The Effect Of Body Fat Ratio On Chemotherapy-Induced Nause-Vomiting

Vücut Yağ Oranının Kemoterapiye Bağlı Bulantı-Kusma Üzerine Etkisi

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ABSTRACT

Introduction: Chemotherapy still occupies an important place in cancer treatment, with the most common acute side effects of nausea and vomiting. Antineoplastic drug doses are adjusted according to the body surface area, calculated according to height and weight. The impact of the body-fat ratio on chemotherapy-induced nausea and vomiting was investigated in the study.

Methods: Fifty-two patients who had received highly emetogenic chemotherapy without previous treatment were included in the study. Nausea and vomiting side effects were evaluated three weeks after the first chemotherapy under standard anti-emetic treatments before chemotherapy.

Results: 75% of the patients were female, and the most common diagnosis was breast cancer. The most commonly used chemotherapy regimen was the combination of cyclophosphamide-doxorubicin-5-FU. The relationship between fat, fluid, and muscle tissue distributions was significantly correlated between SIRI and BCM methods. In 17 of 52 patients, nausea and vomiting developed due to chemotherapy. There was no significant effect of changes in body fat ratio (Siri method, p = 0.921), (BCM method, p = 0.783), body mass index (p=0.858), body surface area (p = 0.705), and body fluid compartment on nausea and vomiting after chemotherapy.

Conclusion: Our study found no relationship between body composition and nausea and vomiting after chemotherapy. Therefore, especially in obese patients, it is recommended not to limit the dose by worrying about side effects and to give chemotherapy according to the actual results calculated.

Keywords: Nausea, Vomiting, Chemotherapy, Body fat ratio, Body surface area, Body mass index

ÖZET

Giriş: Kanser, dünyada en önde gelen ölüm nedenleri arasındadır. Kanser tedavisinde kemoterapi hala önemli bir yer tutmaktadır ve en sık akut yan etkileri bulantı ve kusmadır. Antineoplastik ilaç dozları boy ve kiloya göre hesaplanan vücut yüzey alanına göre ayarlanmaktadır. Vucut yüzey alanı boy ve kilo ile ilişkili olmakla beraber vücut yağ-kas kompozisyonu farklılıklar göstermektedir. Çalışmada vücut yağ oranının kemoterapiye bağlı bulantı-kusma üzerine etkisi araştırıldı.

Yöntemler: Daha önce herhangi bir tedavi almamış ve yüksek emetojenik kemoterapi alan 52 hasta çalışmaya dahil edildi. Hastaların tedavi öncesi deri altı yağ kalınlıklarına göre SIRI metodu ile yaklaşık vücut yağ oranları hesaplandı, Elektriksel empedans yöntemi kullanılarak sıvı kompartmanları ve yağ oranları belirlendi. Kemoterapi öncesinde standart anti-emetik tedaviler uygulanarak ilk kemoterapileri sonrasındaki 3 haftalık dönem boyunca bulantı kusma yan etkisi değerlendirildi.

Bulgular: Hastaların %75'i kadın ve en sık tanı meme kanseriydi. En sık kullanılan kemoterapi rejimi ise siklofosfamid-doksorubisin-5-FU kombinasyonuydu. SIRI ve BCM metodları arasında yağ, sıvı ve kas dokusu dağılımları ilişkisi istatistiksel olarak anlamlı olarak korele bulundu. 52 hastanın 17'sinde kemoterapiye bağlı bulantı ve kusma gelişti. Vücut yağ oranı (Siri metod, p = 0.921), (BCM metod, p = 0.783), vücut kitle indeksi (p=0.858), vücut yüzey alanı (p = 0.705) ve vücut sıvı kompartmanı değişimlerinin kemoterapi sonrasında oluşan bulantı-kusma üzerine anlamlı bir etkisi saptanmadı.

Sonuç: Çalışmamızda vücut kompozisyonunun kemoterapi sonrası bulantı kusma ile ilişkisi saptanmadı. BU nedenle özellikle obez hastalarda yan etkilerden endişe edilerek doz sınırlamasına gidilmemesi gerektiği ve hesaplanan aktüel sonuçlara göre kemoterapi verilmesi önerilir. Çalışmanın diğer akut ve kronik toksisiteleri de değerlendirecek şekilde genişletilmeye ihtiyacı vardır.

Anahtar Kelimeler: Bulantı, Kusma, Kemoterapi, Vücut yağ oranı, Beden kitle indeksi

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INTRODUCTION

Cancer is one of the common reasons for death worldwide (1). Although there has been a rapid evolution in cancer treatment lately, antineoplastic agents are still indispensable for treating most cancers (2). The most frequent acute adverse events due to antineoplastic drugs are nausea and vomiting. This adverse event is highly related to the dose and classification of the drug. Antineoplastic drugs are classified into four groups according to their emetogenic effects, and different anti-emetogenic prophylaxis is used for each risk group (3). The other factors affecting the drugs' emetogenic effect are dose, way of administration, and the number of cycles (4). Anthracyclines and cisplatin derivates are the highest emetogenic drugs. Even if these drugs are used with the highest anti-emetogenic prophylaxis due to the increased risk of adverse events, nausea and vomiting may not be prevented in some patients (5). Body surface area (BSA) is the frequent criterion for adjusting the most chemotherapeutic agents' dose. BSA is mainly related to the patient's height and weight, and these two parameters positively correlate with BSA. Body mass index has a positive correlation with weight and a negative correlation with height. In obese patients, BSA is less effective than BMI at reflecting factors affecting drug distribution, such as body fluids and fat content. BMI may be associated with better efficacy than the calculation based on BSA alone when adjusting the chemotherapy dose in this patient group (6).

In non-small cell lung cancer patients, low lean body mass and low BMI as measured by the bioelectrical impedance method have been associated with chemoradiotherapy intolerance (7). Low skeletal muscle mass demonstrated by CT-based body composition measurements has been shown to be a strong predictor of chemotherapy toxicity in early-stage nonmetastatic breast and colorectal cancers (8). However, studies on chemotherapy-induced nausea, vomiting, and body fat ratio could not be found in the literature. Determining the effect of body fat ratio on nausea and vomiting may contribute to the prevention of nausea-vomiting in patients receiving high emetogenic risk chemotherapy.

This study aimed to investigate body fat and fluid ratio effects in body compartments on chemotherapy-induced nausea and vomiting (CINV).

METHODS

Patient Selection

Fifty-two patients receiving high emetogenic risk chemotherapeutic agents such as cisplatin and anthracycline were included in the study. None of the patients have received chemotherapy before. The patients were evaluated on the first cycle of their treatment. The body fat ratio of the patients was calculated. The time and frequency of nausea and vomiting symptoms are assessed with the patient observation from three weeks after the first cycle of chemotherapy. Patients who received prior chemotherapy, those who received low emetogenic risk chemotherapy during the study, those with concurrent dyspeptic symptoms due to gastrointestinal disorders, and those with uremic were excluded from the study.

Anti-emetogenic prophylaxis

All patients were given intravenous 3 mg granisetron on the first day, oral aprepitant for three days (125 mg on Day 1, 80 mg on Days 2 and 3), and 2x8 mg oral dexamethasone for three days as the recommended prophylaxis regimen.

Fat Rate Measurements

Two different methods were used in patients included in the study:

The approximate body fat ratio was calculated in the first method by formulating the subcutaneous fat thickness measurements made from different regions with the Siri Method (9). This method is based on the

hypothesis that 50% of total body fat is collected in subcutaneous fat deposits, related to the total amount of fat. Measurements were made from the chest, abdomen, and thigh for male patients and from the triceps, thigh, and suprailiac regions for female patients with a pincer-type caliper (10).

The second method measured total body fluid volume, intracellular fluid volume, extracellular fluid volume, and body fat ratio using ion currents with four electrodes placed on the hands and feet with the Body Composition Monitor (BCM) device (11,12).

Ethics

This study was approved by the Akdeniz University Clinical Studies Scientific Ethics Committee (Date approved: 18.01.2013. Approval number: 09). All patients were informed about the study and written informed consent was obtained.

Statistical Analysis

The association of acute or chronic nausea and vomiting with a body fat ratio measured by both methods was evaluated with regression analysis. Besides, gender, age, disease stage, body surface area, body mass index, total body water amount, extracellular water amount, intracellular water amount, and extracellular and intracellular water amounts for nausea and vomiting were evaluated via the regression analysis method. P-value ≤ 0.05 was considered statistically significant.

RESULTS

Of the 52 patients included in the study, 39 were female (75%), and 13 were male (25%). The youngest patient was 26 years old, and the oldest was 72 (mean 51.75). Patients included in the study had six different types of cancer. The most common diagnosis was breast cancer following lung cancer; one patient had two primary tumors. The most commonly used chemotherapy regimen was Cyclophosphamide + Doxorubicin + 5-Fluorouracil combination (Table 1).

The results of the body measurements of the patients are summarized in Table 2. Nausea/vomiting was not observed in 35 of 52 patients. Chemotherapy-induced nausea developed in one of the remaining seventeen patients in the acute period, eleven in the chronic period, and five in both acute and delayed periods. Chemotherapy-induced vomiting developed in five patients, one patient in both the acute and delayed period, and four patients only in the delayed period.

In comparing the body fat ratio calculated by the SIRI method and measured by BCM, it was observed that both ways were significantly correlated (p: 0,008) (Figure 1).

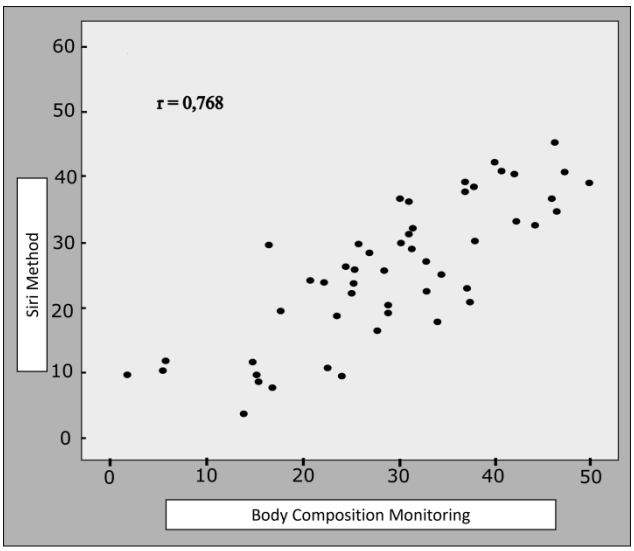

Figure 1. Correlation of body fat ratios calculated by Siri method and measured by BCM

The patients' average body fat ratio calculated by measuring subcutaneous fat thickness was 26.18%. While 9 of 27 patients with a fat ratio below this value developed CINV, 8 of 25 patients developed CINV whose body fat ratio was above this value. There was no significant difference between the two groups in CINV development (p = 0.921). The average fat ratio measured with the BCM method was 29.15%. While CINV developed in 8 of 26 patients with a fat ratio

Table 1. Distribution of patients' age, gender, disease type, disease stage, and chemotherapy regimens received

		Number (%)
Age	Min (26)	
	Max (72)	
Gender	Female	39 (75%)
	Male	13 (25%)
Cancer Type	Breast	34 (65%)
	Lung	8 (15%)
	Pancreas	4 (8%)
	Bladder	2 (4%)
	Biliary Tract	2 (4%)
	Osteosarcoma	1 (2%)
	Lung+Bladder (Two Primary)	1 (2%)
Stage	I	5 (10%)
	II	17 (32%)
	III	15 (29%)
	IV	15 (29%)
Chemotherapy Regimen	Cyclophosphamide + Doxorubicin	9 (17.4%)
	Cyclophosphamide + Doxorubicin + 5-Florouracil	19 (36.5%)
	Cyclophosphamide + Ephirubicine + 5-Florouracil	6 (11.5%)
	Docetaxel + Cisplatin	4(7.6%)
	Cisplatin + Gemcitabine	11(21.2%)
	Cisplatin + Doxorubicin	1(1.9%)
	Cisplatin + Etoposide	1(1.9%)
	Cisplatin	1 (1.9%)

CINV: Chemotherapy-induced nausea and vomiting

below this value, CINV developed in 9 of 26 patients whose body fat ratio was above this value. There was no significant difference between the two groups in CINV development (p = 0.783).

The relationship between the gender of the patients and the development of CINV was evaluated. Out of 13 of 39 female patients and 4 of 13 male patients who developed CINV, no significant relationship was found between gender and CINV development (p = 0.865). CINV developed in 7 of 25 patients over 51 and 10 of 27 patients under 51. No relationship was found between statistical analysis of CINV's values and age and CINV development (p = 0.488).

Out of 7 of 25 patients with an average body surface area of over 1.76 m² of the group developed CINV, while CINV developed in 10 of 27 patients below this value. There was no significant difference between the two groups in CINV development (p = 0.705).

When patients with stage I-II disease were compared with patients with stage III-IV disease, it was observed

Table 2. Distribution ranges and means values of the patients' body surface area, body mass index, body fat ratio, and body fluid levels

	Mean	Minimum	Maximum
Body Surface Area (m²)	1.76	1.323	1.896
Body Mass Index	27.65	15.1	42.5
Body Fat Ratio (Siri Method)	26.18	3.730448%	45.214874%
Body Fat Ratio (BCM Method)	29.15	1.6%	49.8%
Total Body Liquid	36.56	22.9	53
Extracellular Liquid Quantity	16.3	10.2	21.1
Intracellular Liquid Quantity	20.25	12.7	28.4

Table 3. Results of the regression analysis according to the age, gender, disease stage, body fat ratio, body mass index, and body fluid ratio classification

	Groups	Total Count	CINV Count	p-value
Gender	Female	39	13	0.865
	Male	13	4	
Age	<51	27	10	0.488
	>51	25	7	
Stage	I-II	22	5	0.377
	III-IV	30	12	
BSA (m²)	<1.76	27	10	0.705
	>1.76	25	7	
Fat percent (Siri Method)	<26.18	27	9	0.921
	>26.18	25	8	
Fat percent (BCM Method)	<29.15	26	8	0.783
	>29.15	26	9	
BMI	<27.6	27	41	0.858
	>27.6	25	7	
Total Body Fluid (Liters)	<36.56	28	9	0.767
	>36.56	24	8	
Extracellular Fluid (Liters)	<16.3	28	8	0.633
	>16.3	24	9	
Intracellular Fluid (Liters)	<20.25	27	9	0.883
	>20.25	25	8	
ECF – ICFratio	<0.81	27	10	0.783
	>0.81	25	7	

CINV: Chemotherapy-induced nausea and vomiting; BSA: Body Surface Area; BMI: Body Mass Index; ECF: Extracellular Fluid; ICF: Intracellular Fluid

that 5 of 22 patients with stage I-II disease had CINV, while CINV was followed in 12 of 30 patients with stage III-IV disease. There was no relationship between the disease stage and CINV development (p = 0.377). The relationship between the amount of body fluid and the intracellular and extracellular distribution of this fluid and CINV was examined. No significant association was found between total body fluid, intracellular fluid amount, extracellular fluid amount, extracellular and intracellular fluids ratio, and CINV.

The regression analysis performed according to the patients' age, gender, disease stage, body fat ratio, body mass index, and body fluid ratio classifications are summarized in Table 3.

DISCUSSION

The main factors affecting the tissue distribution of drugs are body fat ratio, intracellular-extracellular fluid volumes, regional blood flow, the drug's affinity for plasma proteins and tissue components, and some of the cancer drugs partly distributed adipose tissues.[13] A study examining the relationship between lean body mass and chemotherapy showed drug toxicity increased as the drug dose ratio to lean body mass increased (14). The nutritional status of cancer patients is frequently evaluated during cancer treatment (15).

Two different methods were used to calculate the patients' body fat ratios, allowing us to evaluate the compatibility of these two methods in our study. Compared with the non-parametric Correlation Analysis, the body fat ratio calculated with the Siri method and BCM measurement seemed significantly correlated. Our study showed no significant effect of body fat ratio determined by both ways on nausea and vomiting periods after chemotherapy. Similarly, the measured total body fluid and intracellular-extracellular components did not affect nausea and vomiting after chemotherapy. These results may be associated with a few patients and a wave of good nausea and vomiting control after chemotherapy. A study evaluated 5-FU toxicity in patients with colon cancer; in patients whose lean body mass was measured by computed tomography, toxic side effects such as nausea, vomiting, diarrhea, and neutropenia are more common in female patients with low lean body mass. This study

shows that gender difference and lean body mass may contribute to chemotherapy toxicity (14).

Since the 1950s, BSA has been used to calculate chemotherapy dose, but obese patients are not considered here. In a study conducted that BMI reflects body fat tissue better, the inclusion of BMI in the chemotherapy dose calculation was observed with less toxicity and more efficiency (6). However, in clinical practice, the dose calculation for obese patients with BSA> 2 m² is routinely limited to a maximum of 2 m². This approach is derived from the concerns of increasing toxicity. According to the actual BSA, no increased toxicity was observed in obese patients by adjusting the chemotherapy dose when the dose was adjusted according to the patient's total weight.[16–18] Patients given sub-optimal doses were associated with a poor prognosis (19,20). In the present study, only two patients' body surface area exceeds two m², one of these patients developed late-stage nausea, but it is impossible to evaluate it statistically. A study evaluating the patients receiving oxaliplatin, 5-FU, and folic acid combination showed that BMI was significantly associated with nausea and vomiting (21). However, no significant effect of BMI on CINV development was observed in this study.

It is known that the frequency of CINV is higher in women and young people. In a systematic review evaluating patient-related risk factors for CINV; it was emphasized that female sex (odds ratio: 2.79, 95% CI 2.26-3.44, $p < 0.05$), and younger age (odds ratio: 2.59, 95% CI 2.18-3.07, $p < 0.05$) are independent risk factors for CINV (22). However, we could not find a significant relationship between CINV and age and gender in the present study.

Weight loss in advanced-stage cancers may change drug distribution with a marked decrease in body fat ratio. No publications show that the development of nausea and vomiting increases with the increase in the cancer stage. Our evaluation found no significant relationship between chemotherapy-induced nausea and vomiting and cancer stage.

The main limitations of our study are that it was conducted with a relatively small number of patients and presented with single-center data. In the future, subgroup analyzes can be made on the effect of body fat ratio on nausea and vomiting according to the chemotherapy agents given by increasing the number of patients. In addition, the impact of body fat ratio on other side effects of chemotherapeutic agents can be investigated.

This is the first prospective observational study comparing the SIRI and BCM methods to assess the effect of body composition on CINV. Our study evaluated the relationship between chemotherapy-induced nausea and vomiting development with body fat ratio. As a result of our analysis, we could not find a statistically significant association. Apart from body fat ratio, other factors such as body surface area, body mass index, and fluid body distribution were not associated with CINV. There is no study in the literature evaluating the relationship between body fat ratio and CINV. In the light of these findings, considering the side effects of nausea and vomiting associated with chemotherapy, the use of chemotherapeutics according to weight in obese patients is supported.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Conflict of Interest: There is no conflict of interest

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