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The effect of erythropoietin on blood parameters in thalassemia intermedia patients

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Abstract

Background: β-thalassemia is the most common hereditary disease in Iran, and more than 2 million carriers of β-thalassemia live in Iran. On the other hand, our country is located in the thalassemia belt, and no comprehensive study has been conducted regarding the effect of erythropoietin on blood parameters in thalassemia intermedia patients in our region. Therefore this study aimed to investigate the effect of erythropoietin on blood parameters of thalassemia intermedia patients.

Materials and Methods: This prospective cross-sectional study was conducted on all patients suspected of thalassemia intermedia in Shahid Sadoughi hospital from March 2021 to M 2022. In the case of diagnosis of microcytic anemia, an electrophoresis test was performed, and people diagnosed with thalassemia intermedia entered the study. Then patients were divided into two groups (the intervention and control groups). The erythropoietin dose was 50-100 units/ kilogram (body weight) three times a week for six months. The measurement of hematocrit and hemoglobin were done using CBC cell counter (Sysmex KX21). Other data were extracted from medical records.

ResultL: In the current study, the mean age of patients in the intervention and control groups was 9.15±1.53 and 8.35± 6.90 years old, respectively (p=0.9). The mean hematocrit level in the intervention and control groups was 28.05± 4.06 and 23.45± 3.22 %, respectively (P<0.001). The mean hemoglobin level in the two groups was 9.15± 1.53 and 7.65± 1.23 g/dL respectively (p=0.002). The mean hematocrit level before and after the intervention was 25±3.71 and 28.05±4.06 %, respectively. The mean hemoglobin levels before and after therapy were 7.9±1.52 and 9.15±1.53 g/dL, respectively.

Conclusion: According to the findings, hemoglobin and hematocrit increased in thalassemia intermedia patients taking erythropoietin. Therefore it seems that recombinant erythropoietin can be helpful in these patients.

Keywords: Blood parameters, Erythropoietin, Thalassemia intermedia

Introduction

Beta-thalassemia (β-Thalassemia) is a heterogeneous group of hereditary disorders yielded by various mutations in the regulatory elements and b-globin gene (1-4). The severity of the disease differs from asymptomatic thalassemia minor to severe b-thalassemia major in terms of levels of functional hemoglobin and genetic background (1-4). β-Thalassemia intermedia or non–transfusion-dependent thalassemia is a disorder characterized by anemia, ineffective erythropoiesis, systemic iron overload, and splenomegaly (1), eventually leading to iron overload. These patients don't need a blood transfusion, but the anemia in patients often worsens over time and leads to transfusion dependence (5, 6).

Erythropoietin is a hormone mainly released upon hypoxia in the kidneys, enhancing the production of red blood cells (erythropoiesis) via stimulating the proliferation of precursors and erythroid

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progenitors in the bone marrow. The effect of erythropoietin is mediated by the homodimeric erythropoietin receptor (7). Recombinant human erythropoietin is applied to treat anemia in patients with hemodialysis (8,9) or chemotherapy (10). Erythropoietin therapy in splenectomized patients with β-thalassemia intermedia leads to dose-dependent improvement in anemia (7). Long-term prescription of erythropoietin substantially increases the level of hemoglobin (Hb) in patients with HbE-β-thalassemia (11). Though the binding effect of erythropoietin is through stimulation of erythropoiesis, its anti-anemic impact in patients with chronic renal failure on dialysis may be associated with an increase in the survival of mature red blood cells (7).

Phosphatidylserine, a senescence biomarker, is increased in red blood cells following various stress situations, such as oxidative stress (12). Red blood cells and platelet from patients with β-thalassemia under oxidative stress show an increased level of reactive oxygen species and a reduced level of reduced glutathione compared to their normal counterparts (13). Studies have shown that the number of red blood cells exhibiting surface phosphatidylserine (14) is decreased within 4 hours after erythropoietin therapy (7).

Given that β-thalassemia is the most common hereditary disease in Iran and more than 2 million carriers of β-thalassemia live in Iran (15), and no comprehensive study has been conducted in this regard in our region, this study aimed to investigate the effect of erythropoietin on blood parameters of thalassemia intermedia patients.

Materials and Methods

This prospective cross-sectional study was conducted on all patients suspected of thalassemia intermedia in Shahid Sadoughi hospital from March 2021 to March 2022.

These patients had the symptoms of weakness, fatigue, pale skin, decreased appetite, decreased growth, dark urine, and a family history of thalassemia.

In the diagnosis of microcytic anemia (MCV less than 2.5th percentile for age and sex), an electrophoresis test was performed, and people with thalassemia intermediate diagnosed by electrophoresis (the increase in HbA2 and HbF) entered to the study. The unwillingness of patients and underlying diseases caused the patients to be excluded from the study.

Then patients were divided into two groups (the intervention and control groups). The intervention group received erythropoietin (dose 50-100 units/ kilogram, three times a week for six months). The measurement of hematocrit and hemoglobin were done using CBC cell counter (Sysmex KX21). The side effects, including thrombotic events, headache, increased blood pressure, and pain at the injection site were extracted from medical records. In case of infection, high blood pressure, thrombotic complications, and flu symptoms, patients were excluded from the study. Data were entered into SPSS, version 19. Chi-square test, paired sample t-test, and independent sample t-test were used to analyze data. $P<0.05$ was assumed significant.

Results

This study was conducted on 40 thalassemia intermedia patients. These patients were randomly divided into two groups (n=20). One group treated erythropoietin. The other group did not receive erythropoietin and was considered the control group. Drug side effects, including thrombotic events, headache, increased blood pressure, and pain at the injection site, were not observed in the intervention group.The range of aspartate transaminase (AST) and alanine transaminase (ALT) was 30 -54 and 14-56 U/L, respectively. The mean AST and ALT level in the intervention group was 40.65 and 31.50 U/L. The frequency of patients in terms of gender is shown in Table I. As shown in Table I, the majority

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of patients were girls. The comparison of the two groups in terms of the mean age of patients is shown in Table II. There was no significant difference between the two groups regarding hematocrit and hemoglobin levels before intervention (P>0.05). The comparison of blood parameters in the two groups after intervention is shown in Table III. As shown in Table 3, a significant difference was observed between the two groups in terms of hematocrit and hemoglobin (P<0.01). The comparison of blood parameters before and after intervention (in the case group) is shown in Table 4. As demonstrated in Table 4IV, the mean hematocrit and hemoglobin levels increased after the intervention (P<0.01).

Table I: The frequency of patients in terms of gender

Variables	Intervention group	Control group	p-value
Gender			
Girl	14 (70)	12 (60)	
Boy	6(30)	8 (40)	0.570
Total	20 (100)	20 (100)	

Table II: The comparison of patients in terms of the mean age of patients

Variables	Intervention group	Control group	P-value
Age	9.15±1.53	8.35± 6.90	0.9

Table III: The comparison of blood parameters in the two groups after intervention

Variables	Case group	Control group	P-value
Hematocrit (%)	28.05± 4.06	23.45± 3.22	<0.001
Hemoglobin (g/dL)	9.15± 1.53	7.65± 1.23	<0.001

Table IV: The comparison of blood parameters before and after intervention

Variables	Before therapy	After therapy	P-value
Hematocrit (%)	25.00± 3.71	28.05 ± 4.06	<0.001
Hemoglobin (g/dL)	7.9 ±1.52	9.15± 1.53	<0.001

* paired t-test

Discussion

β-Thalassemia intermedia is characterized by mild to severe ineffective erythropoiesis (1). Mild type affects asymptomatic patients until adult life, leading to only mild anemia and maintaining the level of hemoglobin in the range of 7- 10 g/dl (16). Thalassemia intermedia is less severe than thalassemia major and can often continue without transfusions for years (17). However, the patients become dependent on blood transfusion and suffer from these complications (17). Recombinant human erythropoietin is used in primary and secondary anemia. Among the various types of anemia, a significant component of congenital hemolytic anemia was

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caused by a mutation in the hemoglobin, especially thalassemia syndrome and sickle cell anemia (18). In the current study, the mean hematocrit and hemoglobin levels were increased in the intervention group than in the control group. Moreover, comparing the hematocrit and hemoglobin levels before and after intervention showed that the mean hematocrit and hemoglobin levels increased after the intervention.

Nisli et al. assessed the role of recombinant erythropoietin therapy in patients with thalassemia intermedia. In this regard, the dose of 500- 1000 U/kg, three times a week for three months, was used. During therapy, 80% of patients demonstrated an increase in hematocrit, hemoglobin, and reticulocyte levels. Blood transfusion was not required during research except in 1 case. In addition, the erythropoietin therapy was well tolerated, and hypertension was not seen in any patients. Therefore according to these findings, recombinant erythropoietin was an effective therapy for anemia of beta-thalassemia intermedia. The results of this study were consistent with our study (19).

Asadov et al. evaluated the application of erythropoietin therapy in thalassemia intermedia, and patients received erythropoietin (10000 IU subcutaneously) for six months. The majority of patients (about 67%) had a good response. It can be concluded that erythropoietin therapy leads to an increase in the levels of hemoglobin and reduce the need for blood transfusions, preventing severe complications of blood transfusion (16).

Amer et al. evaluated the effect of erythropoietin on thalassemic blood cells and reported that erythropoietin stimulates red blood cells and fetal hemoglobin and alleviates hemolytic anemia (13).

Other studies have shown that the application of erythropoietin (150 u/kg x 3/week) led to those patients (3 people) with non-transfusion dependent thalassemia intermedia responding to recombinant erythropoietin treatment. The post-recombinant erythropoietin levels raised than pre- recombinant erythropoietin levels. However, the fetal hemoglobin did not increase during treatment (20).

Another study reported that the application of recombinant erythropoietin (500 u kgx3/week) increased hemoglobin (25 g/l). One patient increased the level of fetal hemoglobin. In addition, three patients needed transfusion-independent, and one increased the interval between injections (16). Another study evaluated the effect of recombinant erythropoietin (l000u/kg/week) twice a week in patients with ß-thalassemia intermedia, and the findings showed an increase in total hemoglobin levels (2g/dl) without changes in fetal hemoglobin and red blood cells indices (21). Another study revealed that the administration of recombinant erythropoietin (200-1000 u/kgx3/week) caused a 2-3 g/dl increase in hemoglobin without any change in other erythroid parameters (16).

Amer et al. also revealed that erythropoietin administration might be helpful in thalassemic patients, reducing oxidative stress, prolonging the survival of red blood cells, and decreasing the state of activation of their platelets (13). Adosov et al. reported that erythropoietin promoted proliferation, differentiation, and survival of erythroid precursors and red blood cells, inducing fetal hemoglobin synthesis (16). Some studies have shown that erythropoietin treatment improves the state of anemia (13, 22). The rational for this therapy in thalassemia was the stimulation of erythropoiesis and increased fetal hemoglobin production.

Burn et al. revealed that high-dose administration of recombinant human erythropoietin in the long term may be effective in increasing total hemoglobin in patients with thalassemia intermedia and may improve the adverse effects of this situation. This was due to thalassemic red blood cell release into peripheral circulation (17). They also reported that

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the cost of recombinant erythropoietin was higher than blood transfusions, but the risk of blood transfusions was high. Therefore recombinant human erythropoietin treatment was more cost-effective in the long term.

Amer et al. revealed the antioxidative potential of recombinant erythropoietin on platelet and red blood cell. Its activity was shown at concentrations above normal levels. However, at physiological concentrations, this cannot rule out and erythropoietin was not appropriate as an antioxidant because it is much more expensive and less potent. In addition, it should be prescribed by injection. Nevertheless, in situations such as severe anemia, massive bleeding, hemodialysis, or chemotherapy, the potential protective effect of recombinant erythropoietin as an antioxidant on platelet and red blood cell survival should be considered (13).

Conclusion

According to the findings, hemoglobin and hematocrit increased in thalassemia intermedia patients taking erythropoietin. Therefore, it seems that recombinant erythropoietin can be helpful in these patients.

Ethical Consideration

Written consent was obtained from patients, and the current study was approved by the Ethics committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICINE.REC.1400. 334).

Conflict of interest

The authors declare no conflict of interest.

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