ISSN: 2651-4451 • e-ISSN: 2651-446X

Turkish Journal of Physiotherapy and Rehabilitation

2024 35(3)290-296

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Received: *22.11.2023 (Geliş Tarihi)*
Accepted: *24.06.2024 (Kabul Tarihi)*

DOES THE PRESENCE OF ANEMIA HAVE AN IMPACT ON PHYSICAL FUNCTIONS IN PATIENTS TREATED WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION?

ORIGINAL ARTICLE

ABSTRACT

Purpose: Anemia is an independent factor that may influence physical functions in patients with hematological malignancy. The aim of this study was to determine the impact of anemia on physical functions in patients with hematopoietic stem cell transplantation (HSCT).

Methods: A total of 82 patients with HSCT were retrospectively analyzed. The presence of anemia was determined in accordance with the WHO standard. Fatigue, hand grip and peripheral muscle strength, functional performance, and activities of daily living (ADL) were compared between patients with and without anemia. Additionally, impact of transplantation type and duration since HSCT on the results were analyzed.

Results: Patients with anemia had significantly poorer quadriceps femoris muscle strength, functional performance, and ADL level than patients without anemia (p=0.025, p=0.001, and p=0.009, respectively). Additionally, the duration since HSCT were adjusted in two groups, there was still significant difference in functional performance and ADL between patients with and without anemia (p<0.05).

Conclusion: The presence of anemia in patients with HSCT have negative impact on muscle strength, functional performance, and ADL level. Health care professionals should be aware that patients with anemia may have functional problems.

Keywords: Anemia, functional performance, hematopoietic stem cell transplantation, physical function

HEMATOPOİETİK KÖK HÜCRE NAKLİ OLAN HASTALARDA ANEMİ VARLIĞININ FİZİKSEL FONKSİYONLAR ÜZERİNE ETKİSİ VAR MIDIR?

ARAŞTIRMA MAKALESİ

ÖZ

Amaç: Anemi, hematolojik malignitesi olan hastalarda fiziksel fonksiyonları etkileyebilen bağımsız bir faktördür. Bu çalışmada, hematopoietik kök hücre nakli (HKHN) ile tedavi edilen hastalarda aneminin fiziksel fonksiyonlar üzerine etkisinin belirlenmesi amaçlandı.

Yöntem: HKHN ile tedavi edilen toplam 82 hasta retrospektif olarak analiz edildi. Anemi varlığı, WHO standardına göre belirlendi. Yorgunluk, el kavrama ve periferik kas kuvveti, fonksiyonel performans ve günlük yaşam aktiviteleri (GYA) anemisi olan ve olmayan hastalar arasında karşılaştırıldı. Ek olarak, transplantasyon tipi ve HKHN'den bu yana geçen sürenin sonuçlar üzerindeki etkisi analiz edildi.

Sonuçlar: Anemisi olan hastalarda kuadriseps femoris kas kuvveti, fonksiyonel performans ve GYA düzeyi anemisi olmayan hastalara göre anlamlı olarak daha düşüktü (sırasıyla p=0,025, p=0,001 ve p=0,009). Ayrıca, HKHN'den bu yana geçen süre her iki grupta kontrol edildiğinde, anemi olan ve olmayan hastalar arasında fonksiyonel performans ve GYA'da hala anlamlı fark vardı (p<0.05).

Tartışma: HKHN ile tedavi edilen hastalarda anemi varlığının kas kuvveti, fonksiyonel performans ve GYA düzeyi üzerinde olumsuz pek çok etkileri vardır. Sağlık profesyonelleri, anemili hastaların fonksiyonel sorunları olabileceğinin farkında olmalıdır.

Anahtar Kelimeler: Anemi, fonksiyonel performans, hematopoietik kök hücre nakli, fiziksel fonksiyon

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has been widely using as a treatment option for malign or non-malign hematologic diseases (1). Various disease- and/or treatment-related side effects have been occurred in patients treated with HSCT (2). Anemia is one of the most prevalent clinical symptoms in patients (3). Low hemoglobin level is a symptom of the hematological disease and it is also derived from chemotherapy-related bone marrow suppression. Anemia has been seen in majority of patients undergoing HSCT at any stage of the treatment protocol (4,5).

Anemia leads to decreased oxygen-carrying capacity of blood to muscles and the other organs which is associated with decreased exercise capacity (6). For this reason, its' association with the physical functions have been investigated in several populations in the literature. These studies conducted on cancer patients (7), community-dwelling people (8), geriatric population (9), and other disease groups (10,11). Deterioration of activities of daily living (ADL), functional capacity, quality of life level, and increase in fatigue, anxiety, and depression level have been showed in people with low hemoglobin level (6-12). Anemia has been found as an important factor that influenced muscle strength in patients with hematological malignancy (12).

Decrease in cardiopulmonary fitness level between pre- and post-HSCT was associated with decrease in hemoglobin level in patients treated with allogeneic HSCT (13). To our knowledge, there is no study which investigated the effect of low hemoglobin on physical functions in patients treated with HSCT. Since both HSCT and HSCT-related anemia are highly prevalent in this patient population (4,5), there is need to assess anemia-related physical dysfunctions. Hence, this study aimed to compare fatigue level, muscle strength, functional performance, and independency in ADL between patients with and without HSCT-related anemia.

METHODS

The present study was conducted at Hacettepe University in Turkey. Patients treated with HSCT and referred to physical therapy and rehabilitation service at Hacettepe University between January 2016 and January 2020 were included. The medical records and the physical assessment results were retrospectively analyzed; therefore, no informed consent forms were obtained from the participants. Inclusion criteria for the study were being: (a) between 18 and 65 years old, (b) treated with HSCT at least 3 months ago, (c) able to cooperate, (d) evaluated for physical functions. Exclusion criteria were: (a) having severe orthopedic, neurologic, cardiovascular, and/or mental disease, (b) being diagnosed with graft-versus host disease. The Hacettepe University University Non-Interventional Ethical Committee approved the study protocol (GO 20/703).

Recorded Variables

Demographic and medical characteristics

Participants' demographic data consisted of gender, age, body mass index, educational level, and marital status were recorded. Medical data including diagnosis, duration since diagnosis, comorbidities, type of HSCT, duration since HSCT, and HSCT-related complications were collected. Additionally, hemoglobin levels of the participants were recorded from the hospital records. The presence of the anemia was determined in accordance with the World Health Organization (WHO) standard; anemia was defined in males and females with hemoglobin level under 13 gr/dl and 12 gr/dl, respectively (14).

Fatigue level

Fatigue level was assessed using Visual Analogue Scale (VAS). Fatigue severity was assessed between 0 points (not at all tired) and 10 points (extremely tired) during resting and activity (15).

Handgrip strength

Handgrip strength of the participants was assessed using a standard Jamar hydraulic hand dynamometer (JA Preston Corporation, Clifton, NJ, USA). The test was performed on the dominant hand of the participants in accordance with the American Society of Hand Therapists Guidelines. The mean value of three trials was recorded (16,17).

Peripheral muscle strength

A digital hand-held dynamometer (J-TECH, Medical Commander PowerTrack II, USA) was used to measure peripheral muscle strength. Testing was performed in accordance with the statements of Bohannon and the manufacturer's manual. Shoulder flexors, elbow flexors, knee extensors, and hip flexors muscle strength was measured. Participants were allowed to make three trials for dominant side and the mean value was recorded (18).

Functional performance

The 30-second sit to stand test (30-s SST), which is an indicator of lower body strength and endurance capacity, was used to measure functional performance. The number of stands from sitting position in a chair during a 30-second period was recorded. (19).

Activities of daily life

The Turkish version of the Barthel Index (BI), which is a reliable and valid tool was used to measure

Table 1. Demographic and Medical Characteristics of the Participants (n=82)

	Group 1 (n=40) Median (Min-Max)	Group 2 (n=42) Median (Min-Max)	z/chi-square	p
Age, years	51.00 (21.00-60.00)	43.00 (19.00-62.00)	-1.478	0.139*
Body mass index, kg/m^2	25.15 (15.27-42.60)	27.38 (18.95-35.50)	-0.085	0.932*
Duration since HSCT, month	15.00 (5.00-84.00)	29.00 (6.00-96.00)	-4.684	**0.001***
Hemoglobin level, gr/dl	10.90 (6.10-12.00)	13.60 (12.00-16.20)	-7.205	**0.000***
Gender, n (%)				
Female	19 (47.50)	22 (52.30)	0.195	0.659**
Male	21 (52.50)	20 (47.60)		
Diagnosis, n (%)				
Lymphoma	14 (35.00)	12 (28.50)		
Leukemia	13 (32.50)	18 (42.80)	2.052	0.842**
Multiple myeloma	11 (27.50)	9 (21.40)		
Myelodysplastic syndrome	2 (5.00)	3 (7.10)		
Marital status, n (%)				
Married	33 (82.50)	35 (83.30)	0.002	0.962**
Single	7 (17.50)	7 (16.60)		
Education level, n (%)				
Illiterate	2 (5.00)	2 (4.80)		
Elementary school	13(32.50)	15 (35.70)		
Secondary school	4 (10.00)	4 (9.50)	1.279	0.937**
High school	8 (20.00)	8 (19.00)		
Graduate	12 (30.00)	12 (28.60)		
Postgraduate	1 (2.50)	1 (2.40)		
Transplantation type, n (%)				
Autologous	27 (67.50)	20 (47.60)	3.310	0.069**
Allogeneic	13 (32.50)	22 (52.40)		
The presence of comorbidity				
Yes	5 (12.50)	5 (11.90)	0.031	0.860**
No	35 (87.50)	37 (88.09)		
Comorbidities				
Diabetes mellitus	3	2		
Hypertension	2	1		
Asthma	-	2		
HSCT-related complication				
Yes	4 (10.00)	9 (21.42)	1.677	0.195
No	36 (90.00)	33 (78.57)		
HSCT-related complications				
Cataract	2	3		
Diabetes mellitus	1	1		
Venoocclusive disease	1	-		
Dry eye	-	3		
Infection	-	2		

HSCT: Hematopoietic stem cell transplantation, *Mann-Whitney U test, **Chi-Square test, p<0.05

functionality level in activities of daily life (ADL) (21). The BI consisted of 10 items that measures different aspects of ADL including nutrition, bathing, personal care, dressing, toilet use, mobility on flat surfaces (immobile, wheelchair use, assisted or independent walking), transfer (wheelchair to bed and reverse), stair climbing, bowel, and bladder continence. The total score ranged from 0 (full dependence) to 100 points (full independence) (20).

Statistical analysis

The IBM SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. The results were presented as number and percentages (n, %) or Mean ± Standard Deviation. The statistical significance level was determined as $p<0.05$. Participants were divided in to two groups according to the WHO standard described in the methods (14): Group 1 (patients with anemia), and Group 2 (patients without anemia). The normality assumption was analyzed using the Kolmogorov-Smirnov test. Since the data did not meet the normality assumptions, the Mann-Whitney U test was used to compare quantitative variables between the groups. The Chi-square test was used to compare percentages of the categorical variables between the groups. The ANCOVA test was used to assess covariate effect of the duration since HSCT on recorded outcomes. The two-way ANOVA was used to assess interaction between the transplantation type and the presence of anemia on recorded outcomes.

RESULTS

A total of 82 patients (Female/Male: 41/41) treated with HSCT and referred to Faculty of Physical Therapy and Rehabilitation at Hacettepe University were included. The number of patients assigned to the Group 1 and Group 2 were 40 and 42; respectively. Power analysis (Gpower 3.0.10 program) was calculated according to the BI reached 97% power in the 95% confidence interval ($p<0.05$). Since significant difference was found in the BI and 30-sec SST between groups after adjusting data according to the time since HSCT, the power analysis was performed based on the BI scores.

There was no significant difference between the groups in terms of demographic and medical characteristics except for duration since HSCT. The percentage of patients with comorbidity and HSCT-related complications were low in both groups. The demographic and medical data were presented in Table 1.

According to the group comparisons in terms of physical functions, patients with anemia had significantly lower scores in knee extensor muscle strength, the 30-sec SST, and the BI than patients without anemia ($p<0.05$). The comparison analysis between the groups were showed in Table 2. Since the duration after HSCT was significantly lower in patients with anemia, we performed further analysis to assess covariate effect of the duration since HSCT. As a result of the ANCOVA, there was still a significant difference in 30-sec SST [F (1.59) =

Table 2. Comparison of Physical Functions of Patients with and without Anemia

	Group 1 (n=40) Median (Min-Max)	Group 2 (n=42) Median (Min-Max)	z	p
Fatigue, Visual Analogous Scale				
Resting	0.00 (0.00-2.00)	0.00 (0.00-3.00)	-0.663	0.507
Activity	0.00 (0.00-4.00)	0.00 (0.00-5.00)	-1.189	0.235
Handgrip strength, kgf	23.30 (10.00-41.33)	26.80 (15.60-47.30)	-1.584	0.113
Peripheral muscle strength, N				
Shoulder flexor	87.49 (51.30-136.60)	92.30 (45.30-137.66)	-0.878	0.380
Elbow flexor	117.50 (80.00-172.60)	130.13 (83.30-179.00)	-0.138	0.890
Hip flexor	107.49 (55.70-189.66)	119.50 (88.00-146.33)	-0.323	0.747
Knee extensor	129.50 (101.50-293.33)	150.00 (108.66-197.50)	-2.239	**0.025**
The 30-second sit to stand test	13.00 (10.00-23.00)	19.00 (15.00-24.00	-4.925	**0.001**
Barthel Index	100 (65-100)	100 (80-100)	-2.601	**0.009**

Mann-Whitney U test, *p<0.05

28.220, p<0.001] and the BI score [F (1.75) = 6.571, p=0.012] between the groups whilst adjusting for duration since HSCT. A two-way ANOVA was conducted to examine the effect transplantation type and the presence of anemia on recorded outcomes. There was no statistically significant interaction between the effects of transplantation type and the presence of anemia on recorded outcomes (p>0.05).

DISCUSSION

The differences in physical functions of patients with and anemia during the post-HSCT period were investigated. The results revealed that quadriceps femoris muscle strength, functional performance, and ADL level in patients with anemia were lower than patients without anemia. Patients with anemia had still poorer functional performance and ADL level than patients without anemia when time since HSCT was adjusted across the groups. Additionally, there was no interaction between transplantation type and the presence of anemia on the results.

As far as known, there is no study which compared physical functions according to the presence of anemia in patients undergoing HSCT. When considered high proportion of patients treated with HSCT have anemia (4), the effect of anemia on physical functions may have been ignored by physical therapists or rehabilitation specialists. For this reason, it was aimed to compare physical functions according to the presence of anemia in patients treated with HSCT. The impact of anemia on physical functions have been investigated in different cases in the literature (7-12). Duration since HSCT may have an impact on the physical functions as reported by the previous studies. According to a previous study, as duration since HSCT increased, patients' functional level was also improved (13). In our study, duration since HSCT was significantly different between the groups. For this reason, adjusted groups in terms of duration since HSCT were used to understand the impact of anemia.

Low level of fatigue difference across the groups were recorded in the present study. Additionally, the groups had similar fatigue severity. In a relevant previous study performed on community-dwelling elderly persons, a relation between fatigue and anemia was reported (22). This inconsistency may be due to different methodologies used for fatigue assessment. Assessment of fatigue level using VAS in this study might have been insufficient to define any difference between the groups. Similarly, VAS was used to evaluate fatigue level and no association with hemoglobin level has been reported in lung cancer patients receiving chemotherapy (7). We suggest that multidimensional fatigue assessment and its' association with hemoglobin level should be further investigated in patients treated with HSCT.

With regard to muscle strength of the participants, there was no significant difference between the groups except for quadriceps femoris muscle strength. Several studies have shown decreased muscle strength capacity in patients with anemia when compared with the ones without anemia (12,22). Poor muscle oxygenation was suggested as the reason for this weakness (6). In this study, anemia was associated with lower extremity muscle weakness, yet there was no relation with the upper extremity muscle strength. On the contrary, there was significant association between upper extremity muscle strength and anemia in previous studies (23,24). The long-time immobilization and inactivity of patients with HSCT may have more detrimental effect on lower extremity strength than upper extremity which have been reported previously (24). However, there is no data regarding the patients' physical activity level during the HSCT process. On the other hand, immunopathogenetic nature of the diseases may also impact muscle strength which was reported previously (25). Therefore, more studies are needed to highlight effects of anemia on different body functions and variables such as hospitalization, patients' previous physical activity level, and immunopathogenetic nature of the diseases.

In a previous study, it was reported that muscle strength decreased and poor muscle strength persisted after adjusting duration since treatment in patients with both hematologic malignancy and anemia (12). In the present study, since duration was significantly different between groups, data was adjusted to this variable. After data was adjusted, there was no significant difference in muscle strength across the groups. Therefore, it is con-

sidered that muscle weakness was associated with duration since HSCT in the present study. There was only one study that investigated the effect of change in hemoglobin level on muscle strength in patients treated with HSCT, and no interaction was found (13). Therefore, we suggest that muscle strength is influenced by multiple factors and the presence of anemia or duration since HSCT alone does not explain muscle weakness in patients treated with HSCT.

Patients with anemia showed weaker functional performance as measured with the 30-sec SST than patients without anemia in the present study. Similar findings have been reported in different populations with anemia (26, 27). Decrease in functional performance have been attributed to decrease in oxygenation of human body during functional activities (26). In addition, since quadriceps femoris muscle strength was lower in anemia group, this might have led to a decrease in the 30-sec SST performance. Because, one of the primary responsible muscle during sit to stand activity is quadriceps femoris (28). On the other hand, our finding was regardless from the type of transplantation. Further research is needed to highlight functional problems related to anemia in cancer patients (especially hematological cancer) and patients treated with HSCT. It is suggested that when evaluating functional performance capacity of patients treated with HSCT, hemoglobin level should also be considered by physiotherapists.

Regarding ADL, patients with anemia showed lower ADL capacity than patients without anemia. Similarly, lower ADL level have been found in previous studies and this result have been attributed to a high fatigue level in patients with anemia (7,29,30). Patients' fatigue level was low in the present study, yet this was our limitation that we assessed fatigue only with VAS. Therefore, assessment of fatigue using one question may be insufficient to determine fatigue severity in the patients. On the other hand, anemia was associated with poor functional capacity which may lead to decrease in independency in ADL. This result suggests that ADL should be examined in more detail in patients with anemia during clinical practice by physiotherapist and/or rehabilitation specialists. Since Barthel Index which was used in this study asks only about basic daily living activities, further studies should also examine the instrumental daily living activities. In accordance with the findings, it is advisable to physiotherapists to prescribe programs including muscle strengthening exercises, functional activities, and ADL training for patients with anemia.

Limitations of the Study The present study has some limitations. Firstly, the patients with no physical assessments were excluded. Therefore, patients with higher motivation may have been included in the present study. Additionally, since this study has a retrospective design, some data could not be collected such as hospitalization time during HSCT, medication use, and immunopathogenetic nature of the diseases. Lastly, VAS may not be a sufficient questionnaire to determine fatigue level in patients treated with HSCT. Therefore, use of a multidimensional fatigue assessment to evaluate fatigue level in patients with anemia is suggested.

Conclusion

In conclusion, patients with HSCT-related anemia have weaker quadriceps femoris muscle strength, decreased physical performance, and more dependency in ADL than the patients without anemia. Duration since HSCT have been also considered as a confounder for muscle strength. It is suggested that deficiency in muscle strength of HSCT patients is multifactorial and should be further analyzed. Additionally, poor physical performance and ADL level in patients with anemia are regardless from duration since HSCT. Since anemia has an impact on physical functions of the patients, physiotherapists should be aware regarding the hematological signs.

Sources of Support: None.

Conflict of interest: The authors declare no competing interests.

Author Contributions: VYK: Data collection, Materials, Analysis-interpretetation, Literature review, Writing; SAU: Data collection, Materials, Critical review; EA: Supervision, Critical review; HG: Supervision Critical review; TD: Conseption, Design, Critical review.

Explanations: None.

Acknowledgement: None.

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