramide group was lower than granisetron. With respect to relatively poor control of nausea and vomiting with both antiemetic regimes In this study, especially in those under 49 years with chemotherapy containing adriamycine, both antiemetic regimen do not have adequate and there is a need for the addition of newer drugs to control CINV. This study supports the use of metoclopramide due to its lower cost and nearly the same efficacy and safety comparable to granisetron in CMF regimen.

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Conflicts of Interest

There is no conflict of interest in this article.

Authors' Contribution

Kazem Anvari, Mehdi Seilanian Toussi have designed the present study. Soodabeh Shahidsales has written the article, and Kazem Anvari, and Mehdi Seilanian Toussi have edited the article. Hossein Hosseinzad Ashkiki has been responsible for collecting the data, and Kazem Anvari, Mehdi Seilanian Toussi, Hossein Hosseinzad Ashkiki and

Soodabeh Shahidsales have contributed to the analysis and data interpretation.

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