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Comparison of acute and delayed antiemetic effect of adding Aprepitant to Odansitron and Dexamethasone regimen in patients with Hodgkin lymphoma receiving highly emetogenic chemotherapy

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ABSTRACT

Cancer is a class of disease in which group of cells show out of control growth, invasions and sometimes metastasis to different parts of the body. Few side effects of cancer treatment are more feared by the patient than nausea and vomiting. Although nausea and emesis (vomiting and retching) can result from surgery or radiation therapy, chemotherapy-induced nausea and vomiting (CINV) are potentially the most severe and most distressing. A randomized, single-blind controlled clinical trial conducted in Hiwa Center for Cancer in Sulaimani city for the period from January to December 2015. A total of 70 Hodgkin lymphoma patients presented to Hiwa Center for Cancer and treated with ABVD chemotherapy regimen were selected. The patient's received either the treatment (Aprepitant, Odansitron and Dexamethasone) or the standard regimen (Odansitron, Dexamethasone) in a 1:1 ratio, computer-generated, random allocation schedule. A total of sixty-three Hodgkin lymphoma patients were included in the present study with a mean age was 47.8±14.4 years; 34.9 % of them were ageing 60 years and more. Nausea and vomiting score was significantly higher in the treatment group from 2nd day to 4th days; the number of rescue therapy was significantly higher in the standard therapy group. In conclusion, the use of Aprepitant, Odansitron and Dexamethasone regimen showed superior and valuable results in the prevention of cancer induced nausea and vomiting by patients on chemotherapy.

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INTRODUCTION

World Health Organization (WHO) defined cancer as a chronic health problem like hypertension and diabetes that increasing rapidly in incidence all over the world. It is predicted to be a worldwide critical cause of morbidity and mortality in the next few decades. By the year 2020 in the world approximately 24.6 million people will live with cancer with about 12.5% of all deaths attributable to cancer (Yeh et al., 2012). Cancer is a class of disease in which group of cells show out of control growth, invasions and sometimes metastasis to different parts of the body (Nguyen and Massague, 2007). Chemotherapeutic agents are the preferred drug typically cytotoxic in nature, which can destroy most of the cancer cells. Chemotherapy works by preventing or slowing the increase of cancer cells which develop and divide quickly 3. Nausea and vomiting are among the most distressing and debilitating adverse effects identified by patients receiving chemotherapy treatment (LeBaron et al., 1988).

Cytotoxic chemotherapies used in the treatment of different malignancies are known to cause significant side effects. One of the immediate side effects that are most distressing to the patients is nausea and vomiting. Poorly controlled chemotherapy-induced nausea and vomiting (CINV) can lead to dehydration, malnutrition and electrolyte imbalance and can cause physical damage, including Mallory-Weiss tears of the esophagus. These symptoms can result in treatment delays, or a patient may refuse to continue treatment. CINV can also have an economic impact on the management of patients with cancer, including increased hospitalization and nursing costs (Aoki et al., 2013). More than 90% of patients undergoing highly emetogenic chemotherapy (HEC) will experience emesis without antiemetic prophylaxis, and 30% to 90% of those undergoing moderately emetogenic chemotherapy (MEC) will vomit without the prophylactic administration of antiemetic. From 10% to 30% of the patients receiving low emetogenic risk chemotherapy (LEC), and <10% of patients receiving minimal emetogenic risk chemotherapy (MinEC), will experience emesis without the administration of antiemetics (Sankhala et al., 2009).

In the past three decades, more effective antiemetic medications were introduced and widely adopted. Serotonin (5-HT3) receptor antagonists' are considered safe and work alone or in combination with corticosteroids (e.g., dexamethasone) or other agents. Most recently, neurokinin-1 (NK-1) receptor antagonists, a new class of antiemetic, have been studied. One such drug (aprepitant [Emend]) has been approved for use in combination with other antiemetics (Van Ryckeghem, 2016).

Aprepitant (APR) is a selective NK-1 antagonist for the substance P in the central nervous system. Several eligible clinical trials evaluating the antiemetic effect of APR in patients receiving high doses of cisplatin (≥70mg/m^2) or anthracycline/cyclophosphamide demonstrated that APR combined with the standard antiemetic medication, comprising 5-HT3 antagonist and DEX, significantly improved complete response (no emesis and no rescue treatment) compared to the standard antiemetic therapy (Grunberg et al., 2011). APR is shown to be effective against acute as well as delayed emesis, in which the efficacy is independent of gender. However, the involvement of the NK1-sensitive mechanism may vary among different chemotherapeutic regimens, even in the HEC regimens (Hesketh et al., 2006). The objective of the current work was to compare the acute and delayed antiemetic effect and the change in the quality of life of (Aprepitant, Odansitron and Dexamethasone) and (Odansitron, Dexamethasone) in patients receiving highly emetogenic chemotherapy in Hiwa centre for cancer in Sulaimaniya /Kurdistan region.

MATERIALS AND METHODS

Study design & settings

A randomized, single-blind controlled clinical trial conducted in Hiwa Center for Cancer in Sulaimani city for the period from January to December 2015.

The population of the study

All patients with Hodgkin lymphoma presented to Hiwa Center for Cancer were the study population.

Inclusion criteria

1. Hodgkin lymphoma
2. Patients receiving ABVD chemotherapy regimen which consist of (Adriamycin, Bleomycin, Vinblastine and Dacarbazine)
3. Age between 18-70 years
4. Patients receiving the first day of the chemotherapy

Exclusion criteria

1. Patients with another type of tumor or treated with another chemotherapy regimen
2. Pregnancy
3. Patients with severe hepatic impairment, congestive heart failure, renal failure
4. Radiation therapy to the abdomen or pelvis any time from 1 week before day 1 to day 6
5. Active infection
6. A symptomatic primary or metastatic CNS malignancy
7. Vomiting and dry heaves/retching 24 h before chemotherapy.

Sampling & randomization

A total convenient sample of 70 Hodgkin lymphoma patients presented to Hiwa Center for Cancer and treated with ABVD chemotherapy regimen was selected. Patients received either the treatment (Aprepitant, Odansitron and Dexamethasone) or the standard regimen (Odansitron, Dexamethasone) in a 1:1 ratio, computer-generated, random allocation schedule. The selection of both groups was known by the researcher after taking the agreement of Physician responsible for patients' treatment.

Treatment protocol

Study regimens were administered in a triple-dummy fashion. In the treatment regimen, oral aprepitant was given on days 1–3 (day 1, 125 mg 1h before chemotherapy; days 2–3, 80mg); ondansetron was given on day 1 only (day 1, 32 mg i.v. infused over 15 min at 30–60 min prior to chemotherapy; and oral dexamethasone was given

on days 1–4 (day 1, 12 mg 30 min before chemotherapy; days 2–4, 8 mg in the morning. In the standard regimen, ondansetron was given on days 1–4 (day 1, 32 mg i.v. infused over 15 min at 30–60 min prior to chemotherapy; days 2–4, 8 mg orally twice daily); and oral dexamethasone was given on days 1–4 (day 1, 20 mg 30 min before chemotherapy; days 2–4, 8 mg twice daily). Because aprepitant has been shown to increase dexamethasone levels approximately two-fold via a CYP3A4 interaction (Schwartzberg et al., 2011), the dose of dexamethasone was reduced in the treatment regimen to ensure similar plasma levels between the treatment groups.

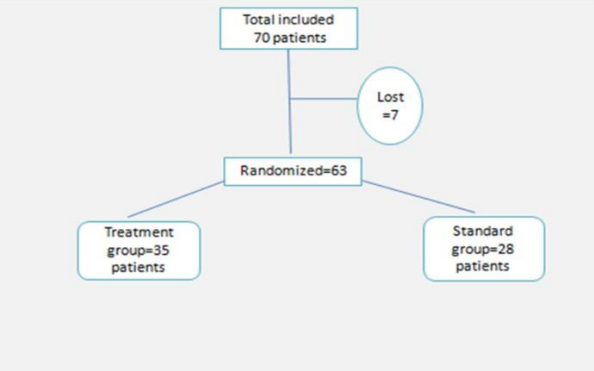

Figure 1: flow chart

Quality of life score

Quality of life will be measured using a validated patient self-assessment FLIE tool. The FLIE consists of nine nausea-specific and nine vomiting-specific items that address the effect of nausea and vomiting on daily functioning following chemotherapy. Responses to each of the 18 items will be marked by the patient with a vertical line on a 100-mm visual analog scale, with anchors being "a great deal" and "none/not at all." The tic marks on the visual analog scale range from 1–7, with the end of the scale indicating no effect on QOL.

Because optimal antiemetic treatment should eliminate any impact of CINV on QOL, the FLIE endpoint of impact on daily life (NIDL) will evaluate, NIDL is defined as an item score or average domain score ≥ 6 on the 7-point FLIE scale (i.e., > 83.3 mm). Likert scale measurement was used to measure nausea and vomiting score for each patient. Patients with No effect are those who had nausea or vomiting average score ≥ 6, while patients with Effect are those patients who had nausea or average vomiting score < 6.

FLIE questions

Nausea and vomiting Domain:

1. Quantity of nausea.
2. Ability to maintain usual recreation or leisure activities
3. Ability to make a meal or do minor household repairs
4. Ability to enjoy a meal
5. Ability to enjoy liquid refreshment
6. Willingness to spend time with family/friends
7. Affected daily functioning
8. Imposed personal hardship
9. Imposed hardship on others

Ethical protocol

Approval was obtained from the Ethical Committee of Sulaimani University, written informed consent was taken from each patient before participation in the study. Rescue medications used when the patient status is deteriorated; each patient had the right to withdrawal anytime; each patient was managed and followed up by a medical team with the help of researcher.

Statistical analysis

All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 23 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Kolmogorov Smirnov analysis verified the normality of the data set. Multiple contingency tables conducted and appropriate statistical tests performed. Chi-square test was used to compare categorical variables, and Independent sample t-test was used to compare two means. One-way ANOVA analysis was used to compare more than two means. In all statistical analysis, level of significance (p-value) set at ≤ 0.05 and the result presented as tables and graphs. Statistical analysis of the study was done by the community medicine specialist.

RESULT

Table 1: assessment of demographic variables

Variables	Value
Age (years), mean ± SD	47.8 ± 14.4
Age group, n (%)	
<20 years	2 (3.2%)
20 – 29 years	5 (7.9%)
30 – 39 years	14 (22.2%)
40 – 49 years	12 (19%)
50 – 59 years	8 (12.7%)
≥60 years	22 (34.9%)
Gender, n (%)	
Female	40 (63.5%(
Male	23 (36.5%)

Demographic data of all patients are illustrated in table 1. Additionally, figure 2 shows both nausea and vomiting scores from 1st day to the 4th day.

Table 2: assessment of demographic variables according to treatment

Variables	Treatment group	Standard group	p-value
Age group, n (%)			0.2
<20 years	1 (2.9%)	1 (3.6%)	
20 – 29 years	1 (2.9%)	4 (14.3%)	
30 – 39 years	10 (28.6%)	3 (10.7%)	
40 – 49 years	8 (22.9%)	4 (14.3%)	
50 – 59 years	4 (11.4%)	5 (17.9%)	
≥60 years	11 (31.4%)	11 (39.3%)	
Gender, n (%)			0.9
Female	22 (62.9%)	18 (64.3%)	
Male	13 (37.1%)	10 (35.7%)	
Rescue medications			0.02
Needed	0 (0%)	7 (25%)	
Not needed	35 (100%)	21 (75%)	

Table 3: Distribution of nausea scores of study participants according to study groups

Variables	Treatment group	Standard group	p-value
Score			
Nausea at 1st day	6.5±0.5	6.6±0.4	0.3
Nausea at the 2nd day	5.6±0.7	5±0.69	0.001
Nausea at the 3rd day	5.5±0.8	4.9±0.6	0.001
Nausea at 4th day	6.4±0.49	5.6±0.8	<0.001
Total nausea	6±0.5	5.5±0.5	0.001
Nausea			
Nausea at 1st day	4 (11.4%)	0 (0%)	0.06
Nausea at the 2nd day	23 (65.7%)	27 (96.4%)	0.003
Nausea at the 3rd day	21 (60%)	26 (92.9%)	0.003
Nausea at 4th day	4 (11.4%)	13 (46.4%)	0.002
Total nausea	12 (34.3%)	22 (78.6%)	<0.001
Age group			
<40 years	6.2±0.3	5.1±0.4	<0.001
≥40 years	5.9±0.6	5.7±0.5	0.1
Gender			
Male	6.1±0.5	5.7±0.4	0.01
Female	5.9±0.6	5.2±0.5	0.01

Table 4: Distribution of vomiting scores of study participants according to study groups

Variables	Treatment group	Standard group	p-value
Score			
Vomiting at 1st day	6.4±0.4	6.8±0.2	0.04
Vomiting at the 2nd day	6±0.6	5.3±0.7	<0.001
Vomiting at the 3rd day	6.1±0.59	5.2±0.79	<0.001
Vomiting at 4th day	6.4±0.49	5.6±0.8	<0.001
Total Vomiting	6.3±0.48	5.7±0.5	<0.001
Nausea			
Vomiting at 1st day	2 (5.7%)	0 (0%)	0.1
Vomiting at the 2nd day	13 (37.1%)	17 (60.7%)	0.06
Vomiting at 3rd day	10 (28.6%)	23 (82.1%)	<0.001
Vomiting at 4th day	4 (11.4%)	13 (46.4%)	0.002
Total Vomiting	8 (22.9%)	16 (57.1%)	0.005
Age group			
<40 years	6.4±0.3	5.5±0.5	<0.001
≥40 years	6.2±0.5	5.8±0.5	0.02
Gender			
Male	6.3±0.4	5.9±0.4	0.007
Female	6.3±0.6	5.3±0.6	0.001

The number of rescue therapy was significantly higher in the standard therapy group, while age and gender show no significant difference, as illustrated in table 2.

DISCUSSION

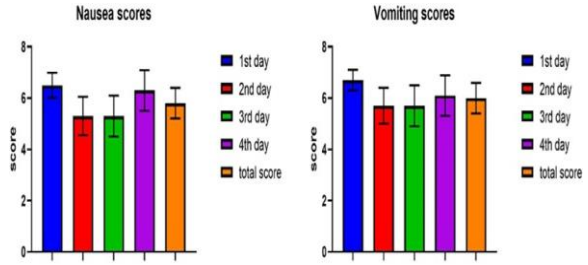

Figure 2: assessment of nausea and vomiting scores and emetic effect of study participants

Nausea and vomiting have long been acknowledged to be among the most feared and distressing side effects of chemotherapy. Chemotherapy-induced nausea and vomiting (CINV) can have significant effects on both qualities of life and physical functioning; in severe cases, CINV can lead to serious complications or a clinical decision to delay, reduce, or even stop chemotherapy (Vidall et al., 2011). As a consequence, control of CINV is a high priority for improving clinical outcomes in patients with cancer (Boccia et al., 2011). Cisplatin is the main example of a drug with high emetogenic potential; doses greater than 50 mg/m^2 lead to nausea and vomiting in more than 90% of patients if no prophylactic therapy is used. Other drugs with high emetogenic potential include cyclophosphamide (>1,500 mg/m^2), carmustine (>250 mg/m2), and dacarbazine (Hesketh et al., 1997).

Studying demographic characteristics of all study participants with Hodgkin's lymphoma revealed that the mean age of them was 47.8±14.4 years; about two-thirds of studied patients were in the middle age group. These findings are similar to results of a retrospective study conducted in Sulaimani that reported a median age of Hodgkin's lymphoma patients as 31 years (Mohammed et al., 2011).

The incidence of Hodgkin's lymphoma has increased among adolescents and young adults in the Nordic countries in the past few decades, whereas it has decreased strikingly among those aged 40 years or more (Hjalgrim et al., 2001). In developing countries, Hodgkin's lymphoma appears more during childhood, and its incidence decreases with age, while in developed countries, young children are rarely affected by Hodgkin's lymphoma in contrast with young adults where incidence increase with age (Thomas et al., 2002). It has a bimodal age distribution in both sexes, peaking in young adults (aged 15-34 y) and older individuals (>55years) (Thomas et al., 2002). In the United States, Nodular sclerosing subtype predominates in young adults, while mixed cellularity subtype is more common in children (aged 0-14 y) and older individuals. From 2004-2008, the median age at diagnosis for Hodgkin's lymphoma was 38 years of age, and approximately 12.3% were diagnosed under age 20 years and 27.7% above 55 years of age (Hjalgrim et al., 2001).

The present study found no significant difference between treatment group Hodgkin's lymphoma patients treated with (Aprepitant, Odansitron and Dexamethasone) and the standard group treated with (Odansitron, Dexamethasone). This finding is in agreement with results of (Ng and Della-Fiorentina, 2010) study in England which concluded that Odansitron and Dexamethasone regimen did not adequately control acute nausea of patients with carcinoma. This finding is inconsistent with Aziz study in the USA which stated that NK1R antagonists improved control of CINV in the acute, delayed, and overall phases for patients who received highly and moderately emetogenic chemotherapy. CINV control in the acute phase seemed to be a surrogate for CINV control in the delayed phase (Aziz, 2012).

Our findings regarding the weak effect of (Aprepitant, Odansitron and Dexamethasone) regimen at acute phase are similar to results of Hesketh et al. 20 studies in USA which reported an overall significant effect of aprepitant when added to odansitron and dexamethasone in suppressing CINV but week antiemetic effect was documented in the first day.

NK1R antagonists are known to increase the bioavailability of dexamethasone, and this pharmacokinetic interaction could potentially play a role in the higher incidence of infection among patients who have been treated with NK1R antagonists (Aziz, 2012). The (Chawla et al., 2003) study did not decrease the day 1 dexamethasone dose in the NK1R arm, whereas the (Schmoll et al., 2006) and (Poli-Bigelli et al., 2003) studies did. Nevertheless, it seems unlikely that increased dexamethasone bioavailability could have any impact on the infection rates because these three trials presented similar findings. NK1R antagonists can also increase the bioavailability of chemotherapy agents metabolized by cytochrome P450 3A4 (CYP3A4), such as etoposide, taxanes, irinotecan, vinca alkaloids, anthracyclines, and cyclophosphamide. Two of three studies suggested that adverse events could be more common among patients receiving an NK1R antagonist plus CYP3A4-metabolized chemotherapy (Grunberg et al., 2009).

Nausea occurred in fewer patients in the aprepitant group, but the results were not significantly different from those in the control group. This

result is in line with other aprepitant studies in which patients received either highly or moderately emetogenic chemotherapy, which suggests that the neurokinin-1 receptor antagonists may have less impact on the nausea component of chemotherapy-induced nausea and vomiting. In general, the control of nausea lags behind the control of vomiting, perhaps because of the difficulty of measuring this subjective symptom and the possibility that patients confuse nausea with anorexia, fatigue or pyrosis (Schmoll et al., 2006).

The current study revealed that delayed nausea score for patients taking treatment (Aprepitant, Odansitron and Dexamethasone) regimen was significantly lower than those taking standard regimen. In other word, nausea effects were significantly decreased among patients taking the treatment regimen in comparison to patients taking the standard regimen. These findings are consistent with results of (Schmitt et al., 2014) study in the USA which found that addition of aprepitant resulted in significantly less CINV and had a positive effect on the quality of life. (Aoki et al., 2013) Study in Japan which retrospectively investigated the rates of emetic control by a combination of granisetron, 5-HT antagonist and dexamethasone in various HEC regimens, including 5 single-day chemotherapy regimens such as gemcitabine/cisplatin(GEM/CDDP), epirubicin/cyclophosphamide(EPI/CPA), pemetrexed or vinorelbine/cisplatin (PEM or VNR/CDDP),doxorubicin/bleomycin/ vinblastine/dacarbazine(ABVD) and rituximab/doxorubicin/cyclophosphamide/vincristine/prednisone (R-CHOP21), and 2 multiple-day chemotherapy regimens such as 5-fluorouracil/cisplatin (5-FU/CDDP) and bleomycin/etoposide/ cisplatin (BEP). Complete response (no emesis, no rescue treatment) during the overall period (days 1-5) was assessed as the primary endpoint. Chemotherapy-induced nausea and vomiting was well-controlled (complete response >70%) in GEM/CDDP and R-CHOP21, but not in other regimens. The effect of a triple antiemetic medication including aprepitant (APR) was subsequently examined in patients receiving EPI/CPA and 5-FU/CDDP. Complete response was significantly improved in patients receiving 5-FU/CDDP but not in those receiving EPI/CPA, although the complete protection from vomiting significantly increased in both cases. Of note, the administration of APR for 5 days, but not for 3 days, was required to completely block the incidence of vomiting during the 7 days of the observation period in patients receiving 5-FU/CDDP. These findings suggest that APR should be used appropriately based on the emetogenicity of HEC regimens (Aoki et al., 2013).

Vomiting scores for cancer patients on treatment regimen (Aprepitant, Odansitron and Dexamethasone) were significantly lower than vomiting scores reported for cancer patients on standard regimen Odansitron, Dexamethasone) (p=0.04). This is similar to results of (Schmoll et al., 2006) study in the USA which reported that in comparison an antiemetic regimen in which ondansetron + dexamethasone was given for 4 days, the aprepitant regimen was superior in the acute, delayed and overall phases of chemotherapy-induced nausea and vomiting.

Vomiting scores with delayed effect for patients taking treatment regimen as acute phase were significantly lower than vomiting scores for the patient's taking standard regimen. These findings are consistent with results of (Poli-Bigelli et al., 2003) study in Brazil which concluded that aprepitant regimen had a superior effect in suppressing delayed vomiting effect for cancer patients on chemotherapy.

Whereas acute vomiting is known to depend primarily on serotonin, the pathophysiology of delayed vomiting is less well understood, and multiple mechanisms may contribute (Roila et al., 2002). Neurokinin-1 (NK) receptors are found in brain regions critical to regulating the vomiting reflex, and a recent analysis of studies suggested a possible predominance of NK1-related mechanisms during delayed-phase vomiting (Hesketh et al., 2003).

The need for rescue medications was significantly constrained only among patients taking the standard regimen (p=0.02). This finding is in agreement with results of (Yeo et al., 2009) study in China which reported that use of aprepitant regimen reduces the requirement of rescue medications when compared to control regimen for prevention of CINV in patients receiving chemotherapy and is associated with a better quality of life. (Hu et al., 2014) study in South Korea which was a prospective study on patients with lung cancer and investigating the role of aprepitant among those patients found that no patients on aprepitant regimen needed rescue medications.

CONCLUSION

The use of Aprepitant, Odansitron and Dexamethasone regimen showed superior and valuable results in the prevention of cancer induced nausea and vomiting by patients on chemotherapy. Aprepitant, Ondansetron and Dexamethasone regimen had good delayed effect in suppressing nausea induced by chemotherapy. Aprepitant, Ondansetron and Dexamethasone regimen had good acute and delayed effect in suppressing vomiting

induced by chemotherapy. Aprepitant, Ondansetron and Dexamethasone regimen prevent the need to rescue medications.

CONFLICTS OF INTERESTS

All authors have none to declare

Author contributions

All author contributed equally

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