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Treatment of chemotherapy induced anemia; a randomized clinical trial to compare quality of life in patients taking intravenous versus oral iron

Ali Hajigholami[1], Ahmad-Reza Maghsoodi[2], Hourieh Ansari[3*], Marzieh Kafeshani[4]

[1]Department of Internal Medicine, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Internal Medicine, Faculty of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran
[3]Family and Community Medicine Department, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[4]School of Nutrition, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

***Correspondence to**
Hourieh Ansari,
Houri_ansari@yahoo.com

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Abstract

Introduction: Malignancy is one of the causes of anemia in chronic diseases. Anemia can commonly complicate the malignancy process.
Objectives: This study aimed to compare improvement in the quality of life and hemoglobin levels between cancer patients with chemotherapy-related anemia receiving erythropoietin and injectable iron supplement versus patients receiving erythropoietin and oral iron supplement.
Patients and Methods: This investigation was a randomized clinical trial carried out on 79 anemic individuals with metastatic and non-metastatic carcinoma who were undergoing chemotherapy. Individuals included in the study were randomly assigned to the two groups. The first group received erythropoietin and Venofer while the second group received erythropoietin and ferrous sulfate for 6 weeks. The quality of life for patients was assessed using the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30).
Results: Hemoglobin levels in both groups increased significantly while the difference between them was not significant. Despite improvement in more indexes of the questionnaire, post-treatment quality of life in both groups had no significant statistical difference ($P>0.05$). The changes in indices after interventions showed no difference between the oral and injectable iron supplements groups ($P>0.05$).
Conclusion: The results of this study showed that administration of erythropoietin and iron supplements, either orally or intravenously, even with a shorter duration of treatment could increase hemoglobin levels in chemotherapy-induced anemia group, however to improve the quality of life, it may be necessary to employ larger sample sizes and prolong treatment courses.
Trial Registration: This randomized controlled trial was registered in the Thai Clinical Trials Registry (identifier: TCTR20200915003; http://www.clinicaltrials.in.th).

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Introduction

Malignancy is one of the causes of anemia in chronic diseases (1). Anemia can commonly complicate the malignancy process which may be due to anti-neoplastic therapy (erythropoietin suppression through chemotherapy or radiation), progressive disease, the direct effect of malignancy (bleeding from tumors or bone marrow infiltration) and malignant products (amyloid-inflammatory cytokines, auto-antibodies or microangiopathy) and also the effect of renal failure due to chemotherapy (2-4). Several factors involved in the development of anemia in the patients with malignancy such as abnormal metabolism of iron, or iron trapping in the macrophages, the inability to increase erythropoietin in response to anemia, a relative decrease in erythropoietin production, inflammation associated with the disease, myelosuppressive chemotherapy of malignancies, and other causes consisting of gastrointestinal bleeding, iron, folate and cobalamin deficiency (5-8). The management of anemia with chemotherapy, hematopoiesis stimulating agents such as erythropoietin or darbepoetin increase hemoglobin levels and reduce the need for blood transfusion. Regarding the lack of access to iron in the course of malignancy, the use of iron supplementation is necessary to develop a proper hematological response. Although some types of malignancies respond well to oral iron, it is still not proven that this treatment is effective enough in the patients receiving erythropoietin stimulating agents.

Key point

In a randomized clinical trial carried out on 79 anemic individuals with metastatic and non-metastatic carcinoma who were undergoing chemotherapy, we found that the changes in indices after interventions showed no difference between the oral and injectable iron supplements groups. We concluded that administration of erythropoietin and iron supplements, both orally and intravenously, even with a shorter duration of treatment could increase hemoglobin levels in chemotherapy-induced anemia group.

However, injectable iron supplements can quickly amplify erythropoiesis by providing a bioavailable form of iron (9,10). In addition, due to lower prices of oral drug, the use of oral iron compared with its injectable form reduces the cost of treatment for patients.

Malignant anemia can affect the patient's functional status, reduce the patient's physiological capacity as well as lead to fatigue and disability. Diagnosis and treatment of anemia can result in improved quality of life in patients with malignancy. In addition to the development of symptoms, the presence of anemia in some cancers worsens prognosis because the response to anticancer and ionizing radiation and some types of chemotherapy for cytotoxicity requires adequate oxygenation (11-14).

Objectives

In this study, we compared the quality of life, and hemoglobin levels between cancer patients with chemotherapy-related anemia receiving erythropoietin and injectable iron supplement with patients receiving erythropoietin and oral iron supplement.

Patients and Methods

Study design

This investigation was a randomized clinical trial conducted on 79 anemic individuals with metastatic and non-metastatic malignancy who were undergoing chemotherapy. The inclusion criteria were anemia secondary to malignancy and chemotherapy, the grading of anemia according to the National Cancer Institute (NCI) system(grade 0-4), remission phase in hematological malignancies and the Karnofsky performance status scale (an assessment tool for functional impairment) greater than or equal to 70%. Exclusion criteria were unwillingness to continue cooperation during the study, banning from erythropoietin administration due to thromboembolic events or systolic blood pressure more than 160 mm Hg during the study or any infection suffering from digestive disorders caused by oral iron intake or gastrointestinal bleeding, anemia due to other causes than malignancy, death due to complications of the illness, total gastrostomy, gastric cancer, lack of response to more than 20% of questions in the questionnaire or serum ferritin level greater than 500 ng/mL. The patients who had inclusion criteria were randomly assigned to the two groups using a random number table and the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) was completed for all patients (15) (Figure 1). The first group received erythropoietin (150 units/kg subcutaneously three times a week) and Venofer (100 mg, intravenously at each chemotherapy session), and the second group received erythropoietin (150 units/kg subcutaneously three times a week) and ferrous sulfate (one tablet every 8 hours) for six weeks. Hemoglobin less than 8 mg/dL or presence of organ dysfunction and coronary artery disease were considered as the limit of blood transfusion in patients. In order to reduce gastrointestinal complications and maximum drug intake by patients, the correct method of taking iron tablets was trained. In the oral iron receiving group, three patients were excluded from the study due to lack of completeness of the questionnaire, one patient due to oral iron intolerance and one person due to death during the treatment. In the group receiving the injectable iron, two patients were excluded from the study because of the lack of completion of the questionnaires, one patient due to lack of proper control of blood pressure and two persons due to lack of willingness to continue cooperation. Finally, 40 subjects in the oral group and 39 in the injectable group completed the study and at the end of the study, once again, the questionnaire was completed for both groups. In this study, blindness was not performed due to differences in iron administration in the two groups. Information about the patient's tests was extracted from the patient's file.

The quality of life was measured using EORTC (European Organization for Research and Treatment of Cancer quality of life questionnaire) QLQ-C30, a standard questionnaire for assessing the quality of life of cancer patients. The questionnaire consists of three parts, 1) General health status or quality of life, which includes two questions (Questions 29 and 30) with a scoring range from 1 (very bad) to 7 (excellent), 2) The functional status consists of five subsets; physical function includes five questions (Questions 1 to 5), social role including two questions (questions 6 and 7), emotional status including four questions (questions 21-24), cognitive status including two questions (question 20 and 25), social status includes two questions (questions 26 and 27), and 3) Symptoms include 9 items; fatigue including three questions (questions 10,12,18), nausea and vomiting including two questions (questions 14 and 15), pain including two questions (questions 9 and 19), shortness of breath including one question (question 8), sleeplessness includes a question (question 11), appetite reduction including one question (question 13), constipation including one question (question 16), diarrhea including one question (question 17), and financial problems including one question (question 28). The scoring for physical status and symptoms; was as not at all (1), low (2), high (3) and very high (4). The score for each item in the questionnaire ranged between 0 and 100 that the method of calculating score was based on the resource guide provided by the

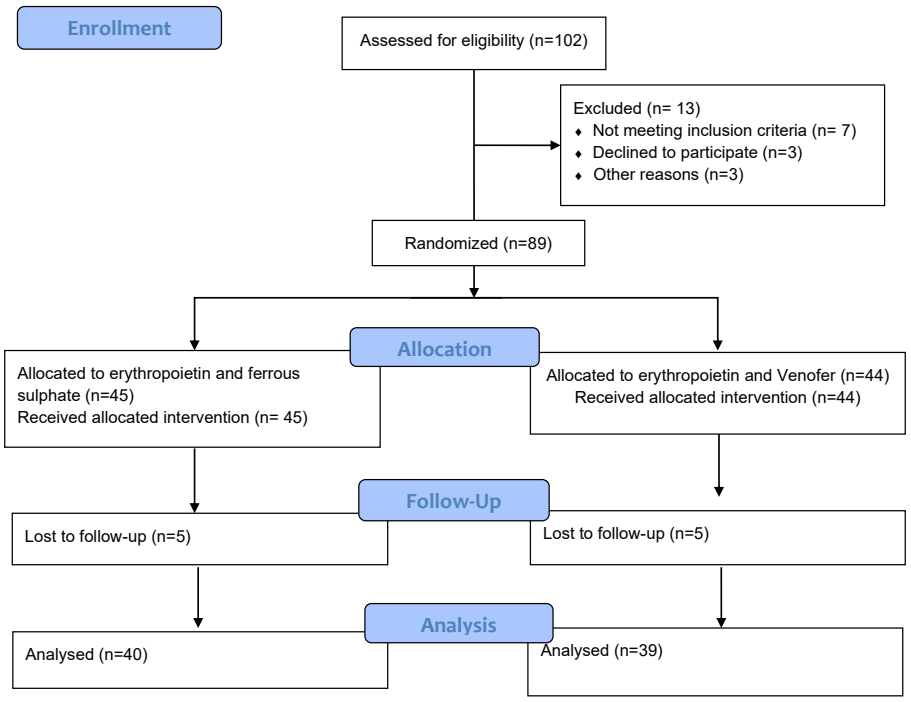

Figure 1. CONSORT flow diagram.

European Organization for Research and Treatment of Cancer Quality of Life (EORTC) as the statistical formulas for each group of different questions (15). A higher score in the functional section indicates higher levels of performance and a higher score in general health indicates a higher level of quality of life. The high score in symptoms suggests a high level of difficulty.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The study was approved by the institutional ethics committee of Shahrekord University of Medical Sciences and registered as a randomized clinical trial (identifier: TCTR20200915003; http://www.clinicaltrials.in.th/). Written informed consent was obtained from all participants too. This paper is extracted from the internal medicine residential thesis of Ahmad-Reza Maghsoudi (Thesis# 997).

Statistical analysis

The SPSS version 18.0 (SPSS Inc., Chicago, IL) was applied for statistical analysis. The normality of data was checked using the Kolmogorov-Smirnov test. In this regard, age, hemoglobin level, quality of life score, physical status score, emotional status score and pain score had a normal distribution. For inter-group comparison, *t* test was used for variables with normal distribution and Wilcoxon signed-rank test used for variables with abnormal distribution. Independent *t* test and Mann-Whitney U test were used for variables with normal distribution and abnormal distribution respectively. Accordingly, *P* values of 0.05 or less were considered significant.

Results

In the group receiving the oral iron supplement, the mean age was 48.1 ± 14.6 years ranging from 22 to 78 years, 55% were female and 82.5% were married. The mean serum level of hemoglobin before the intervention was 10.4 ± 1.1 g/dL ranging from 8 to 12 g/dL that reached 11.2 ± 1.4 g/dL after intervention with a significant increase ($P = 0.005$). In the group receiving the injectable iron supplement, the mean age was 50.9 ± 13.1 years ranging from 20 to 84 years. The mean serum hemoglobin level before the intervention was 10.1 ± 1.3 g/dL ranging from 7 to 12 g/dL and after the intervention was 11.4 ± 1.6 g/dL that indicates significant change after drug administration ($P < 0.001$; Table 1).

In the patients who received injectable iron, the level of quality of life, physical function score, and emotional score, the scores for fatigue, pain, insomnia, constipation nausea, anorexia, and diarrhea did not change significantly (Table 2), however the physical index increased after intervention compared to the previous status ($P = 0.005$). In the group received oral iron, all indices did not change significantly after intervention (Table 3), nevertheless similar to another

Table 1. Baseline characteristics of the patient participated in the study

Variable		Group I (n= 39)	Group II (n= 40)	*P* value
Age (y)		50.90 ± 13.1	41.8 ± 16.6	0.37
Gender, No (%)	Female	23 (59)	22 (55)	0.72
	Male	16 (41)	18 (45)	

group, the physical index increased after intervention ($P=0.02$). Additionally, the changes in indices after interventions showed no difference between the oral and injectable iron supplements groups ($P>0.05$; Table 4). The change in serum hemoglobin level between the two groups showed no significant difference ($P=0.665$).

Discussion

In our study, the serum hemoglobin level increased in both groups however, this increase had no significant difference between groups. These results disagree with the findings of other studies, such as Henry et al (16) that revealed the use of injectable iron supplement caused more improvement in serum hemoglobin level compared to oral iron supplement. The possible reason for this significant change in the study by Henry et al could be related to weekly administrating injectable iron or considering an 8-week course for treatment, since in our study, the patients received intravenous iron every three weeks and the duration of the treatment was six weeks (totally, the patients received intravenous iron twice in six weeks).

Another possible explanation for the lack of a significant difference in increased hemoglobin during injectable versus oral iron group may be due to the effect of erythropoietin too.

Straus et al (14) showed that the rapid treatment of mild anemia with erythropoietin in the patients with hematological malignancies especially lymphoma significantly improved the quality of life. A review study by Katodritou et al (17) indicated that co-administration of erythropoietin and iron supplement intravenously improved hematological response. Our study was conducted on patients with severe anemia; hence it takes more time to regain an acceptable level of quality of life. In the study by Lind et al (12), a longer course of treatment led to a normalization of hemoglobin levels whereas, in our study, the mean of hemoglobin level had not reached normal levels in any of the two groups. Perhaps due to this reason, despite a significant increase in hemoglobin levels in both groups, improvement in the quality of life has

Table 2. Changes in the mean quality of life scores in the group received erythropoietin and ferrous sulfate

Variable	Baseline	6 weeks	*P* value
Global health status	56.25±20.47	57.50 ± 3.25	0.74
Functional status			
Physical function	64.16±17.84	74 ± 21.44	0.02
Social function	69.16 ± 5.31	74.16±32.89	0.39
Emotional function	58.95 ± 0.85	66.66±27.86	0.22
Cognitive function	88.75 ± 6.61	81.25 ± 4.22	0.08
Functional function	79.16 ± 3.79	78.33 ± 9.28	0.79
Hemoglobin (g/dl)	10.4 ± 1.1	11.2 ± 1.4	<0.01
Symptoms			
Shortness of breath	9.16 ± 21.33	15.83 ±31.11	0.29
Pain	35.83 ±29.36	32.08 ±31.66	0.49
Sleeplessness	50 ± 35.40	43.33±38.63	0.33
Appetite reduction	30.83 ± 34.90	31.66 ± 4.55	0.89
Constipation	25 ± 33.54	6.66 ± 34.08	0.90
Diarrhea	5 ± 14.22	6.66 ± 17.21	0.53
Financial problems	55 ± 40.33	51.66 ± 6.50	0.55
Nausea	15.41±21.14	20.83±28.68	0.14
Fatigue	48.61 ±28.76	40 ± 29.28	0.16

Table 3. Changes in the mean quality of life scores in the group received erythropoietin and Venofer

Variable	Baseline	6 weeks	*P* value
Global health status	52.13±27.61	54.27±23.17	0.68
Functional status			
Physical function	62.05±23.55	72.47±23.20	<0.001
Social function	61.96±31.28	71.36±27.55	0.09
Emotional function	58.76±25.85	65.59±26.29	0.22
Cognitive function	77.35±21.41	75.64±23.20	0.78
Functional function	69.23±27.71	69.2 ±27.71	0.79
Hemoglobin (g/dL)	10.1 ± 1.30	11.4 ± 1.6	<0.001
Symptoms			
Shortness of breath	16.23 ± 24.02	13.67 ±18.28	0.29
Pain	47.43 ± 27.44	40.59 ±29.06	0.27
Sleeplessness	41.88 ± 34.80	37.04±30.53	0.27
Appetite reduction	41.02 ± 32.85	34.18 ±28.08	0.30
Constipation	29.05±34.35	25.6±34.08	0.70
Diarrhea	13.67±19.82	17.94± 26.32	0.32
Financial problems	52.99± 37.24	51.28 ±38.11	0.83
Nausea	27.35±29.44	22.64±18.92	0.14
Fatigue	48.14 ±27.96	44.15± 24.11	0.16

Table 4. Changes in the mean quality of life scores in the group received erythropoietin and Venofer with group received erythropoietin and ferrous sulfate after intervention

Variable	Baseline	6 weeks	*P* value
Global health status	54.27±23.17	57.50 ± 3.25	0.71
Functional status			
Physical function	72.47±23.20	74 ± 21.44	0.99
Social function	71.36±27.55	74.16±32.89	0.25
Emotional function	65.59±26.29	66.66±27.86	0.86
Cognitive function	75.64±23.20	81.25 ± 4.22	0.20
Functional function	69.2 ±27.71	78.33 ± 9.28	0.08
Hemoglobin (g/dl)	11.4 ± 1.6	11.2 ± 1.4	0.66
Symptoms			
Shortness of breath	13.67 ±18.28	15.83 ±31.11	0.48
Pain	40.59 ±29.06	32.08 ±31.66	0.15
Sleeplessness	37.04±30.53	43.33±38.63	0.39
Appetite reduction	34.18 ±28.08	31.66 ± 4.55	0.41
Constipation	25.6±34.08	6.66 ± 34.08	0.27
Diarrhea	17.94± 26.32	6.66 ± 17.21	0.02
Financial problems	51.28 ±38.11	51.66 ± 6.50	0.99
Nausea	15.41±21.14	20.83±28.68	0.16
Fatigue	48.61 ±28.76	40 ± 29.28	0.32

not been observed. Accordingly, we found the beneficial effects of erythropoietin to improve brain ischemia. Hence, administration of erythropoietin in cancer patients had various ameliorative effects beyond treatment of anemia (18-20).

Conclusion

The results of this study showed that administration of erythropoietin and iron supplements, both orally and intravenously, even with a shorter duration of treatment (as compared to other studies) could increase hemoglobin levels in chemotherapy-induced anemia group, but in order to improve the quality of life, it may be necessary to employ larger sample sizes and prolong treatment courses.

Limitations of the study

Given the contradicting results of this and other studies, larger-scale studies are recommended to be conducted on the long-term effects of contrast agents on renal function.

Authors' contribution

AHG and ARM conducted the research and contributed to the conception and design of the research. HA and MK prepared the primary draft. ARM contributed to the acquisition of data. AHG finalized the paper. All authors read and signed the final paper.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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